

**PERFORMANCE AND CHARACTERISTICS OF CONTROLLED  
RELEASE MATRICES COMPOSED OF  
HYDROXYPROPYLMETHYLCELLULOSE AND OTHER  
POLYMERS**

A Thesis Submitted in Partial Fulfilment of Requirements  
for the degree of

**DOCTOR OF PHILOSOPHY**

of the

**LIVERPOOL JOHN MOORES UNIVERSITY**

by

**MOHAMMAD ALI DABBAGH**

This research was carried out in collaboration with  
Colorcon Ltd., Kent, U.K.

School of Pharmacy  
Liverpool John Moores University  
Byrom Street  
Liverpool

August 1995

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## ABSTRACT

This thesis examines the use of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC) or ethylcellulose, alone or in combination with other adjuncts, to control the release of propranolol hydrochloride from matrices.

Gels were characterized by U tube viscometry and their cloud points of gels. The properties of polymers and their mixture in matrices or in gels were investigated by differential scanning calorimetry (DSC). Compendial dissolution methodology was used to determine drug release from matrices and their release exponents.

Propranolol hydrochloride increased the solubility of HPMC and altered the water distribution in their gels. The release of propranolol hydrochloride from HPMC matrices was dependent on the square root of time. Release exponents were  $\approx 0.6$ , indicating that diffusion and erosion contributed to drug release.

The release rates of propranolol hydrochloride from NaCMC matrices decreased as the NaCMC content increased. Addition of propranolol hydrochloride to NaCMC gels produced an insoluble complex which, in matrices, controlled the drug release. The interaction between propranolol hydrochloride and NaCMC was confirmed by DSC and dialysis. The viscosity grade of NaCMC affected the drug release. NaCMC matrices showed fast erosion. The release of sodium ions from matrices containing NaCMC was enhanced propranolol hydrochloride, confirming the occurrence of the interaction in matrices. The release of propranolol hydrochloride from NaCMC matrices was not dependent on either the square root of time or time. Large increases in release rates from matrices containing NaCMC in acidic media implied the polymer was unable to gel provide or a sustained release of propranolol hydrochloride at low pH.

A synergistic increase in viscosity in gels containing HPMC and NaCMC probably played a minor role in propranolol release from matrices containing both polymers. NaCMC decreased the cloud point of HPMC. Drug release from matrices containing HPMC and NaCMC was very complicated, but zero order release was achieved from matrices containing 285 mg of 1:3 HPMC : NaCMC. Addition of HPMC to NaCMC matrices suppressed an initial burst release of propranolol. The release of propranolol hydrochloride from matrices containing HPMC and NaCMC was dependent on pH.

Ethylcellulose was capable of binding  $\approx 14\%$  w/w water. Matrices containing ethylcellulose 7 cP ( $<125 \mu\text{m}$ ) showed lower release rates than matrices containing ethylcellulose 10 cP, or at greater particle sizes. Compaction pressure generally did not affect drug release. The release exponent from matrices containing ethylcellulose was 0.44 - 0.49 indicating diffusion predominated drug release.

Admixture of ethylcellulose with HPMC did not change the release exponent ( $0.59 < n < 0.61$ ) from that of HPMC alone, whereas the exponents of NaCMC:ethylcellulose matrices was altered. Addition of ethylcellulose to HPMC increased the initial uptake of water.

The incorporation of a complex of propranolol and  $\beta$ -cyclodextrin failed to retard the release of drug or alter the release exponent.

M.A.Dabbagh

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## ABBREVIATIONS

BP	Bound propranolol
$\beta$ -CD	beta Cyclodextrin
CD	Cyclodextrin
CE	Cellulose ethers
CMC	Carboxymethylcellulose
cP	Centipoise
CPT	Cloud point temperature
cSt	Centistokes
DP	Degree of polymerisation
DS	Degree of substitution
DSC	Differential Scanning Calorimetry
E1% 1 cm	Specific absorbance of E <sup>1%</sup> <sub>1cm</sub>
EC	Ethylcellulose
FP	Free propranolol hydrochloride
HEC	Hydroxyethylcellulose
HEMC	Hydroxyethylmethylcellulose
HPC	Hydroxypropylcellulose
HPMC	Hydroxypropylmethylcellulose
IPT	Incipient gelation temperature
k'	Huggins interaction constant
K <sub>1</sub> , K <sub>2</sub> or K <sub>3</sub>	Dissociation constant
l	Lag time
MC	Methylcellulose
min	Minute
mL	Millilitre
MNm <sup>-2</sup>	Mega Newton square metre
mol. wt.	Molecular weight
n	Release exponent
nm	Nanometre(s)
NaCMC	Sodium carboxymethylcellulose
Pa.s	Poise
PH	Propranolol hydrochloride
pKa	Negative logarithm of the dissociation constant
rev min <sup>-1</sup>	Revolutions per minute
rpm	Revolutions per minute
RR	Release rate
SD	Standard deviation
SI	Standard International
T <sub>50%</sub>	Time for 50% drug released
TGP	Thermal gelation point
USP	United State Pharmacopoeia
UV	Ultraviolet
w/w	Weight in weight
w/v	Weight in volume
$\eta$	Dynamic viscosity
$\eta_{sp}$	Specific viscosity
$\eta_{sp/c}$	Reduced viscosity
$\mu$ m	Micrometre(s)
$\mu$ l	Microlitre(s)
v	Kinematic viscosity



## **CHAPTER 1 INTRODUCTION**

This chapter provides an introduction to controlled release drug delivery and a discussion on controlled release matrices. Cellulose derivatives, especially cellulose ether polymers, and factors that influence drug release from these matrices are discussed. Finally, the aims and objectives of the work described in this thesis are presented.

### **1.1 CONTROLLED RELEASE SYSTEMS**

Historically, the oral route of administration has been the most utilized route for both conventional and novel drug delivery systems. There are many obvious reasons for this, not the least of which are acceptance by the patient and ease of administration. Conventional drug delivery systems are known to provide prompt release of drug. This may lead to high peak drug concentrations beyond therapeutic levels and approaching toxic levels (Grass and Robinson, 1990).

Many drugs have an inconveniently short duration of action and over the years many attempts have been made to overcome this problem by slowing their rate of absorption (Prescott, 1985). If the drug is excreted at a rapid rate, the levels decline below the therapeutic level within a few hours, thereby necessitating frequent dosing. This results in widely fluctuating drug levels. This may not only compromise efficacy of the drug and produce toxic

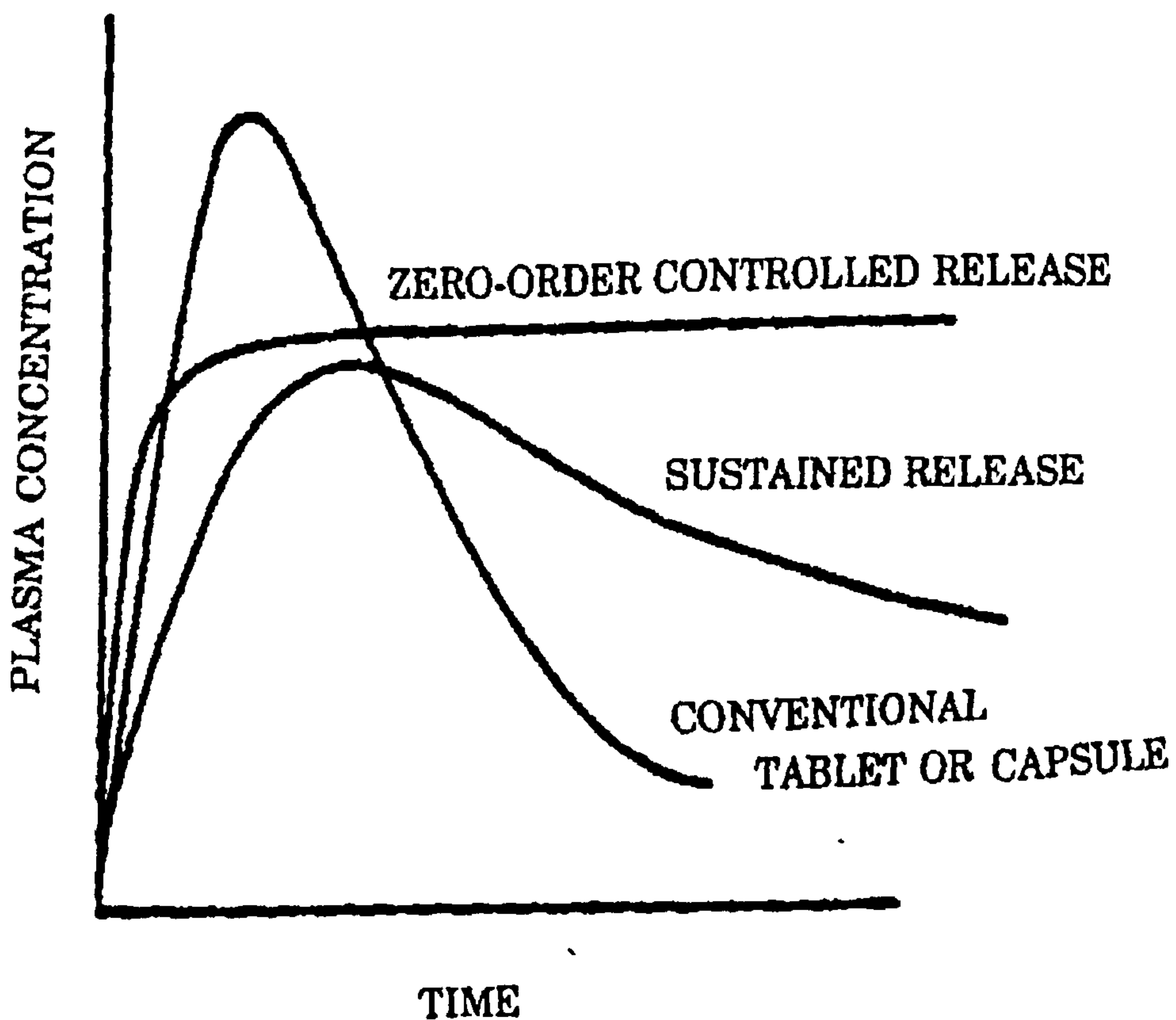
side effects but may also result in poor compliance.

Sustained-release drug delivery systems have received considerable attention from the pharmaceutical and device-manufacturing industries because these systems offer overwhelming advantages over conventional drug delivery systems. Some 40 years ago, oral 'slow release' products started to be marketed and significant advances were made with prolonged action parenteral formulations and implants (Prescott, 1985). It is only within the past few years that the full potential and wide range applicability of sustained release technology has been realized. In a report, Higuchi et al (1983) stated "the approach to the design of oral drug delivery systems is evolving rapidly, both quantitatively and qualitatively, so that the situation is considered to be on the threshold of being revolutionary". All evidence seems to support this statement because the field of oral sustained release is definitely advancing at a rapid pace (Shah, 1988).

With wider appreciation of pharmacokinetic principles and the introduction of therapeutic drug monitoring, it has become apparent that the advantages of rate-control are not restricted to prolongation of drug action. With controlled, constant drug-input, greater selectivity of drug action and reduced toxicity might be achieved by avoiding the succession of peaks and valleys of drug concentration associated with conventional therapy. This concept of 'steady state' or 'zero-order' pharmacokinetics has far-reaching implications and opens up a whole new area of promise in drug therapy (Prescott, 1989).

Figure 1.1 shows comparative blood drug profiles obtained following the administration of conventional, sustained release and zero-order controlled release dosage forms. If drug release kinetics can be controlled, the plasma concentration of a drug can be maintained in the therapeutically appropriate range and harmful side effects can be reduced (Li et al, 1987; Grass and Robinson, 1990).

Figure 1.1: Plasma drug concentration profiles for conventional tablet or capsule, sustained release or zero-order controlled release formulations (after Li et al, 1987).





## **1.1.1 Advantages and disadvantages of controlled release systems**

### **1.1.1.1 Advantages of controlled release systems**

Although, controlled release dosage forms are often more expensive than conventional formulations, they are more attractive dosage forms because they offer some clinical and practical advantages (Welling and Dobrinska, 1987; Baker, 1987a; Ritschel, 1989) such as:

- a- patient compliance by reduction in the frequency of dosing with the use of sustained or controlled delivery systems,
- b- causing a reduction in the fluctuation of circulating drug levels,
- c- a reduction in costs by a reduction in dosages,
- d- achieving a more uniform pharmacological response,
- e- a reduction in side effects by keeping the plasma drug levels within the therapeutic range.

### **1.1.1.2 Disadvantages of controlled release systems**

Controlled release dosage forms have several disadvantages (Welling and Dobrinska, 1987). Therefore, the advantages must be weighed against the potential disadvantages in any specific clinical application. The disadvantages which can be encountered in the use of solid polymeric delivery devices may include:

- a- high cost due to the expense of a particular polymer-drug formulation or its fabrication,



- b- poor in vitro-in vivo correlation, due to poor biocompatibility of the polymer used,
- c- toxicity of the polymer or any biodegradation of the polymer,
- d- reduced potential for accurate dose adjustment,
- e- increased potential for first pass clearance,
- f- failure of the dosage forms would release the drug instantly and since sustained dosage forms generally contain a much greater amount of drug, the total drug content could become available for absorption and toxicity may result (Ritschel, 1989; Grass and Robinson, 1990).

### **1.1.2 Drugs suitable for oral controlled release dosage forms**

The selection of a drug candidate for the design of a sustained release system depends largely upon pharmacological, therapeutic and pharmaceutical considerations. The criteria for the selection of a suitable drug candidate are:

- a- short biological half life,
- b- narrow therapeutic index,
- c- efficient gastrointestinal absorption,
- d- small daily dose,
- f- no first pass metabolism, and
- g- marketing benefits (Shah, 1988).

Therapeutic compounds with short half-lives are excellent candidates for formulation into a sustained-release preparation since this can reduce their dosing frequency and hopefully increase patient compliance (Shah, 1988).

Drugs with very short half-lives will require excessively large amounts of drugs in each dosage unit to maintain sustained effects. This creates a prohibitive situation, forcing the dosage form itself to become too large to be administered, therefore creating a limitation to the amount of drug that can be practically incorporated into such a system. In general, drugs with half-lives shorter than 2 hours, are poor candidates for sustained release preparations. Compounds with relatively long half-lives, generally greater than 8 hours, are not used in sustained-delivery since their effect is already sustained (Li et al, 1987). On the other hand, the transit time of most dosage forms in the gastrointestinal tract is in the range of 8 to 12 hours, making it difficult to increase the absorptive phase beyond this time frame. The maximum half-life for absorption should be approximately 3 to 4 hours, otherwise the device will pass out of the potential absorptive regions before release is complete (Grass and Robinson, 1990). Furthermore, drugs that have a relative narrow therapeutic index will be more efficacious and less toxic if administered in a sustained release form (Shah, 1988; Grass and Robinson, 1990).

If a drug undergoes an extensive first-pass metabolism that is saturable during the administration of conventional fast-release dosages, then systemic availability may be decreased due to non-saturation of the clearance mechanisms following formulation into a sustained release dosage form. However, if hepatic clearance is not saturated during the use of conventional dosage forms, slower absorption of drug should not cause a reduction in the

systemic availability (Welling and Dobrinska, 1987).

### **1.1.3 Terminology**

There is a considerable confusion in the terminology between "controlled release" and "sustained release". Unfortunately these terms have been often used interchangeably (Chien, 1992).

Madan (1985) described 32 terms that relate to prolonged drug release. The United State Pharmacopoeia / National Formulary (USP 23/NF 18, 1995) has also proposed modified release to describe all non-conventional, slow-release systems and have classified them into delayed release and extended release dosage forms. It is thus necessary, to provide a short explanation of the terminology used.

#### **1.1.3.1 Delayed Release**

The term "delayed release" is used to describe systems where it is not intended for the drug to be released immediately after administration. Delayed-release products, such as enteric-coated products, are designed to delay the release of the drug until the dosage forms reaches the intestinal tract. These products are used to prevent side effects associated with the release of the drug in the stomach or to protect the drug from degradation in the acidic gastric environment (Madan, 1985).



### 1.1.3.2 Sustained Release

The term "sustained release" has existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration (Chien, 1992). Sustained release dosage forms carry the delayed-release concept a step further and these products are primarily designed to decrease the frequency with which the patient has to take the dosage form to obtain the desired effect.

### 1.1.3.3 Controlled Release

The term "controlled release" on the other hand, has a meaning that goes beyond the scope of sustained drug release. It also implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredients from a controlled-release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another (Chien, 1992; Li et al, 1987). The term controlled release has gained recognition because it implies that the rate of release is controlled by the delivery system itself and not by the external conditions of pH, enzymes, ions, intestinal motility, etc (Ritschel, 1989).

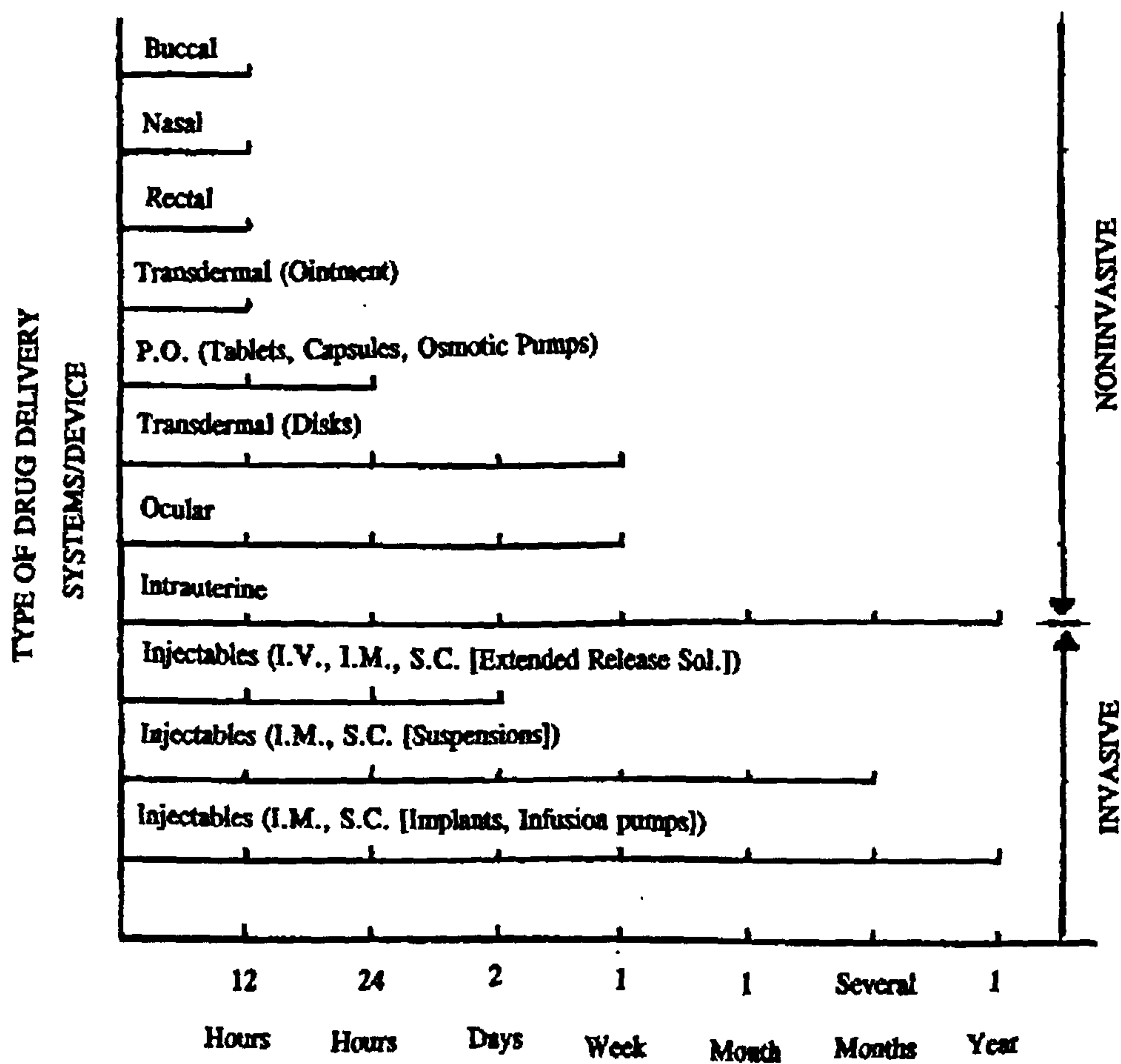
### **1.1.4 Application of controlled-release technology**

The ideal controlled release system maintains drug levels at a constant value

within the desired therapeutic range for a specified time period. By tailoring the polymers appropriately, or by using different drug incorporation procedures, drugs can now be released in a far more precise and prolonged manner than with sustained-release methods. However, polymers are essential for producing controlled-release dosage forms, as formulation aids and for governing the drug release (Doelker, 1987). Controlled-release polymer technology has been used not only in the pharmaceutical industry, but also in agriculture (e.g. fertilizers), biology (e.g. growth factors) and to deliver pesticides (Langer, 1980; Prasad and Kalyanasundaram, 1993). Ritschel (1989) investigated different controlled release dosage forms and different devices for various routes of administration. The length of duration of these products are shown in figure 1.2.

Although polymers, especially hydrophilic ones, are employed in various pharmaceutical dosage forms such as ophthalmic inserts (Langer, 1980; Li et al, 1987; Baker, 1987a), nasal delivery systems (Lin et al, 1992), pessaries (McKenzie and Embrye, 1977), suspensions (Sprockel et al, 1989), parenteral systems (Leung et al, 1987; Tice and Cowsar, 1984), transdermal systems (Brown and Langer, 1988), and capsules (Paggy, 1988; Rao and Ritschel, 1992; Hussain et al, 1994), the scope of this thesis will concentrate on the applications of cellulose ethers in oral controlled release matrix tablets.

Figure 1.2: Schematic diagram of the types of controlled release delivery systems/devices, route of administration and length of duration of action (after Ritschel, 1989).





## 1.2 CLASSIFICATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEMS

A drug delivery device is a prefabricated system that releases a predetermined volume or amount independent of the drug used over a period of 12 to 24 hour (Ritschel, 1989). Over the past 50 years, a number of techniques have been developed and employed to sustain the delivery of medication to the systemic circulation following oral administration (Hui et al, 1987; Li et al, 1987).

There are three basic types of polymeric devices. The most common one, due to its relative ease of production and low cost compared to the other methods of sustained or controlled delivery, is the diffusion-controlled system which has classically been of primary importance in the oral delivery of medications (Grass and Robinson, 1990). The second type, dissolution-controlled systems, is commonly employed in the production of enteric-coated dosage forms. In the last type, the use of polymers is to provide chemically-controlled systems which depend upon chemical reaction to release the drug from the implant. There are many other sustained and controlled release systems which have received a more limited but increasing amount of attention as candidates for oral products.

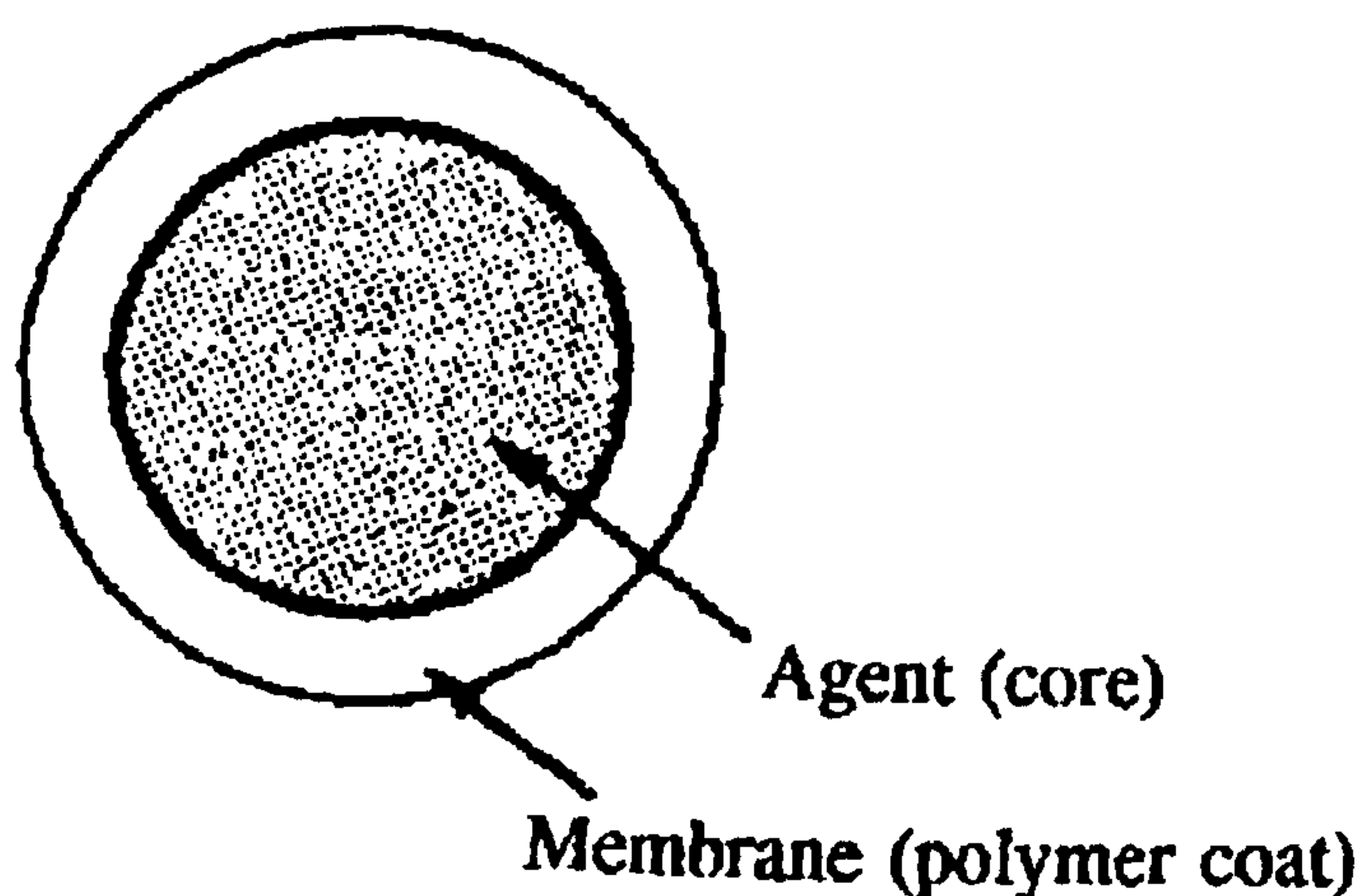
The choice of an oral sustained /controlled release system is limited by the aqueous solubility of the drug. Diffusional systems will be poor choices for slightly soluble drugs since the driving force for diffusion, the concentration

in aqueous solution, will be low. In contrast, such drugs may be effectively incorporated in matrix systems (Li et al, 1987). However, the main controlled release devices are:

### 1.2.1 Membrane-controlled reservoir systems

The reservoir type device has been in use for some time in the U.S.A. and was recently re-introduced in the U.K. by the company Duncan Flockhart, to deliver salbutamol for asthma sufferers (Verrall, 1988). These systems are characterized by a core of drug, the reservoir, surrounded by a polymeric coat which controls the release rate. The active drug is contained within the inert polymer (Linhardt, 1989). These devices are diffusion-controlled and a schematic diagram of a reservoir device is given in figure 1.3.

Figure 1.3: Schematic representation of a reservoir diffusional device (after Baker, 1987a)



Reservoir devices have the advantage of providing a constant rate of release over a substantial portion of their lifetime (Baker and Lonsdale, 1974; Baker, 1987a). Since the amount of drug contained in the reservoir is far greater than the usual dose needed, any error in production or any accidental damage to the dosage forms that would directly expose the reservoir core to the intestinal fluids could expose a potentially toxic dose of the drug to the patient (Grass and Robinson, 1990). Therefore, any failure in this system could be catastrophic. A reservoir device is more expensive and its fabrication is more difficult than a matrix system (Baker, 1987a).

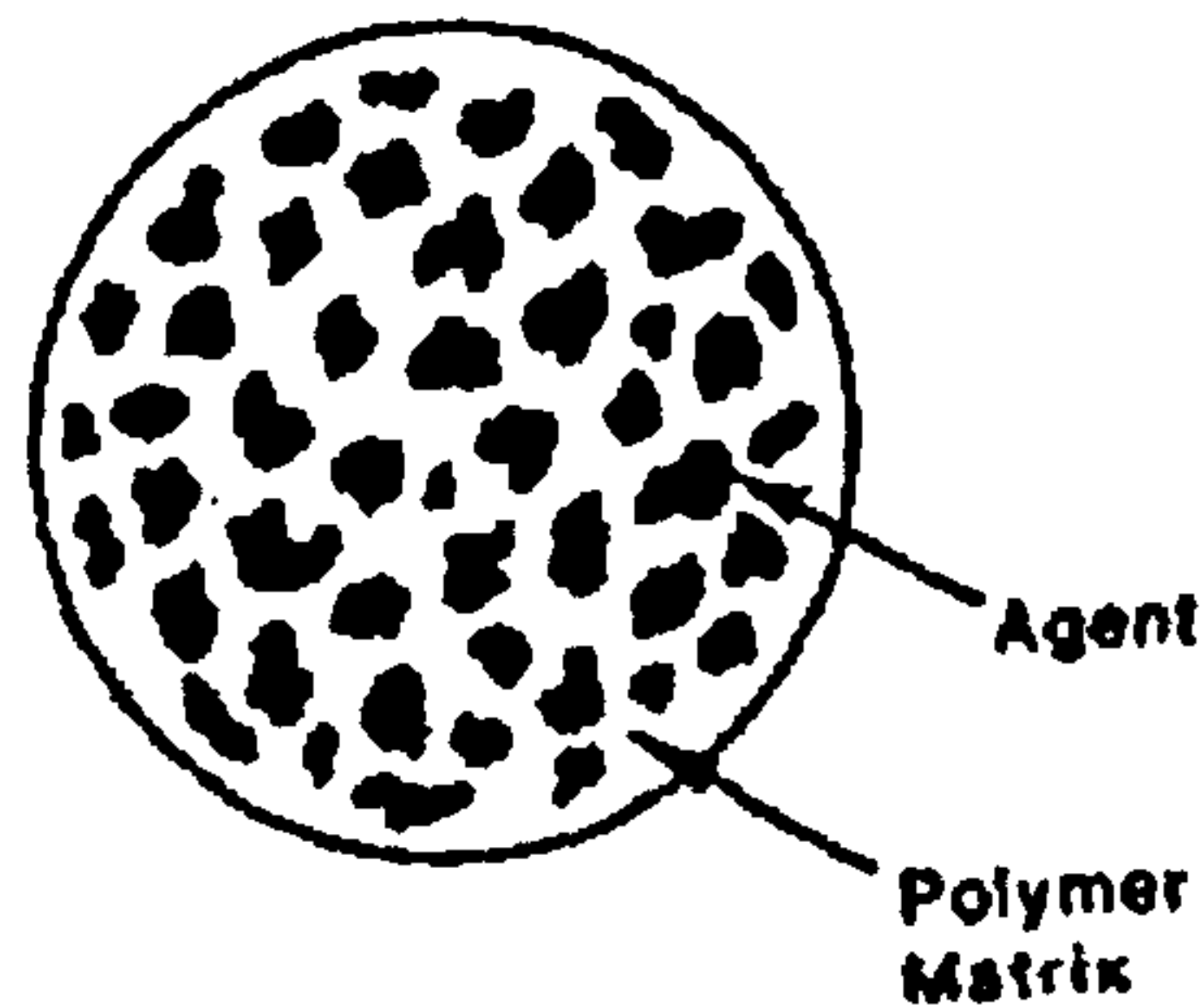
Sutinen et al (1992; 1993), using silicone reservoir devices containing propranolol hydrochloride, reported that the drug release followed zero-order kinetics and was essentially independent of the composition of the dissolution media.

### **1.2.2 Diffusion-controlled monolithic systems**

Much discussion revolves around the innovative work of Higuchi (1961) which used polymeric matrices to deliver drugs (Chandrasekaran et al, 1983). In a monolithic matrix system the active agent is homogeneously dissolved or dispersed throughout the polymer itself, as represented in figure 1.4. In this model, the drug in the outside layer of the matrix exposed to fluid is dissolved first and then diffuses out of the matrix. This process continues with the interface between the solution and the solid drug moving towards the interior (Grass and Robinson, 1990).



Figure 1.4: Schematic representation of a matrix diffusional system (after Grass and Robinson, 1990)



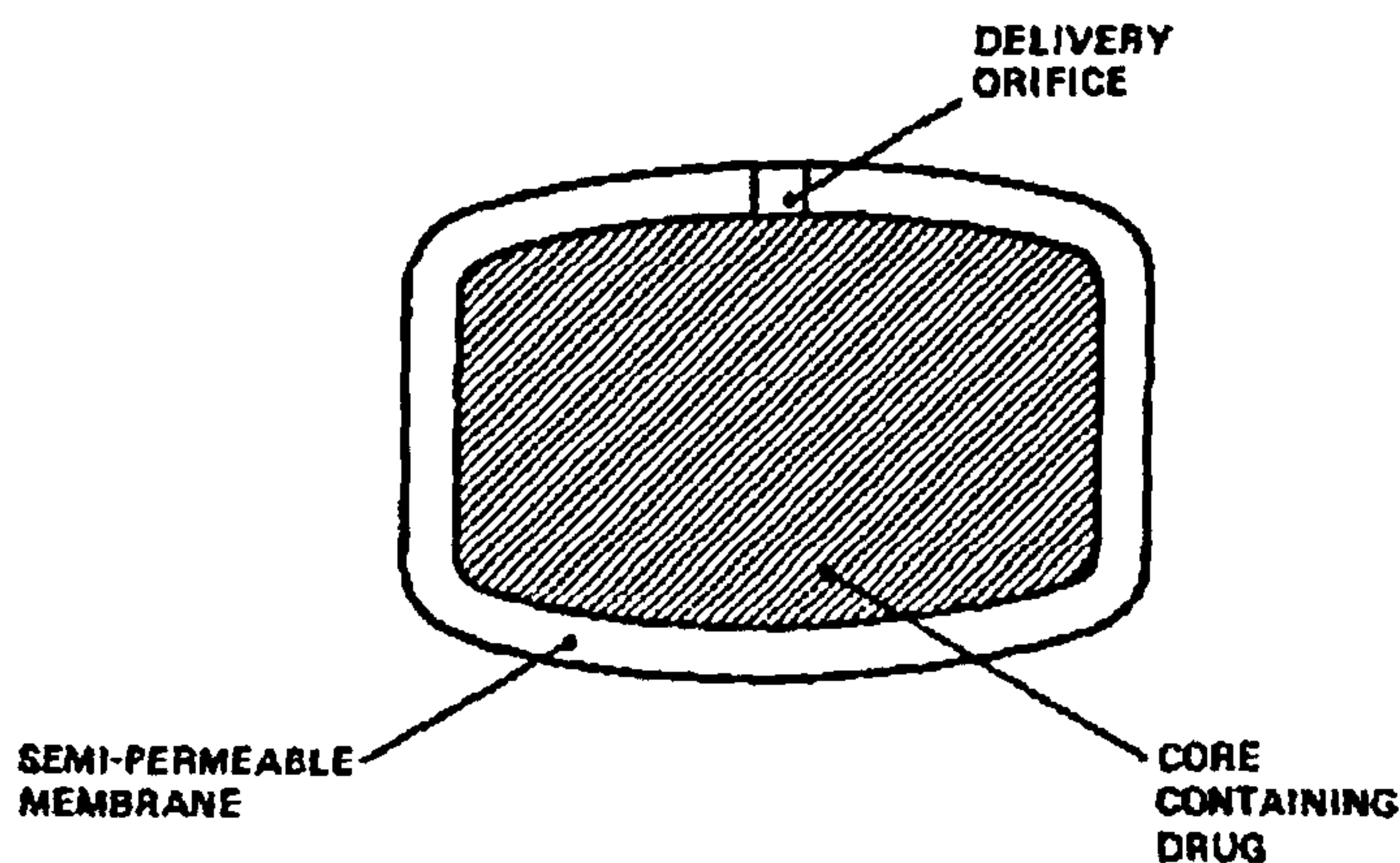
The release pattern depends on the geometry of the system, the identity and nature of the polymer or other carrier material, and the loading of the agent. The advantage of this type of system is that it is easy to manufacture and therefore more cost effective. However, one disadvantage is that it cannot produce zero-order drug release (Baveja et al, 1987; Grass and Robinson, 1990).

### 1.2.3 Osmotic systems

These systems are devices in which the active agent, present alone or with an osmotic driving agent, is surrounded by a semi-permeable membrane having a single delivery orifice (figure 1.5). Water from the environment is continuously imbibed across the semi-permeable membrane by osmosis to produce a fluid drug suspension; the continuous membrane controls the influx of water which drives the formulation through the orifice (Theeuwes and

Eckenhoff, 1980). In recent years, several devices have been developed that utilize osmotic effects to control the release of the active agent (Theeuwes, 1989). Osmotic devices of various designs have found their largest application in oral tablet formulations (Baker, 1987a).

Figure 1.5: A schematic representation of an osmotic pump device for drug delivery (after Theeuwes and Eckenhoff, 1980).



#### 1.2.4 Mechanical Pumps

Mechanical pumps can be miniaturized to deliver an active agent at a constant rate over a prolonged period. Several such devices use batteries as the power source, but pumps have been made that use the elastic tension of stretched rubber balloons or the vapour pressure of low-boiling liquids as the power source. Most of these pumping devices have limited use and are

employed predominantly in pharmaceutical applications, where their expense can be justified (Baker, 1987a).

### **1.2.5 Chemically controlled systems**

Kim et al (1980) reviewed devices in which the drug is covalently bound to a polymer matrix. In this system the drug is usually bound as a pendant group, e.g., poly (amino acid) with a steroid pendant group (Linhardt, 1989).

## **1.3 ORAL SUSTAINED RELEASE MATRICES**

Slow release dosage forms generally contain a much greater amount of drug than conventional forms and, unlike them, these systems do not disintegrate (Melia, 1991). If the system fails and undergoes disintegration, all of the dose will be released immediately causing acute toxicity. Therefore, great care must be taken in the formulation and design of sustained release dosage forms.

Since zero-order release is the most appropriate release pattern, several studies (Baveja and Ranga Rao, 1986; Baveja et al, 1987, 1988a, b; Colombo et al, 1987; Ranga Rao et al, 1989) have attempted to achieve a zero-order release of drug, which is independent of time and the amount of drug in the systems. Therefore, many systems based on polymers have been introduced in the literature, all aiming to achieve zero-order release.



### **1.3.1 Matrices**

A matrix is defined as a well-mixed composite of ingredients fixed into a shape by tableting or by the use of hard shell capsules (Alderman, 1984). Basically, in these systems the drug is homogeneously dispersed throughout the polymer mass (Baker, 1987a). The most commonly used polymers for oral sustained release devices are swellable polymers (Melia, 1991). A variety of other excipients may optionally be included to aid tableting properties (Ford et al, 1987). The release pattern from these systems depends on the geometry of the system, the identity and nature of the polymer or other carrier material and the loading of the agent. However, the materials used in controlled release devices should be inert, remain intact during transit through the gastrointestinal tract and provide a sustained release over a reasonable length of time.

The importance of the choice of matrix material has been illustrated by many studies (Baker, 1987a; Shah, 1988; Chien, 1992). Because the use of a polymeric controlled release device exposes the polymer to an aqueous environment, its interaction with water is of considerable importance. According to the nature of polymer-water interactions, polymers can be broadly classified into **hydrophobic polymers, hydrophilic polymers, water soluble polymers and hydrogels** (Heller, 1987a).

#### **1.3.1.1 Hydrophobic polymers**

These polymers are essentially water impermeable and when placed in an

aqueous environment, will absorb very little water. Clearly, there is no fixed value for the amount of absorbed water below which a polymer is hydrophobic and above it which is deemed hydrophilic. However, Heller (1987b) suggested that hydrophobic polymers should absorb less than 5% water and hydrophilic polymers more than 5% w/w. Structural parameters that contribute to polymer hydrophobicity are chain stiffness and a high degree of crystallinity. Fatty matrices such as carnauba wax, stearyl alcohol, beeswax, glyceryl monostearate and stearic acid are the basis of typical hydrophobic matrix materials (Shah, 1988). In addition, cellulose acetate phthalate, methylhydroxypropylcellulose phthalate and ethylcellulose are substances that are insoluble in water but soluble in organic solvents (Grosse, 1990).

#### 1.3.1.2 Hydrophilic polymers

Hydrophilic matrix dosage forms are attractive to the formulator, because they offer potential advantages such as low cost of manufacture, simplicity of formulation, direct compression of the drug blend, high drug loading and a wide choice of polymers that can be used to control drug release (Doelker, 1987; Melia, 1991).

Amongst the various hydrophilic polymers, cellulose ethers, in particular different grades of hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC) or hydroxypropylcellulose (HPC), have been investigated (Ford et al, 1985a, b; Baveja, 1987; Ranga Rao et al, 1988a , b; Melia, 1991).

### 1.3.1.3 Water-soluble polymers

Some polymers are freely soluble in water, even though they are of very high molecular weight. Examples of such polymers include poly (vinyl alcohol), poly (acrylic acid), poly (N-vinylpyrrolidone), poly acrylamide and poly (ethylene oxide) (Heller, 1987a). The release of different drugs through slabs of poly (vinyl alcohol) and poly (N-vinylpyrrolidone) was studied by Korsmeyer et al (1983a) and Colombo et al (1985; 1987).

### 1.3.1.4 Hydrogels

In drug delivery systems, the term "hydrogel" is typically reserved for polymeric materials that can absorb a significant amount of water (more than 20% of their dry weight) while maintaining a distinct three-dimensional structure (Gehrike and Lee, 1989). These polymers are highly hydrophilic or are water soluble polymers that have been crosslinked by means of covalent bonds. Therefore, hydrogels cannot dissolve due to their covalent crosslinks. Gehrike and Lee (1989) stated that hydrogels have four key properties: swelling degree, biocompatibility, permeability and swelling kinetics. They reported that their high water content leads to good biocompatibility and that the permeability of hydrogels to water, drugs and other solutes is easily adjusted over a broad range by changing the gel precursor, crosslinker, or conditions of synthesis.

### **1.3.2 Methods of matrix preparation**

Compressed hydrophilic matrices are prepared either by direct compression,



wet granulation or by slugging (dry granulation). All comparative studies show, however, that only slight differences in the release profiles are observed between the various methods of preparation (Doelker, 1987).

#### 1.3.2.1 Direct compression

One of the most important characteristics of hydrophilic polymers is their compressibility which makes them capable of being easily blended with active agents and of being easily compressed (Alderman, 1984; Ford et al, 1985a, b; 1987; Baveja et al, 1987; Porter, 1989). In contrast to other types of matrices or to conventional tablets, the compression force used to make hydrophilic matrices does not play a significant role in affecting their release rates (Ford et al, 1987).

#### 1.3.2.2 Wet granulation

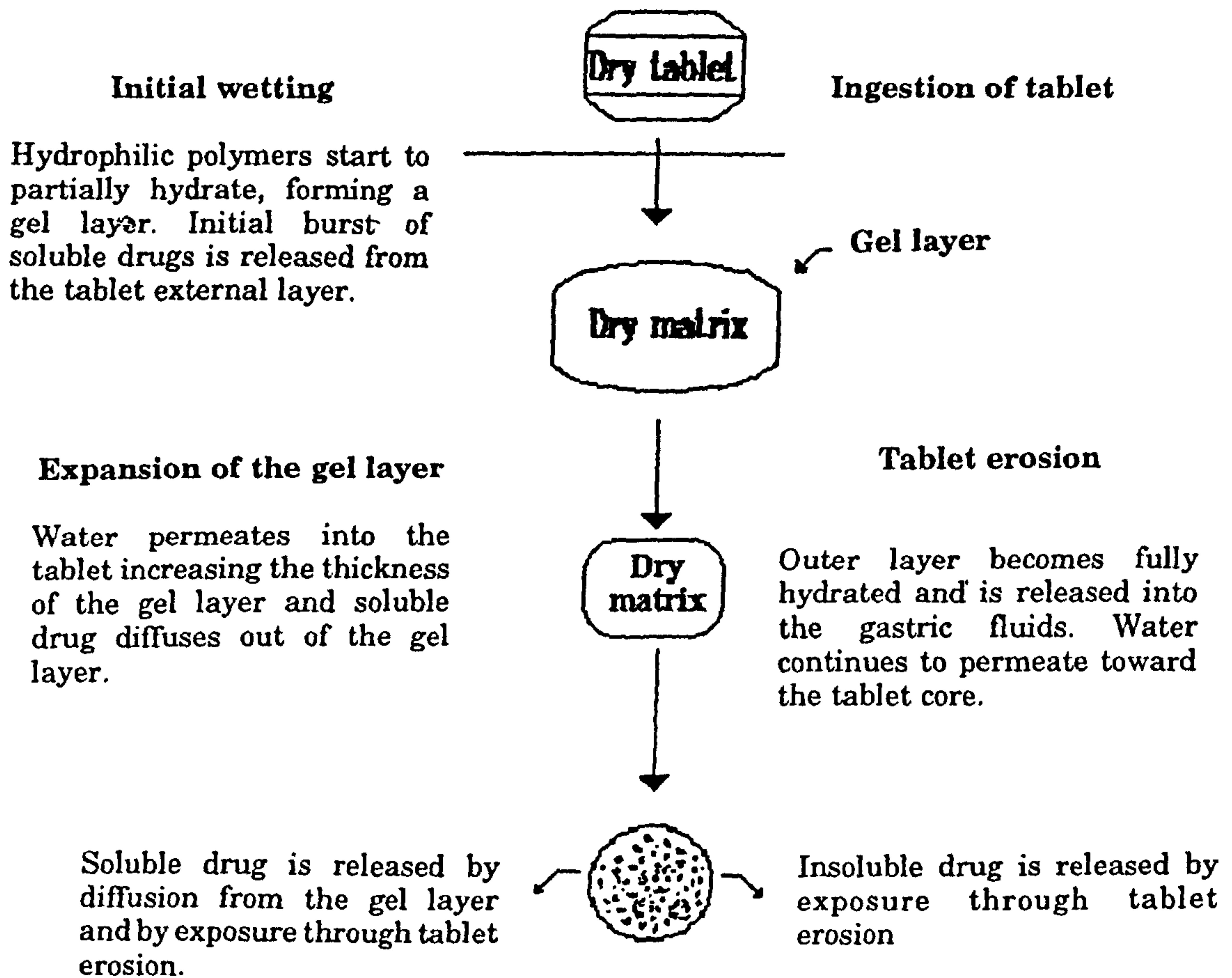
Granulation technology play an important role in the formulation of solid dosage forms (Sheskey et al, 1994). However, when extended drug release times are required, polymer concentration must be increased or higher molecular weight polymers must be chosen to achieve the desired release profiles. This situation occasionally results in powders that, although compressible, demonstrate unacceptable flow characteristics and would be burdensome when tableting on high-speed production equipment (Sheskey et al, 1994). Therefore, a granulation method is required to provide adequate flow for efficient tablet manufacturing. In the wet granulation process, the components are combined and formed into granules with a binder solution

and then sized and / or dried at the desired particle size. Liquids used for granulation include alcohols, hydroalcoholic mixtures, mixtures of alcohols and chlorinated solvents or water that may or may not contain a portion of the polymer (Doelker, 1987).

#### 1.4 MECHANISM OF DRUG RELEASE FROM HYDROPHILIC MATRICES

Although the formation and manufacture of compressed hydrophilic matrices may be simple, the mechanism of drug release is a complex phenomenon resulting from the interplay of many different physicochemical processes (Melia, 1991). In general, when a hydrophilic matrix is placed in a dissolution medium, a gelatinous layer is formed at the tablet surface. The gel layer that forms, is an aggregate mass of water-soluble polymer, drug and excipients experiencing various degrees of hydration or solution (figure 1.6). As a result of these processes, two fronts are established (Hui et al, 1987; Harland et al, 1988). At the swelling front (glassy polymer/gel interface), the hydration, swelling and coalescence of individual polymer particles occur. The gel layer so formed swells as additional water is absorbed. At the eroding front (gel/dissolution medium interface), polymer chain disentanglement and concomitant dissolution of the hydrated matrix occur. The distance between the swelling and eroding fronts, the gel layer thickness, has been termed the diffusion layer thickness or diffusional pathlength (Harland et al, 1988; Conte et al, 1993). This distance is dependent on drug solubility and the relative rates at which the swelling and eroding fronts move in relation to each other. With this general picture, the drug release mechanism of controlled release

Figure 1.6: Diagrammatic representation of a hydrophilic matrix tablet undergoing dissolution (after Alderman, 1984).





matrix tablets can be rationalized as being due to a coupling of diffusion and erosion release mechanisms. However, since hydrophilic matrices are capable of absorbing water while simultaneously releasing an enclosed drug, the release rate of the drug is modified by the degree of hydration of the drug/polymer device and the nature and concentration of the drug modifies the rate and extent of hydration (Good, 1981).

#### **1.4.1 Drug release from matrices**

The kinetics of release of a drug dispersed in a polymeric matrix are of general interest in the context of controlled drug delivery. It is usually desirable that the amount released is proportional to time.

A number of workers have modified and interpreted the dissolution rates from polymeric matrices mathematically. Such studies include those by Higuchi (1963), Schwartz (1968), Lapidus and Lordi (1968), Bamba et al (1979), Korsmeyer et al (1983a), Korsmeyer and Peppas (1983), Ritger and Peppas (1987), Harland et al (1988) and Ford et al (1991).

Korsmeyer et al (1983a) used a simple empirical equation, to describe general solute release behaviour from controlled release polymeric matrices (Equation 1.1):

$$\frac{M_t}{M_\infty} = K_1 t^n \quad \text{Equation 1.1}$$

Where:  $M_t/M_\infty$  is the fraction of the drug released,  $K_1$  is a constant incorporating structural and geometric characteristics of the controlled release device,  $t$  is the release time and  $n$  is the release exponent, indicative of the mechanism of drug release.

Peppas (1985) claimed that this equation could adequately be used to analyze the first 60% of a release curve, regardless of geometric shape and also showed that two competing release mechanisms were the limits of this phenomenon. He stated that the value of the exponent  $n$  is conditioned by the diffusion mechanism ruling the process. Ritger and Peppas (1987) described models of drug release from a planar sheet and gave more details about the terminology of Case-I transport (Fickian diffusion), Case-II transport (Relaxation) and Non-Fickian behaviour which is the coupling of diffusion and relaxation behaviour. They interpreted the values of  $n$  (table 1.1) which give an indication of the mechanism of drug release. Peppas (1985) had previously stated that  $n$  was 0.5 for Fickian diffusion,  $0.5 < n < 1$  for non-Fickian transport and a value of  $n = 1.0$  meant that the drug release is independent of time (zero-order release). When  $n > 1$  super Case-II transport is apparent. Ritger and Peppas (1987) reported that Case-II transport was dependent on the geometry of matrices and only equalled zero-order release for films. The values of  $n$  which were equivalent to Case-II transport for cylinders and spheres were 0.89 and 0.85 respectively. This means that even if Case-II transport was achieved for these devices, zero-order release could not be achieved. Fickian diffusion from cylinders is defined by  $n = 0.451$  (Ritger and

Peppas, 1987).

Table 1.1: Diffusional exponent and mechanism of diffusional release from various swellable controlled release systems (after Ritger and Peppas, 1987)

Diffusional exponent (n)			
Thin Film	Cylindrical sample	Spherical sample	Drug release mechanism
0.5	0.45	0.43	Fickian diffusion
0.5 < n < 1.0	0.45 < n < 0.89	0.43 < n < 0.85	Anomalous (non-Fickian) transport
1.0	0.89	0.85	Case-II transport

In order to describe drug release from matrices containing HPMC and additionally, the influence of temperature on release rate, Ford et al (1991) interpreted the mechanisms of drug release by using and modifying a number of equations. Ford et al (1987) claimed that equation 1.1 is based on the assumption that release occurs as soon as the matrix is placed in contact with fluid, but since a lag time in initial release of drugs was observed, a lag period needed to be introduced into the equation. Therefore, Ford et al (1991) modified equation 1.1 to account for a lag period (l) prior to release to give equation 1.2.

$$Q = K_2 (t-l)^n$$

Equation 1.2



In equation 1.2,  $l$  is the lag time,  $Q$  is the percentage of drug released at time  $t$ ,  $K_2$  is a kinetic constant and  $n$  is the diffusional exponent for drug release.

The lag time generally occurs as a result of a delay in the release of the drug from a dosage form. In spite of the obvious significance of lag time as an important parameter in characterizing the release kinetics of a drug, it has been ignored by several researchers including Baveja (1987) and Ranga Rao et al (1989).

Higuchi (1963) described equation 1.3, stating that a plot of the amount of drug release versus the square root of time would be linear if drug release from the matrix was diffusion-controlled release.

$$Q = K_3 t^{0.5} + C \quad \text{Equation 1.3}$$

In equation 1.3,  $K_3$  is the root time release rate constant and  $C$  is a constant.

Several other investigators have reported equations that have been used to describe drug release from matrices. For instance, Catellani et al (1988) and Harland et al (1988) used equation 1.4 to describe drug release from matrices under Fickian or relaxation mechanisms.

$$M_t/M_\infty = k_1 t^{0.5} + k_2 t \quad \text{Equation 1.4}$$

The right side of this equation contains the two limiting cases involved in the control of drug release from matrices, i.e., Fickian diffusion, by which the first 60% of the release is linearly related to the square root of time and the polymer relaxation transport by which, if penetrant uptake is linearly related to time and diffusion of the drug is faster, zero-order drug release may be obtained. The values of  $k_1$  and  $k_2$  in equation 1.4 express the relative contributions of the Fickian and relaxation mechanisms respectively.

Peppas and Sahlin (1989) derived equation 1.5 by introducing a second term to represent case II transport into equation 1.1.

$$M_t/M_\infty = kt^n + k' t^{2n} \quad \text{Equation 1.5}$$

Where the constants  $k$  and  $k'$  represent, in a manner analogous to equation 1.4, the relative contributions of Fickian and relaxation mechanisms respectively. The value of the Fickian diffusional exponent  $n$  may be determined directly from the aspect ratio of the compact. Ford et al (1991), by introducing lag times in equation 1.5, derived equation 1.6.

$$Q = k(t-l)^n + k' (t-l)^{2n} \quad \text{Equation 1.6}$$

Ford et al (1991) emphasised that all equations must include a value of lag time.

### **1.4.2 Zero-order release**

One of the most important research problems in controlled release technology is the development of monolithic (matrix type) polymeric formulations, which can release drugs at a constant rate over a period of time. These systems are commonly known as zero-order release systems (Korsmeyer and Peppas, 1983).

Whether the matrix releases drug via swelling control or erosion (or both), it is almost impossible to achieve a zero-order release (Langer, 1980). However, admixtures of non-ionic and ionic polymers may allow zero-order release. This has been attributed (Baveja et al, 1987), in the case of matrices containing HPMC and NaCMC, to a high degree of cross-linking between the non-ionic HPMC and anionic NaCMC (Walker and Wells, 1982) leading to a synergistic increase in gel viscosity at the tablet periphery. This was claimed to decrease the rate of advancement of the swelling front into the glassy matrix resulting in a slow diffusion of the drug. As the swelling front advances into the glassy polymer, the rubbery state of the polymer (i.e., the gel at the tablet periphery), which is devoid of the drug, undergoes attrition. When these two rates are equal, the diffusional path length for the drug remains constant and zero-order release will be seen. Therefore, by optimizing the ratio of total polymer to drug and also the ratio between HPMC and NaCMC in the tablet, a constant diffusional path length for the drug may be maintained so that zero-order release rate can be extended for the desired length of time (Baveja et al, 1987).



Since zero-order release is the most appropriate release pattern, several investigators (Baveja et al, 1987; 1988 a, b; Ranga Rao et al, 1989; Padmalatha Devi et al, 1989; Danckwerts, 1994) have tried to achieve a zero-order release of drug which is independent of the amount of drug in the systems.

Korsmeyer et al (1983b) have shown that air incorporated during tableting is entrapped in the gel layers of hydrophilic matrix tablets and results in a prolongation of drug release. They claimed that this would result in the drug-release profile moving away from the square root of time kinetics and towards zero-order release. This phenomenon has been exploited by Hashim and Li Wan Po (1987) who showed that incorporating small quantities of effervescent mixtures into hydrophilic matrix tablets, prolonged zero-order in vitro drug-release profiles can be prepared.

Daly et al (1984) reported that by incorporating 15% w/w of the anionic surfactant, sodium dodecyl sulphate (SDS) into HPMC matrices, zero-order in vitro release of chlorpheniramine maleate was obtained for 6 hours.

Padmalatha Devi et al (1989) developed zero-order release matrix tablets of oxprenolol hydrochloride by mixing drug, HPMC and NaCMC at the ratio of 1:0.4:1.6. They claimed that zero-order release was accomplished with swelling and erosion control of the polymer matrix.

Shenouda et al (1990) reported zero-order release by using a system which contained a core in a cup. The core consisted of the drug, dyphylline, and HPMC while, the cup consisted of HPMC and poly(ethyloxazoline). They examined different ratios of the drug in both the cup and the core. An apparent zero-order release was observed when 80% of the drug content was included in the core and 20% in the cup. A similar system was used by Danckwerts (1994) for caffeine and ibuprofen. HPMC K4M and HPMC K15M was used in the core matrix and carnauba wax and ethylcellulose in the cup. Danckwerts (1994) claimed that zero-order release was obtained between 8 to 23 hour.

### 1.5 CELLULOSE DERIVATIVES

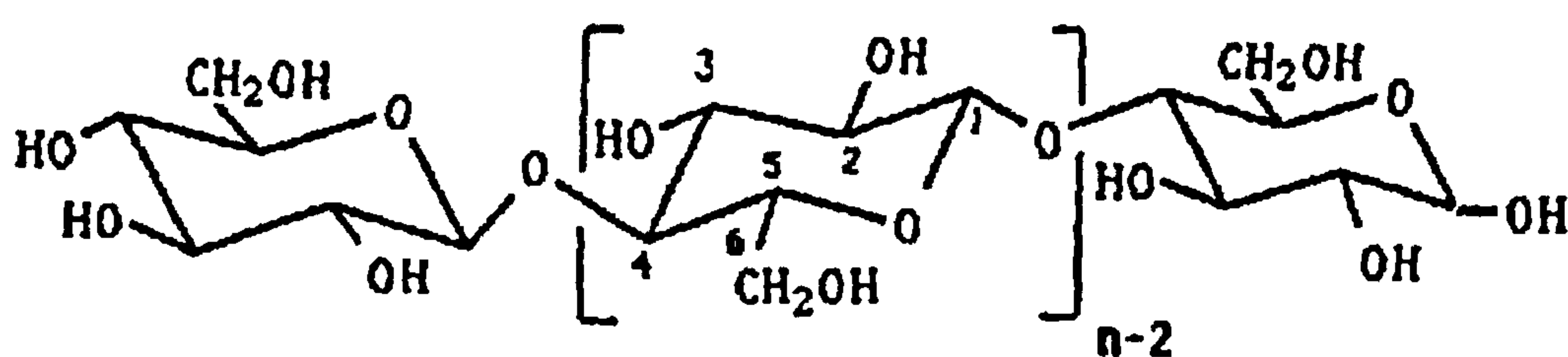
The importance of cellulose derivatives has increased in recent years because of economic factors that have adversely affected the supply and pricing of natural gums and low viscosity products such as starch derivatives (Rekhi and Jambhekar, 1995)

Cellulose, is one of the most abundant natural polymers. Cellulose and its derivatives are generally recognized as the safest and most acceptable polymer for use in food and pharmaceutical products. The reason for this is that these substances have a neutral taste and that they are remarkably non-toxic (Grosse, 1990).

The structural formula of a part of the cellulose molecule is given in figure

1.7. It is composed of anhydroglucose rings linked in the 1,4-position to form  $\beta$ -glucosides. Investigations have shown that in native cellulose numerous anhydroglucose units are combined to form a single molecule. Chain length determination is very difficult and average values are only given, which are referred to as the average degree of polymerization (DP). The DP is fixed by nature and varies with each raw material (Grosse, 1990; Kumar and Banker, 1993).

Figure 1.7: Chemical constitution of cellulose



The anhydroglucose rings contain three hydroxyl groups, a primary group at the C-6 position and two secondary groups at the C-2 and C-3 positions (figure 1.7) which are capable of undergoing chemical reactions such as esterification or etherification. Products can be prepared in which, one, two or three hydroxyl groups per anhydroglucose unit have undergone reaction. The term degree of substitution (DS), is used to identify the average number of sites reacted per ring. It ranges from 0 to 3.

Pure cellulose, despite its free hydroxyl groups, does not dissolve in water, due to active hydrogen bonding across the hydroxyl groups on the cellulose



backbone (Kumar and Banker, 1993). Substitution of the hydroxyl groups with, for example, acetyl groups, decreases the crystallinity by reducing the regularity of the polymer chains and increases the interchain hydrogen bonding (Baker, 1987b). The various chemically-modified cellulose products used in food, cosmetic, pharmaceutical, medical and related applications can be grouped into three classes, based on their methods of preparation (Grosse, 1990). These are: **hydrated cellulose, cellulose esters and cellulose ethers.**

**Hydrated cellulose:** The familiar examples of hydrated cellulose are cellophane and viscose rayon (Grosse, 1990).

**Cellulose esters:** This group of cellulose derivatives can be prepared by treating cellulose with inorganic or organic acids or acid anhydrides. Kumar and Banker (1993) classified this group into 2 subgroups (enteric cellulose esters and non-enteric cellulose esters). The most important polymers belonging to the enteric cellulose esters are: cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP) and hydroxypropylmethylcellulose acetate succinate (HPMCAS). Oral dosage forms coated with these polymers are intended to remain intact in the stomach and to rapidly dissolve and release the drug in the upper intestine (The United State Pharmacopoeia / National Formulary, USP 23/NF 18, 1995). Major examples of the non-enteric cellulose esters include: cellulose acetate (CA), cellulose sodium phosphate (CSP) and cellulose acetate butyrate

(CAB) which, due to their high water permeability, are used in osmotic devices (Baker, 1987b).

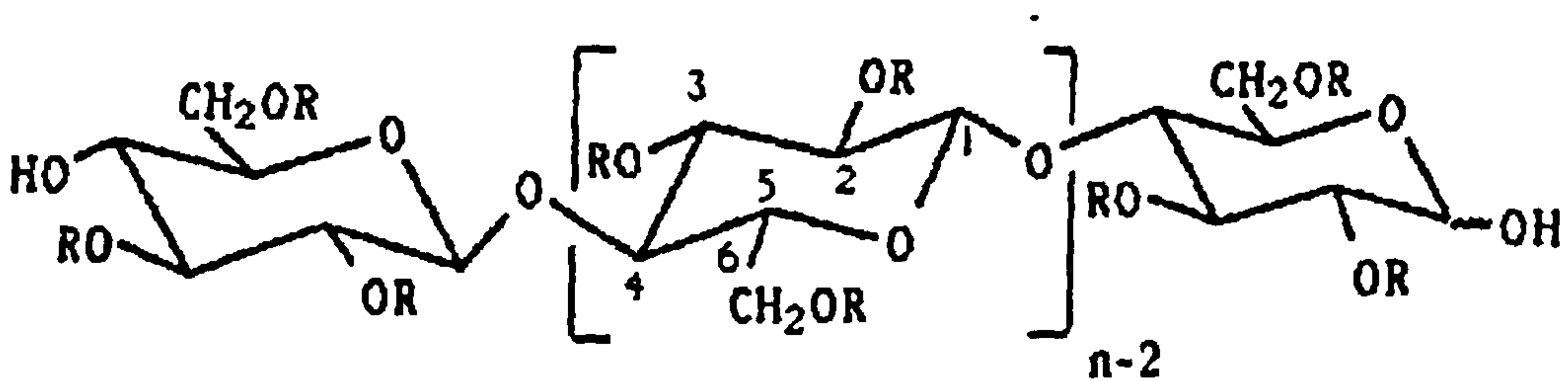
**Cellulose ethers:** Cellulose ethers are widely used in pharmaceutical applications (Korsmeyer, 1983; Grosse, 1990; Melia, 1991). This group of cellulose derivatives can be classified into two subgroups: water-insoluble cellulose ethers such as ethylcellulose and another class of compounds, the water-soluble cellulose ethers. The latter group, has a wide field of applications and, due to its importance and special interest, several polymers were chosen from it for examination. Examples are discussed in the next section.

### **1.5.1 Cellulose ethers**

Cellulose ethers are popular as matrix polymers since they are cheap, easy to prepare, can accommodate a large percentage of the drug and drug release is not-greatly influenced by the processing variables (Alderman, 1984; Doelker, 1987). The various cellulose ethers currently described in the United State Pharmacopoeia / National Formulary (USP 23/NF 18, 1995) are: methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), sodium carboxymethylcellulose (NaCMC), calcium carboxymethylcellulose (CaCMC) and ethylcellulose (EC). The structures of these polymers are shown in Figure 1.8. Except EC, all the other cellulose ethers are water soluble. The applications of cellulose ethers have been the subject of many reviews (Greminger and Krümel, 1980;

Doelker, 1987; Melia, 1991; Kumar and Banker, 1993). Among the cellulose ethers, HPMC, HPC, MC and NaCMC are the most popular in controlled release dosage forms (Ranga Rao and Padmalatha Devi, 1988; Melia, 1991).

Figure 1.8: Typical structures of cellulose ether polymers (after Kumar and Banker, 1993)



Methylcellulose (MC),  
 Hydroxyethylcellulose (HEC),  
 Hydroxypropylcellulose (HPC),  
 Hydroxypropylmethylcellulose (HPMC),  
 Sodium carboxymethylcellulose (NaCMC),  
 Calcium carboxymethylcellulose (CaCMC),  
 Ethylcellulose (EC)

R = -H, -CH<sub>3</sub>  
 R = -H, -CH<sub>2</sub>-CH<sub>2</sub>OH, -CH<sub>2</sub>-CH<sub>2</sub>-OCH<sub>2</sub>-CH<sub>2</sub>OH  
 R = -H, -CH<sub>2</sub>-CH(OH)-CH<sub>3</sub>  
 R = -H, -CH<sub>3</sub>, -CH<sub>2</sub>-CH(OH)-CH<sub>3</sub>  
 R = -H, -CH<sub>2</sub>COONa  
 R = -H, -CH<sub>2</sub>COOCa  
 R = -H, -C<sub>2</sub>H<sub>5</sub>

### 1.5.2 Preparation

The preparation of cellulose ethers dates back to 1912 (Lilienfeld, 1913) and, since then, there have been several articles describing the developments in the processes and the reactions involved (Greminger and Krümel, 1980). The most common method to prepare cellulose ethers is by nucleophilic substitution (Kumar and Banker, 1993). The cellulose ether is prepared by the reaction of cellulose pulp with caustic soda to form alkali cellulose. The



alkali cellulose is then reacted under controlled conditions with an alkylhalide and alkylene oxide to form the cellulose ether. The alkali cellulose can be prepared by treating cellulose with a base. Sodium hydroxide is usually used, but other alkali metal hydroxides can also be utilized. The alkali treatment also causes swelling and decrystallization of cellulose and consequently increases the number of accessible regions in the cellulose (Kumar and Banker, 1993).

### **1.5.3 Hydroxypropylmethylcellulose (HPMC)**

Hydroxypropylmethylcelluloses, are commercially available in various grades, under several tradenames, including Methocel™ E, F and K from The Dow Chemical Co., U.S.A. Their nonproprietary names are HPMC 2208, HPMC 2906 and HPMC 2910 (USP 23/NF 18, 1995), Hypromellose (in the British Pharmacopoeia, 1993) and "Hydroxypropyl Methylcellulose" (Lin et al, 1986). The various grades available under a given trade-name represent differences in methoxyl and hydroxypropoxyl content as well as molecular weight. The methoxyl content ranges from 16.5 to 30% w/w and the hydroxypropoxyl content ranges from 4 to 32% w/w (Greminger and Krumel, 1980). Commercial designations of the various HPMCs are based on the viscosities of their 2% aqueous solutions at 20°C. The viscosities range from 15 cP to 30,000 cP and represent number average molecular weights ranging from about 10,000 to over 150,000, as calculated from the data in "Handbook of Methocel Cellulose Ether products" (The Dow Chemical Co., 1974). The Methocel K products, owing to their reduced methoxyl content, are claimed

to have the fastest hydration rates and therefore, are suitable for use in preparing controlled release matrix tablets (Alderman, 1984).

Doelker (1987), Ranga Rao and Padmalatha Devi (1988), Hogan (1989) and Melia (1991) reviewed the use of HPMC in pharmaceuticals. One of the most important aspects of HPMC that governs its performance in a sustained release matrix is the rate of polymer hydration. Rapid gel formation on the tablet surface is critical for preventing excessive dose dumping and even immediate dissolution of the tablet core itself (Ford and Mitchell, 1995). In addition, this group of polymers exhibit a range of physical, chemical and biological properties which makes them attractive as drug delivery system (Knuth et al, 1993).

#### **1.5.4 Sodium carboxymethylcellulose (NaCMC)**

Sodium carboxymethylcellulose (NaCMC) is a hydrophilic swellable polymer and is manufactured by reacting sodium monochloroacetate with alkali cellulose (Batdorf and Rossman, 1973). NaCMC is one of the few ionic cellulose ether derivatives and therefore it is easily identified by its poorly-soluble copper salt, which rapidly precipitates (Grosse 1990). NaCMC products are commercially available from Aqualon<sup>TM</sup> (France) under the trade name Blanose. Their nonproprietary names are carboxymethylcellulose sodium (in the United State Pharmacopoeia / National Formulary, USP 23/NF 18, 1995), carmellose sodium or sodium carboxymethylcellulose (in the British Pharmacopoeia, 1993) and "Carboxymethylcellulose Sodium" (Bruno



et al, 1986). By varying the length of the cellulose chain and the degree of the cellulose substitution, DS, sodium carboxymethylcellulose with different properties can be obtained. The highest theoretical DS value is 3, but for commercial products it is much lower, e.g., 0.6-0.8 (Aggeryd and Olin, 1985). Bonferoni et al (1993) suggested that NaCMC in gastric juice reverts to the unionized form which is characterized by poor hydration and solubility properties. Sodium carboxymethylcellulose has been used as a base for controlled release matrices (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Baveja et al, 1985).

Huber and Christenson (1968) reported that NaCMC is a useful gum since it hydrates readily and rapidly at body temperature. Early work by Lapidus and Lordi (1968) showed that the release rate of chlorpheniramine was significantly lower than that of sodium salicylate from NaCMC matrices and attributed this response to a drug : polymer interaction between the chlorpheniramine and the carboxymethylcellulose. Baveja et al (1985) reported a successful sustained release dosage form of diethylcarbamazine citrate from matrices containing 1:7 drug: NaCMC.

Due to the interaction of NaCMC with some drugs (Tucker et al, 1988; Ranga Rao et al, 1988b) and being insoluble at the pH of stomach contents (Batdorf and Rossman, 1973; Bonferoni et al, 1992) the potential of using NaCMC alone as a matrix tablet is very limited.



### **1.5.5 Ethylcellulose (EC)**

Ethylcellulose is a water-insoluble polymer, but dissolves in a wide variety of organic solvents (e.g., esters, aromatic hydrocarbons, alcohols, chlorinated solvents). The viscosities of its solutions increase with an increase in molecular weight and concentration. Concentrated solutions of ethylcellulose are usually prepared in binary solvent systems consisting of appropriate ratios of an aromatic hydrocarbon solvent (e.g., toluene) and ethyl alcohol. The minimum value for ethoxyl content is at about 48.5% ethoxyl substitution (Kumar and Banker, 1993). Ethylcellulose is available, for instance, as three types of ethoxyl substitution from Dow Chemical Co. (Trade name Ethocel<sup>R</sup>, grade S, M or HE).

Ethylcellulose has been used as a controlled-release carrier (Stamm and Tritsh, 1986; Shaikh et al, 1987a, b; Porter, 1989; Aoki et al, 1992a, b; Upadrashta et al, 1993; Hernandez et al, 1994). Primarily however, ethylcellulose is used as a coating or film forming agent (Borodkin and Tucker, 1975; Donbrow and Friedman, 1975; Shaikh et al, 1987a, b).

The release of soluble drugs from ethylcellulose matrices has been studied by several workers (Stauffer, 1985; Stamm and Tritsh, 1986; Shaikh et al, 1987a, b). Stauffer (1985) described that diffusion of a water-soluble drug out of a porous matrix (ethylcellulose) can be compared to the "ant in the labyrinth". This will be discussed in greater detail in chapter 7.

## **1.6 FACTORS AFFECTING DRUG RELEASE FROM HYDROPHILIC MATRICES**

A review of current literature has shown that many technological factors can affect the release of drugs from hydrophilic matrices (Langer, 1980; Doelker, 1987; Capan, 1989). In order to prevent immediate release of drug from the tablet, which is necessary to achieve controlled release, the polymer(s) in the matrix must hydrate rapidly to form a protective gel layer. The physical properties of the gelatinous layer formed in tablets or capsules control drug dissolution. The choice of matrix material, amount of drug incorporated in matrix, matrix additives, the hardness of the matrix, density variation and tablet shape may affect the release rate (Capan, 1989). The following parameters are the major factors influencing the hydration rate of the gel layer.

### **1.6.1 HPMC in hydrophilic matrices**

#### **1.6.1.1 Viscosity of polymer**

The effect of viscosity grade of polymers on drug release has been the subject of many reports (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Korsmeyer, 1983; Daly et al, 1984; Ford et al, 1985a, b, 1987; Pagay, 1988; Baveja et al, 1988a; Wan et al, 1991; Colombo et al, 1992 and Cheong et al, 1995). The viscosities of HPMCs are used as an indication of their molecular weight. Alderman (1984) suggested that the viscosity grade of HPMC

incorporated into the matrices would alter the release rates of drug. This was related to the molecular weight of the polymers and he claimed that increasing the viscosity would increase the gel layer viscosity and thereby slow drug diffusion. Ford et al (1985a), examining four viscosity grades of HPMC, showed that the lowest viscosity grade (HPMC K100) gave the highest release rates of promethazine hydrochloride, whereas three other grades (HPMC K4M, HPMC K15M, HPMC K100M) behaved similarly.

Salomon et al (1979) reported that the viscosity grade of HPMC only affected the lag time for potassium chloride diffusion to become quasi-stationary but did not affect the rate of release. Ford et al (1985 b) showed that both the lag time and release rate were unaffected by the viscosity grade of the polymer for HPMC K4M, HPMC K15M and HPMC K100M.

Cheong et al (1992) investigated the effect of viscosity grade of Metolose K4, K15, K30, K50 and K100 (from Shin-Etsu Chemical, Japan) on the release of propranolol hydrochloride. They claimed that in matrices of higher HPMC content (50-75% w/w), the effect of viscosity on drug release was not apparent whereas, in the range of 5-25% w/w the viscosity grade controlled the release of the drug.

#### 1.6.1.2 Polymer particle size

The particle size of HPMC has been identified as an important factor influencing the performance in hydrophilic matrices. Alderman (1984)



reported that the dissolution of riboflavin from matrices prepared with the coarsest particle size of HPMC K4M was too fast whereas, tablets made from a fine particle size (<150 µm) hydrated quickly and provided sustained release.

Mitchell et al (1993d) studied the release of propranolol hydrochloride from matrices containing 57, 95, 140 or 285 mg of HPMC K15M, reported that at low HPMC contents, a coarse particle size (< 355 µm) gave faster propranolol release than a smaller particle size (<75 µm). They claimed that as the HPMC content increased, the effect of particle size became less important and for matrices containing 285 mg HPMC, there was no difference in release rates between unsieved and other particle size fractions of the polymer.

#### 1.6.1.3 Effect of substitution type of polymer

In a comprehensive study on the use of HPMC and MC in hydrophilic devices, Alderman (1984) concluded that different substitution levels of HPMC gave rise to different drug release profiles. These widely accepted ideas have subsequently been challenged by Mitchell et al (1990a) who used DSC to elucidate water uptake by four grades of cellulose ether, commercially available as methylcellulose A4M, HPMC E4M, HPMC F4M and HPMC K4M, each manufactured by Dow Chemicals, U.S.A. and equivalent to USP types methylcellulose, hydroxypropylmethylcellulose (HPMC) 2910, HPMC 2906 and HPMC 2208. Mitchell et al (1990a; 1993a) and Ford and Mitchell (1995) published data to suggest there was no difference in the rates of water

uptake between the different grades.

Dahl et al (1990) found that if polymer particle size and other variables were kept constant, the release of naproxen was directly related to the hydroxypropyl substitution irrespective of the source of the polymer. Dahl et al (1990) claimed that satisfactory and reproducible dissolution profiles for naproxen was obtained only with tablets manufactured with HPMC containing greater than 7.5% hydroxypropyl content.

#### 1.6.1.4 Added excipients

Formulation of matrix tablets may require the addition of excipients to alter the size of the tablet, to provide lubrication, to change the colour or to replace a portion of the polymer to modify drug release rate. The effects of excipients on the release rates of various drugs have therefore been studied by authors such as Lapidus and Lordi (1968), Alderman (1984), Ford et al (1987) and Pagay (1988).

Lapidus and Lordi (1968) showed that the addition of lactose increased the release rate of chlorpheniramine maleate more than the equivalent amount of calcium phosphate. Ford et al (1987) investigated the effects of adding soluble materials such as lactose and insoluble materials such as calcium phosphate on the dissolution of promethazine hydrochloride and reported that only tablets containing low quantities of HPMC and high diluent quantities, displayed apparent differences in release rates between the two excipients,

despite their vastly differing solubilities.

Ford et al (1991a) evaluated the influence of sodium dodecyl sulphate on the release of propranolol hydrochloride from HPMC matrix tablets and reported that the surfactant reduced the release rate of propranolol hydrochloride by the in situ formation of propranolol dodecyl sulphate. Ford et al (1991a) also showed that the release rates of propranolol hydrochloride from tablets containing cetrимide increased despite an increase in viscosity of HPMC gels containing cetrимide.

Feely and Davis (1988) reported that ion exchange resins incorporated into the matrix delayed the release of oppositely charged drugs, but drug release rate was dependent on the ionic strength of the medium. A similar study showed that the release of chlorpheniramine maleate from HPMC matrices is slowed by anionic surfactants and that this effect was primarily due to the formation of an insoluble complex rather than increased HPMC viscosity, as had previously been proposed (Daly et al, 1984).

#### 1.6.1.5 Effect of drug incorporated in matrix

The influence of the amount of drug incorporated in a matrix is interesting and of practical importance in the field of sustained release tablets. This can be a very important factor as frequently it is desirable to produce different matrices containing different concentrations of the same drug to provide a variety of dosage schedules.



Baveja et al (1988b) examined the formulation of 6 structurally related water-soluble broncodilators namely phenylpropanolamine hydrochloride, ephedrine hydrochloride, salbutamol sulphate, terbutaline sulphate, reproterol hydrochloride, and aminophylline into HPMC matrices. They determined the release rates from compressed matrices of HPMC and observed that, although all the drugs had similar aqueous solubility (freely soluble), they gave different release rates. They attributed this phenomenon to the different molecular weights and molecular sizes of the drugs.

#### 1.6.1.6 Effect of drug/polymer ratio

Ford et al (1985a, b) reported that the drug : HPMC ratio is the most important factor affecting the rate of release from matrices containing HPMC. Ford et al (1985a) considered the effects of some formulations variables on the release of promethazine hydrochloride from HPMC matrices and produced a straight line relationship between the drug release rate against the reciprocal polymer content and the following relationship was derived from experimental results:

$$R = M \frac{1}{W} + C \quad \text{Equation 1.7}$$

Where R= Higuchi-type release rate ( $\% \text{ min}^{-1/2}$ ), M= slope of the derived line, W= weight of HPMC (mg) in tablet, C= constant.

Similarly Baveja et al (1988b), using propranolol hydrochloride, alprenolol

hydrochloride, oxprenolol hydrochloride and metoprolol tartrate incorporated in HPMC K4M, NaCMC or their mixture, at different drug / polymer ratios, reported that when the proportion of HPMC in the matrix increased, the time to release 50% ( $T_{50\%}$ ) of drug increased. Baveja et al (1988a) confirmed that the equation 1.6 proposed by Ford et al (1985a) was valid for HPMC matrices.

#### 1.6.1.7 Effect of drug particle size

Ford et al (1985d) stated that the particle size of drugs was important only in the case of insoluble drugs, i.e., indomethacin. They reported that the release rates of promethazine hydrochloride from HPMC matrices were unaffected by particle size, except in the extreme case where the polymer : drug ratio was low and the particle size of drug was high (Ford et al, 1985a, b).

#### 1.6.1.8 Compression pressure

Studies investigating the effect of compression pressure or tablet crushing strength on release rates have yielded different results. Ford et al (1985a) used pressures ranging from 93 to 1395  $\text{MNm}^{-2}$  for compressing HPMC matrices containing promethazine hydrochloride and reported that the release rates were not affected by the applied pressure. Hashim and Li Wan Po (1987) similarly showed that varying the compression pressure from 148 to 448  $\text{MNm}^{-2}$  did not affect the release rate of potassium chloride from HPMC matrices. Similarly, Huber and Christenson (1968), Lapidus and Lordi (1968), Salomon et al (1979) and Conte et al (1993) reported that tablet hardness or

compaction pressure did not affect the release characteristics of soluble drugs from different hydrophilic polymers. However, Korsmeyer et al (1983b) reported that compression pressures ranging from 28 to 280 MNm<sup>-2</sup> affected release during the first four hours and that this could be ascribed to the presence of entrapped air in the matrices.

#### 1.6.1.9 Effect of electrolytes on drug release

Changes in the hydration state of a polymer in solution are manifested primarily by changes in solution viscosity and cloud point. The effect of ions on the degree of hydration of cellulose ethers have been studied by Lapidus and Lordi (1968), Klug (1971), Marriott and John (1973), Sarkar (1979) and Mitchell et al (1990b, 1993a).

Lapidus and Lordi (1968) were the first to note the effect of ionic strength on matrix integrity and drug release. They demonstrated the rapid release of chlorpheniramine from HPMC 2208 matrices in solution containing 0.2 M sodium sulphate or magnesium sulphate. Mitchell et al (1990a) investigated the effect of electrolytes on HPMC gels and reported that electrolytes reduced the hydration of HPMC gels and, consequently, decreased the cloud point of the gel. This study was similar to the report of Fagan et al (1989) that certain ionic salts and drugs may cause complete failure of sustained release formulations and this has been attributed to a depression of the gelation temperature of the polymer. Mitchell et al (1990b) investigated the effects of various ions and concentrations on the disintegration time and dissolution of



propranolol hydrochloride from HPMC 2208 matrices. They also showed that under certain conditions, premature disintegration of the matrix could occur, resulting in the immediate release of all drug in the matrix.

Another study suggested that simple anions might be more important than cations in lowering the cloud point of HPMC, and that increasing the ionic strength of the dissolution medium caused drug dissolution rates to slow, with a minimum being reached just before disintegration occurred (Mitchell et al, 1990b). It was concluded that even small amounts of electrolytes in the dissolution media might therefore affect drug-release rates from HPMC matrices. Propranolol hydrochloride, a drug which increases the cloud point of HPMC, appeared to affect HPMC hydration at low water content and it was concluded that a propranolol : polymer interaction might also play a role in controlling the development of gel structure in HPMC matrices during hydration (Mitchell et al, 1989). Mitchell et al (1990b) suggested that the nearer the dissolution temperature is to the gelation temperature, the greater the contribution of erosion to the dissolution mechanism, suggesting an increased fragility of the gel network as the thermal gelation point is approached.

Johnson et al (1993) investigated the effect of varying the ionic strength of solutions containing sodium chloride on the physical integrity of pure and binary compacts of HPC of different particle sizes and molecular weights. They claimed that a fine particle size of the polymer was more resistant to

the influences of ionic strength changes than a coarse particle size.

#### 1.6.1.10 Effect of pH of dissolution medium

It has been shown that the use of the salt of an acidic or basic drug can lead to precipitation of an insoluble layer on the surface of a dissolving tablet and this can hinder further dissolution. Lapidus and Lordi (1968) reported that the release rates of chlorpheniramine maleate from matrices containing HPMC were affected by the pH of media. In contrast, Alderman (1984) claimed that HPMC matrices were relatively free from problems induced by pH, i.e., the polymer is stable. A decrease in release at pH 7.5 was attributed to a decrease in the solubility of chlorpheniramine near its pKa value.

Ford et al (1985c) showed that the dissolution rates of promethazine hydrochloride from matrices composed of HPMC were high at a pH of 1 or 3 but dropped considerably in media of pH 7 or above. This was attributed to the formation of the insoluble, unionized form of promethazine which has a pKa of 9.1, rather than to a specific pH effect on HPMC.

Pagay (1988) showed that the release rates from HPMC matrix formulations were controlled by the presence of buffering agent and not by the pH of the dissolution medium. He determined that nearly 40% of a weakly basic drug was released from HPMC within the first hour. Bonferoni et al (1992) concluded that, in the case of polyelectrolyte polymers, both the hydration and gelation properties of the polymer and the ionic interactions between

polymer and drug are likely to be affected by the dissolution medium characteristics, such as ionic strength and pH.

#### 1.6.1.11 Effect of temperature

Lapidus and Lordi (1968) reported that an increase in temperature of dissolution media will alter the texture of the gel layer around a matrix, subsequently increasing the diffusion coefficient of the drug and will also increase the rate of erosion of the matrix. Mitchell et al (1990c), using promethazine hydrochloride incorporated in HPMC K15M, reported that at low levels of polymer content, a zero-order release may be obtained when the thermal gelation temperature of the matrix is near to the dissolution temperature.

#### 1.6.1.12 Effect of tablet shape

Salomon et al (1979) obtained zero-order release by coating potassium chloride tablets with HPMC and reported that, at a constant polymer to drug ratio, an increase in thickness of tablet slightly increased the drug release rate. Ford et al (1985a) demonstrated that the square root of time release rate of promethazine hydrochloride from HPMC matrices was proportional to the surface area of the tablet, since release rates decreased as the tablet surface area decreased.

### **1.6.2 NaCMC in hydrophilic matrices**

Some factors affecting the release of drugs from NaCMC matrices have been



studied. These include:

#### 1.6.2.1 Effect of pH of dissolution medium

Baveja et al (1987) studied the release of three  $\beta$ -blocker drugs namely propranolol hydrochloride, metoprolol tartrate and alprenolol hydrochloride from HPMC, NaCMC and their mixtures. They reported that the release of drugs from matrices containing NaCMC alone was linear at pH 3, but the release rate increased in phosphate buffer solution pH 7.4. Baveja et al (1987) claimed that increase in release rate may be due to increase in erosion rate of NaCMC. Similar observations were reported by Ranga Rao et al (1988a). Bonferoni et al (1992) reported that since NaCMC has a pKa value of 4.3, the solubility of NaCMC would be lower in acidic medium than in distilled water.

#### 1.6.2.2 Interaction with drugs

Interaction of drugs with NaCMC have been studied by Tucker et al (1988) and Ranga Rao et al (1988b). Tucker et al (1988) reported an interaction between propranolol hydrochloride and NaCMC and claimed that one propranolol cation would be bound to each carboxyl anion of the NaCMC. Ranga Rao et al (1988b) using DSC showed an interaction between pindolol and NaCMC and claimed that the produced mass might be governing the release of drug.

#### **1.6.3 Mixtures of HPMC and NaCMC in hydrophilic matrices**

Walker and Wells (1982) reported that when NaCMC is blended with a non-

ionic polymer (such as HPMC), a synergistic effect occurs whereby the resultant viscosity is considerably higher than anticipated, due to hydrogen bond-induced cross-linking. Baveja and Ranga Rao (1986) were the first to suggest the use of both anionic and non-ionic cellulose ethers in matrix tablets. These observations have been utilized in several other studies (Baveja et al, 1987, 1988a and b, 1989; Ranga Rao and Padmalatha Devi 1988).

The release profiles of freely soluble drugs from hydrophilic matrices normally follow the classic square root of time relationship, i.e., the release rate decreases with time. Therefore, Baveja et al (1987) reported that zero-order release from matrices containing only one hydrophilic polymer is difficult to achieve, but admixtures of ionic and non-ionic polymers may allow zero-order release.

Drug release from anionic/non-ionic cellulose ethers has been studied extensively by Baveja et al, (1987, 1988a, b) and Ranga Rao et al, (1990). Baveja et al (1987), using a series of soluble  $\beta$ -blocker drugs, showed that incorporating NaCMC into an HPMC matrix tablet reduced the initial burst of drug release and by optimizing the ratios of HPMC, NaCMC and drug, the shape of the dissolution profile could be changed from a root-time relationship to one where almost 100% drug was released by zero-order kinetics.

Ranga Rao et al (1990) also showed that a range of freely soluble cationic drugs were released more slowly from NaCMC:HPMC combinations than

from HPMC alone, whereas for sodium saccharin (the only freely soluble anionic drug studied), the reverse was true.

In addition, Ranga Rao et al (1989) formulated zero-order release tablets, containing very soluble drugs such as alprenolol hydrochloride and metoprolol tartrate by using a combination of NaCMC and hydroxypropylcellulose (HPC). They reported that the erosion rate of the matrix was fairly constant and was about 2.5 times higher when alprenolol hydrochloride (as model drug), NaCMC and HPC were present compared to the matrices containing the same ratio of the drug and polymer but only HPC. Similarly the release of 23 drugs with various solubilities and molecular weights from matrices of HPMC and NaCMC was studied by Ranga Rao et al (1990).

Baveja and Ranga Rao (1986) using centperazine, aerosil 200, NaCMC and HPMC in the ratio of 1 : 0.7 : 4 : 4, showed that the release of centperazine was also independent of the pH of the dissolution media.

### 1.7 AIMS AND OBJECTIVES

The aims of this thesis were to examine how the dissolution rates and the kinetics of their release from HPMC matrices could be modified by including other materials into the matrices. Sodium carboxymethylcellulose and ethylcellulose were chosen initially because they offer some advantages that have been discussed in previous sections. During the last few years, studies have been published on the uses of HPMC, NaCMC or EC alone in matrix



tablets, but few studies have been carried out to investigate the physio-chemical properties of admixtures of these polymers. The objectives of the present work are as follows, using propranolol hydrochloride as a model drug:

- To investigate the characterization of HPMC, NaCMC or EC on their own and their admixtures in order to obtain a better understanding of how these polymers function in hydrophilic matrices.
- To study various physical properties of HPMC, NaCMC or their mixtures and discover what effects propranolol hydrochloride had on their properties. The studies investigated the hydration and erosion of the polymers and their interaction with propranolol hydrochloride.
- To characterize the mechanisms and the kinetics of drug release from matrices containing HPMC, NaCMC, EC or their mixtures, to determine under which circumstances and to what extent the ratio of the polymers could be of assistance in controlling drug release and providing zero-order release.
- To study the effects of the viscosity grade of NaCMC, alone and in combination with HPMC, on drug release.
- To study the effect of pH of the dissolution medium on drug release from matrices containing NaCMC and HPMC.

- To study of the use of  $\beta$ -cyclodextrin in matrices. It is well known that  $\beta$ -cyclodextrin complexes with a number of drugs and it is hoped that this property would make it possible to achieve a modified drug release.

## **CHAPTER 2 MATERIALS AND GENERAL EXPERIMENTAL**

This chapter describes the materials and basic techniques which were used throughout this study.

### **2.1 MATERIALS**

#### **2.1.1 Cellulose ethers**

##### **2.1.1.1 Hydroxypropylmethylcellulose**

Hydroxypropylmethylcellulose type 2208 (Methocel™ K4M), of 4000 cP viscosity, manufactured by Dow Chemicals (U.S.A.), was used. The apparent viscosity of an aqueous 2% solution of this polymer given by the manufacturer in their product description was 3500-5650 cP. The percent of methoxyl content and hydroxypropoxyl content of this polymer were 19-24 and 7-12 respectively. Details of this polymer are presented in table 2.1.

##### **2.1.1.2 Sodium carboxymethylcellulose**

Sodium carboxymethylcellulose type Blanose 7H4XF, was supplied by Aqualon (France). 7H4XF is the coding for Blanose in which 7 means the typical degree of substitution is approximately 0.7, H means high viscosity, 4 means 4000 mPa.s maximum viscosity, X means fine particle size and F means food grade. The apparent viscosity of an aqueous 1% solution of this polymer given by the manufacturer in their product description was 3400 cP.



Two different viscosity types of NaCMC, (Courlose P 800 B.P., and Courlose P 350 B.P.) were manufactured and supplied by Courtaulds Fine Chemicals (U.K.). Their apparent viscosities of an aqueous 1% solution of these polymers were 600-1120 cP and 262-490 cP for Courlose P 800 B.P., and Courlose P 350 B.P. respectively. For the sake of simplicity the different viscosity grades of NaCMC polymers are coded: Blanose for high viscosity grade, P 800 for medium viscosity grade and P 350 for low viscosity grade. Details of their batch numbers and degree of substitution are shown in table 2.1.

#### 2.1.1.3 Ethylcellulose

Two grades of ethylcellulose were used. Ethylcellulose 7 cP (Ethocel STD 7 PREM), had a viscosity of 5.6-8.4 cP as a 5% solution in 80% w/w toluene/20% w/w ethanol at 25°C (certificate of analysis by Dow Chemical, U.S.A.). Ethylcellulose 10 cP (Ethocel STD 10 PREM), had a viscosity of 9-11 cP as a 5% solution in 80% w/w toluene/20% w/w ethanol at 25°C. Both types were manufactured by Dow Chemicals (U.S.A.). Their batch numbers and degree of substitution are presented in table 2.1.

#### **2.1.2 $\beta$ -Cyclodextrin**

$\beta$ -Cyclodextrin, (lot No. K15973927), manufactured by Merck (Germany) was used. Its molecular formula is  $C_{42}H_{70}O_{35}$ , molecular weight is 1135, melting point is 290-300°C. Its aqueous solubility at 25°C is 1.85% w/v (Merck Index, 1989).

### 2.1.3 Magnesium stearate

Magnesium stearate manufactured by BDH, Poole, Dorset, was used throughout the study.

### 2.1.4 Lactose

Lactose monohydrate B.P. (<105  $\mu\text{m}$ ) manufactured by Zeparox, Barclo Whey Product U.K., was used.

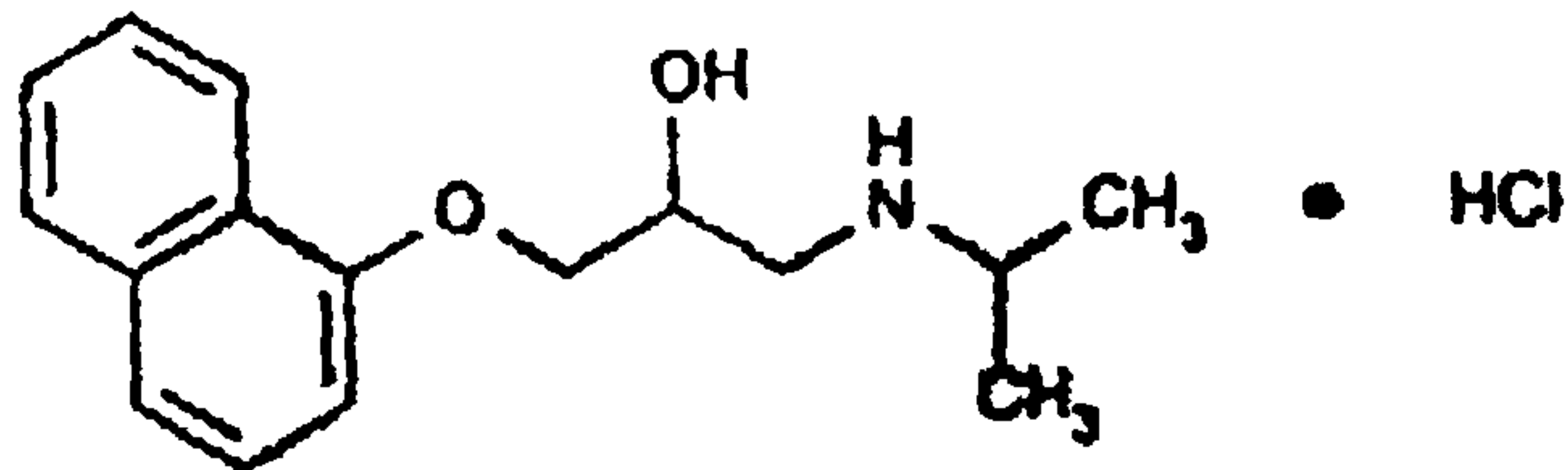
Table 2.1: The batch number and degree of substitution of cellulose ether polymers used for matrices or preparation of gels

Polymer	Batch Number	Degree of Substitution
HPMC K4M	MM92031903K	1.36 - 1.42
Blanose	22-8623	0.73
P 800	T895	0.7 - 0.85
P 350	T516	0.7 - 0.85
EC 7 cP	930654	0.44 - 0.51
EC 10 cP	920029	0.44 - 0.51

### 2.1.5 Propranolol hydrochloride

Propranolol hydrochloride <125 µm, which is a beta-adrenoceptor blocking agent, was used as a model drug throughout the study. Its structure is given in figure 2.1 and its characteristics are as below:

Figure 2.1: The structure formula of propranolol hydrochloride



It is a white powder, with the molecular weight of 295.8, the molecular formula is  $C_{16}H_{21}NO_2 \cdot HCl$ . Its melting point is  $164^\circ C$  and its solubility is 1 in 20 parts of water at  $25^\circ C$  (British Pharmacopoeia, 1993). The pKa of propranolol hydrochloride is 9.5 (Clark's Isolation and Identification of Drugs, 1986).

## 2.2 EXPERIMENTAL METHODS

The basic methods which were used throughout the study are discussed in this section.

### 2.2.1 Characterisation of polymers

Hydroxypropylmethylcellulose and NaCMC were characterized by determining their viscosities, cloud points and water distribution in their gels and their admixtures. The water uptakes of HPMC, NaCMC and their



mixtures were also determined.

#### 2.2.1.1 Preparation of gels

Quantities of gels (50 g) containing HPMC, NaCMC or their mixtures, at concentrations from 0.01 to 0.5% w/w for viscosity determination, from 1 to 5% w/w for cloud point determination and from 5 to 20% w/w for evaluating the water distribution in their gels, were prepared according to the methods of Mitchell et al (1993b). The required amounts of polymer powder were dispersed into approximately one third of the required volume of freshly glass-distilled water previously heated to 80°C and stirred until the polymer particles were thoroughly wetted. Then the remaining amounts of water (at ambient temperature) were added and dispersed. When the gels had cooled to ambient, the weights were checked and more water added if needed. The gels were covered and stored at 4°C for 24 hours in a refrigerator. This method was used to prepare all gels which were used in chapters 4 and 5.

#### 2.2.1.2 Viscosity determination

Viscosities were determined using U-tube viscometers, at 37°C, according to the British Standard method for the determination of viscosity of liquids (British Standard 188, 1975). The U-tube viscometer grade A for low viscosity gels (0.01 - 0.05% w/w), grade B for gels containing higher concentrations of polymer (0.1-0.5% w/w) and grade D for viscosity determination from gels containing mixtures of the two polymers at 0.5% w/w were used. Prior to the work, all viscometers were cleaned with distilled water, dried using acetone

and calibrated against water at 20°C and 37°C. The viscometers were suspended vertically in a water bath maintained at the required temperature. The viscometers were placed in the bath for 30 minutes to allow the sample to reach temperature equilibrium with the bath liquid. Pressure was then applied to raise the meniscus of samples to about 5 mm above the timing mark. The flow time was the time taken for the bottom of the meniscus to pass between the two timing marks. The dynamic viscosity of water at 20°C was taken to be 1.002 cP (British Standard 188:1975). The time taken was a mean of three successive measurements, which were within 0.5% of each other. This method was used in section 4.2.

#### 2.2.1.3 Determination of cloud point

Cloud points of HPMC gels were determined by the methods of Mitchell et al (1990b). After preparing the gels as described in section 2.2.1.1, and keeping them at 4°C for 24 hours to hydrate, the samples were transferred to disposable cuvettes 1 cm pathlength (Kartell, U.K.). Any air bubbles entrapped in the gels were removed by centrifugation at 2000 rpm in a centrifuge (Auto Bench Centrifuge, Baird & Tatlock, U.K.) for 5 minutes to prepare homogeneous gels. The samples were placed in a water bath (Grant Instruments Ltd., U.K.) with a temperature regulator. The temperature was gradually increased from 40°C to 75°C. Initially readings were taken at intervals of 5°C which were then reduced near the cloud point to 1°C intervals. The samples were measured spectrophotometrically at 800 nm, using a Phillips spectrophotometer (PU8625), against a 2% w/w aqueous gel

as a reference which had been maintained at room temperature. The temperature at which the light transmission reached 50% of the reference was taken as the cloud point temperature of the solution (Sarker, 1979; Mitchell et al, 1990b). This method was used in sections 4.3 and 5.2.

## **2.2.2 Differential Scanning Calorimetry (DSC)**

### **2.2.2.1 Aims of using DSC**

A Perkin-Elmer differential scanning calorimeter DSC-7 (Beaconsfield, U.K.), with automatic cooling facilities was used throughout the study. This equipment was controlled by a Perkin-Elmer TAC-7. The equipment was calibrated using indium and zinc. The objectives of the studies using DSC were:

- a) to determine the water distribution of gels containing HPMC, NaCMC or their mixtures,
- b) to determine the effect of propranolol hydrochloride on water distribution of the gels containing HPMC,
- c) to determine the rate of water uptake by the polymers or their combinations,
- d) to evaluate any interactions between propranolol hydrochloride with NaCMC or  $\beta$ -cyclodextrin.

### **2.2.2.2 Calibration of DSC**

DSC was used in two different conditions with the cooling block set at  $-80^{\circ}\text{C}$



or at ambient. In order to determine free water in the gels or wafers, prior to the calibration, the DSC cooling block was cooled to  $-80^{\circ}\text{C}$  using liquid nitrogen. Indium,  $\Delta H_f$   $29.7 \text{ mJg}^{-1}$ , melting point,  $156.16^{\circ}\text{C}$  (Standard  $156.60^{\circ}\text{C}$ ) and zinc, melting point,  $416.27^{\circ}\text{C}$  (Standard  $419.47^{\circ}\text{C}$ ) were used as calibrants. Peak areas were automatically calculated by the instrument. The calculated peak area of indium and the melting temperatures of indium and zinc were given to the DSC as calibration data. Finally in order to investigate the interaction between propranolol hydrochloride and NaCMC or  $\beta$ -cyclodextrin, prior to the work, a similar calibration was performed at ambient (without liquid nitrogen) and the heating rate was  $3^{\circ}\text{C min}^{-1}$ .

#### 2.2.2.3 State of water in gels

Since the distribution of water within matrices is very important and modifies the matrix structure (Mitchell et al, 1989), the state of water in gels was evaluated.

Gels (50 g) containing 5, 10, 15 or 20% w/w of HPMC K4M, NaCMC or their 1:1 mixtures, were prepared as described in section 2.2.1.1. Samples, (5-10 mg) were accurately weighed into aluminium sample pans (40  $\mu\text{l}$ , Perkin-Elmer). After sealing the sample pans, they placed in the DSC holder and were cooled from  $20^{\circ}\text{C}$  to  $-30^{\circ}\text{C}$  at a controlled rate of  $-5^{\circ}\text{C min}^{-1}$  using liquid nitrogen as coolant. This rate was used because Mitchell et al (1993a) reported that fast cooling of HPMC K15M gels could produce double endotherms; slow cooling ( $5^{\circ}\text{C min}^{-1}$ ) resulted in only one endotherm around

0°C, for the melting of ice. Then the samples were scanned at 10°C min<sup>-1</sup> to 30°C in order to measure the enthalpy of melting of the free water at approximately 0°C. Empty sample pans were used as reference. Melting enthalpies were determined in at least triplicate for each gel concentration. This method was used in sections 4.4 and 5.2.2.

#### 2.2.2.4 Water uptake by polymer

Since a study of water uptake by polymers could provide knowledge of the imbibing of water by the polymers, the following study was performed using HPMC K4M, NaCMC (Blanose), ethylcellulose,  $\beta$ -cyclodextrin, lactose or their mixtures.

Mixtures of polymer powders were prepared in a glass jar using a tumbler mixer for 15 minutes. For this study, approximately 10 mg samples (HPMC K4M, NaCMC, ethylcellulose,  $\beta$ -cyclodextrin, lactose, 1:1 HPMC : NaCMC, 1:1 HPMC : ethylcellulose, 1:1 HPMC :  $\beta$ -cyclodextrin or 1:1 HPMC : lactose) were manually compressed into wafers of 6.35 mm diameter, using flat-faced punches and die and a Manesty F3 single punch tableting machine according to the method of Mitchell et al (1993a). The wafers and the aluminium sample pans (Perkin-Elmer, 6.35 mm diameter) were accurately weighed separately. Approximately 10 mg double distilled water (approximately equivalent to the wafer weight) was placed in the pan and the wafers were placed above the water in the pan. A loosely fitting aluminium lid (6.35 mm diameter, Perkin-Elmer) was placed on top of the wafer to prevent water loss

by evaporation. The pans were left unsealed and were kept at room temperature for 1, 5, 15 or 30 minutes. After storage for the prescribed time, the pans and their contents were placed into the sample compartment of a Perkin-Elmer DSC-7 differential scanning calorimeter which was maintained at 20°C and wafers were immediately chilled to -30°C at a controlled rate of -10°C min<sup>-1</sup> using liquid nitrogen. This cooling rate was performed to freeze any unbound water and prevent the production of double peaks (Mitchell et al, 1993c). Samples were scanned from -30°C to 20°C at 5°C min<sup>-1</sup> and the enthalpy of fusion of unbound ice measured.

In order to investigate the water uptake of the polymers at the temperature of the dissolution studies, a similar method was used for HPMC, NaCMC or their 1:1 mixture, except that the pans containing the wafers and water were held in the sample compartment of the Perkin-Elmer DSC-7 differential scanning calorimeter at 37°C for 1, 5, 15 or 30 minutes prior to analysis.

The means of at least 3 determinations were used to calculate the water uptake for each type of disc. The quantity of bound water was then calculated from the difference between the weight of water in the pan and the amount of unbound water equivalent to the observed enthalpy of fusion. This method was used in sections 4.5, 7.6 and 8.6.

### **2.2.3 Determination of propranolol solubility**

Propranolol hydrochloride has a pKa of 9.5 (Clark's Isolation and

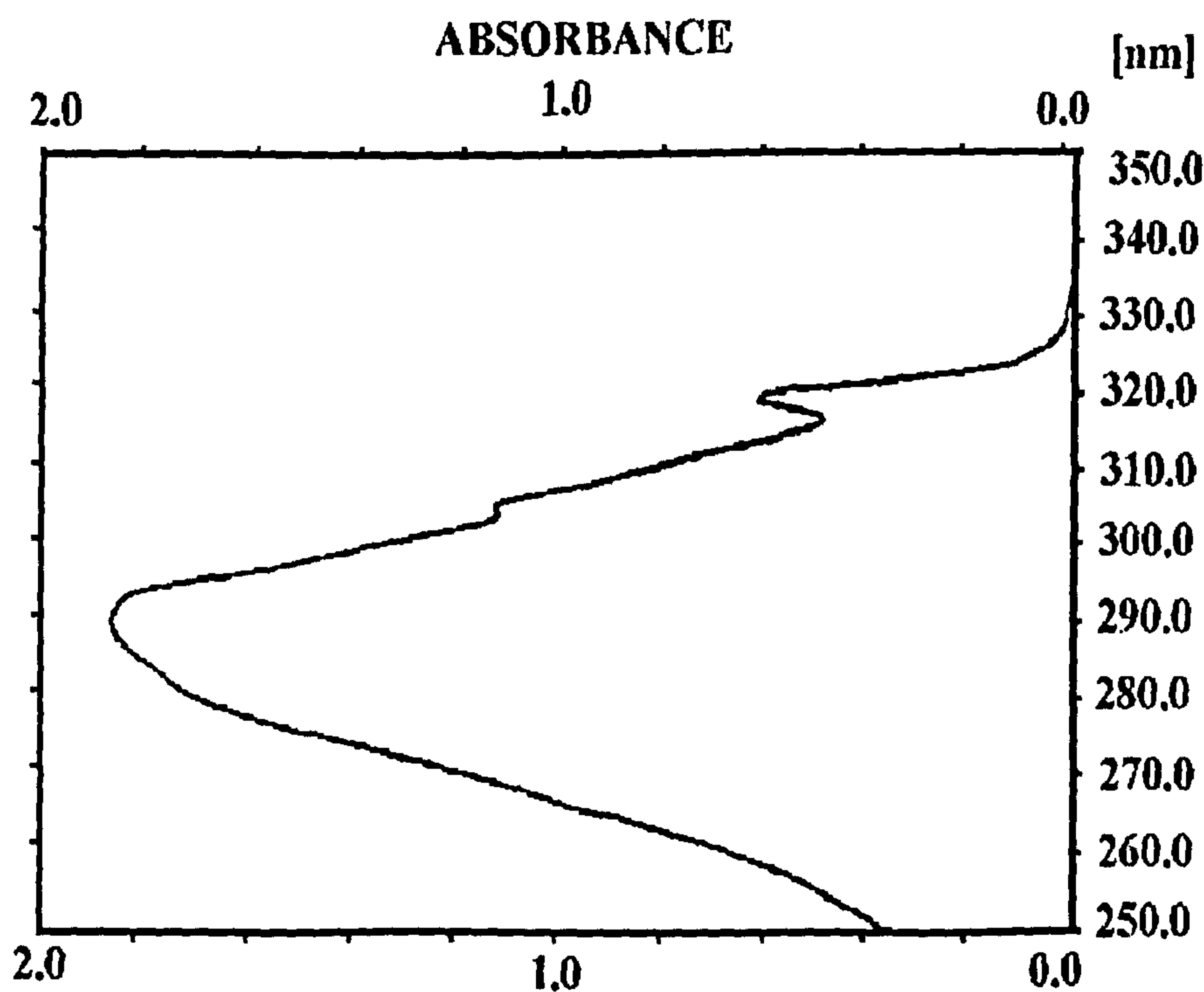


Identification of Drugs, 1986) and its solubility is markedly dependent on pH. Therefore it was necessary to determine the solubility of propranolol hydrochloride in the different media which were used throughout this study.

### 2.2.3.1 UV calibration of propranolol hydrochloride

The UV spectrum for a propranolol hydrochloride solution is shown in figure 2.2. The UV absorbance for a solution containing 0.1 mg/mL propranolol hydrochloride was determined at 288 nm ( $1.847 \pm 0.03$ ,  $n=3$ ) and its E 1%, 1 cm value determined experimentally and used in this study, was 184.7.

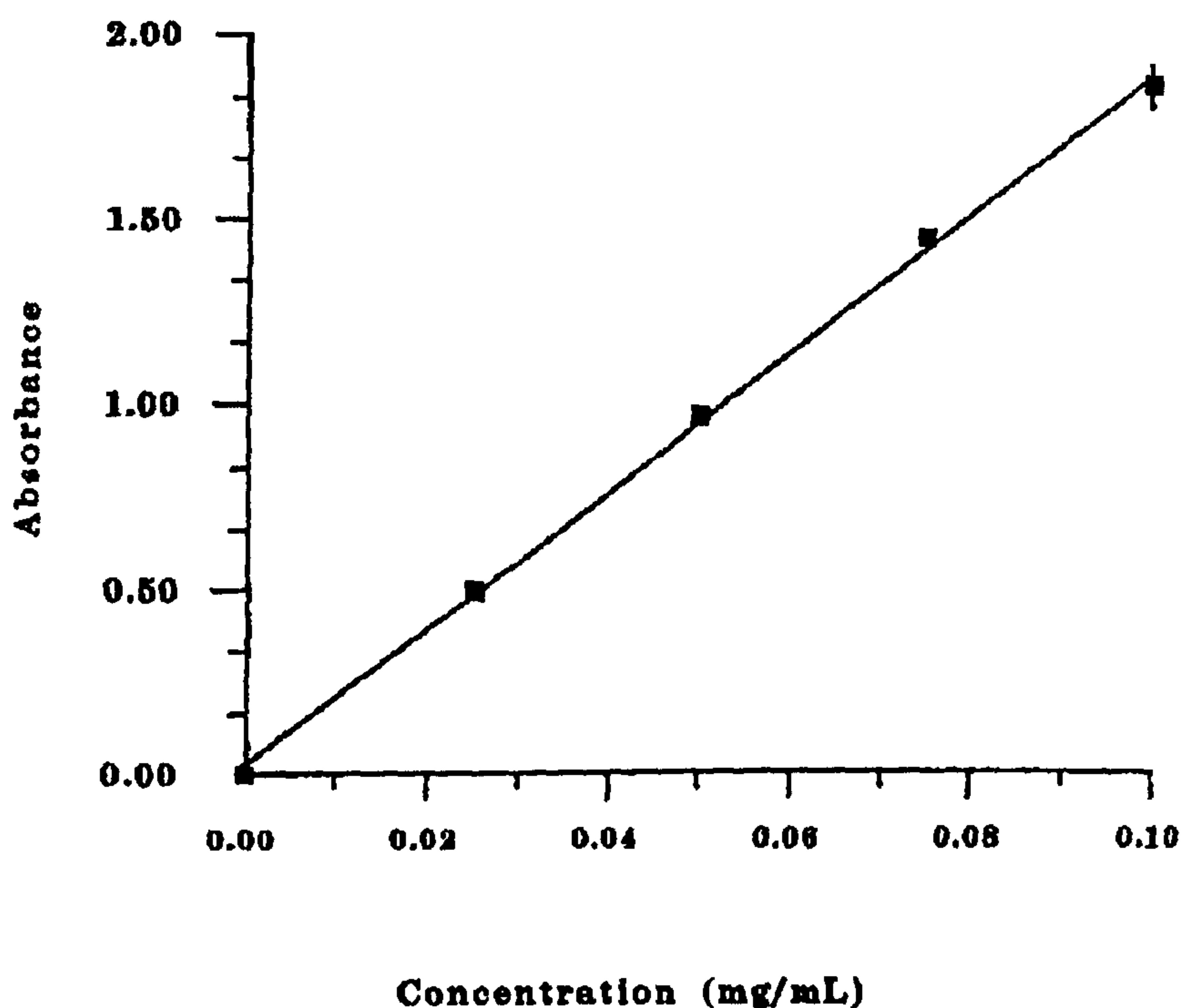
Figure 2.2: UV spectrum of an aqueous solution containing propranolol hydrochloride (0.1 mg/mL).



The UV absorbances of different concentrations of propranolol hydrochloride ( 0.0 to 0.1 mg/mL) in freshly distilled water at 288 nm were determined (figure 2.3). The best fit equation for the Beer's law plot of the UV absorbance versus drug concentrations, is given by equation 2.1.

$$Y = 18.11 C + 0.054 \quad (r=0.9994) \quad \text{Equation 2.1}$$

Figure 2.3: Calibration curve of propranolol hydrochloride in distilled water at 288 nm. Mean (n=3)  $\pm$  SD



In this equation, Y is the absorbance at 288 nm and C is the concentration of propranolol hydrochloride (mg/mL). This equation was used for calculation

of propranolol solubility throughout the study (chapters 6 and 8).

#### 2.2.3.2 Determination of solubility

Samples (1 g) of propranolol hydrochloride powder were placed into 5 mL test tubes with 3 mL of distilled water, 0.1 M hydrochloric acid, phosphate buffer solution pH 6.8 or alkaline borate buffer solution pH 9.4 according to the method of Shivanand and Sprockel (1993). The formulae of the buffers are presented in appendix 1. The test tubes were placed in a shaker bath (Companstat 882942, England), at 37°C for seven days. Then the suspended solid was allowed to settle and the supernatant was sampled and filtered through a Whatman No. 1. The first 1 mL of the filtrate was discarded. The drug concentration was determined spectrophotometrically at 288 nm after appropriate dilution. The mean of three determinations was used to calculate the solubility of propranolol hydrochloride in each media. This method was used in sections 6.3 and 8.5.

#### **2.2.4 Preparation of matrices**

Flat-faced tablets, 12.7 mm diameter, were directly compressed on a Manesty F3 single punch tableting machine (Manesty Machines Ltd. U.K.) at 182 MNm<sup>-2</sup>. Compaction was accomplished by direct compression of blends containing propranolol hydrochloride <125 µm, polymers and magnesium stearate that had been mixed for 15 minutes using a tumbler mixer. This method was also used to prepare matrices containing ethylcellulose, HPMC:ethylcellulose, NaCMC:ethylcellulose and HPMC: β-cyclodextrin.



### **2.2.5 Dissolution Methodology**

Dissolution was measured by a Pharmatest (GmbH, Germany) dissolution tester and a Hewlett Packard HP8452A Diode Array spectrophotometer. The USP XXII (Apparatus I) was used, rotating at  $100 \text{ rev min}^{-1}$ , in 1000 mL distilled water maintained at  $37^\circ\text{C}$ . Propranolol hydrochloride was monitored at 288 nm. The mean of six determinations was used to calculate the drug release for each formulation.

# **CHAPTER 3 DISSOLUTION OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING HYDROXYPROPYLMETHYLCELLULOSE AND SODIUM CARBOXYMETHYLCELLULOSE**

## **3.1 INTRODUCTION**

Matrices containing solely hydroxypropylmethylcellulose (HPMC) generally provide a controlled drug release which approximates to square root of time kinetics (Ford et al, 1985a, b; 1987). Since zero-order release is the most desired release pattern, several investigators (e.g., Baveja et al, 1987; 1988 a, b; Ranga Rao et al, 1989; Padmalatha Devi et al, 1989) have tried to achieve a zero order release of drug from hydrophilic matrices. This release is characterized by being independent of time and the amount of drug remaining in the systems. Baveja et al (1987) reported that the major disadvantage of hydrophilic swellable polymers is that zero-order release has not generally been observed but they advocated the use in matrices of admixtures of HPMC and sodium carboxymethylcellulose (NaCMC) to provide a near zero-order release of propranolol hydrochloride. Similarly, Ranga Rao et al (1989) claimed that the admixture of a non-ionic hydrophilic polymer such as HPMC and an ionic polymer such as NaCMC may allow zero-order release of soluble drugs.

However, it is well known that the viscosity grade of HPMC does not normally affect the drug release (Ford et al, 1985a, b) and that admixture of

HPMC and NaCMC would produce a synergistic increase in the viscosity of their gels (Walker and Wells, 1982) which could be used to modify drug release (Ranga Rao et al, 1989). This increase in the viscosity of the two polymers was confirmed by Manion et al (1990) who derived equations which predicted the total viscosity of mixed aqueous solutions of anionic and nonionic cellulose ethers and showed that the enhanced viscosity observed in the mixture might be explained in terms of coil expansion of the anionic polymer. However, there seems to have been few studies on the performance of these polymers in controlling drug release. This investigation evaluates if changes in the viscosity grade of NaCMC in its admixtures with HPMC, lead to zero-order release of drugs.

### **3.1.1 Aims and objectives**

The main aim of the studies presented in this chapter was to investigate how HPMC, NaCMC or their combinations affect the dissolution rate of propranolol hydrochloride from matrices. The other aim was to study the effect of the viscosity grade of NaCMC on the drug release. For this purpose, matrices containing different viscosity grades of NaCMC, on their own and in admixture with HPMC, were made and the dissolution rates of propranolol hydrochloride were examined.

### **3.1.2 Experimental**

#### **3.1.2.1 Materials**

Propranolol hydrochloride, HPMC, NaCMC, and magnesium stearate used in



the matrix tablets are described in the section 2.1.

#### 3.1.2.2 Tablet preparation

Tablets were prepared containing 160 mg propranolol hydrochloride (<125  $\mu\text{m}$ ), 0.75% w/w magnesium stearate as lubricant and 57, 71, 95, 140, or 285 mg of HPMC K4M, NaCMC (Blanose) or their 1:3, 1:1 or 3:1 blends at 182  $\text{MNm}^{-2}$  as described in section 2.2.4. Matrices containing 57, 95, 140 or 285 mg of NaCMC P 800 or NaCMC P 350 or their admixture with HPMC K4M in the ratio of 1:1 were similarly made.

#### 3.1.2.3 Dissolution methodology

Dissolution studies were carried out at 37°C as described in section 2.2.5.

#### 3.1.2.4 Statistical analyses of release

In order to investigate the kinetics of drug release from matrices, attempts were made to fit the data corresponding to 5 - 60% release to equations 1.1, 1.2 and 1.3 which were discussed in section 1.4.1. Equations 1.1 and 1.2 are popularly used to determine the release exponent (n) of drug release from the matrices. Fitting the data points, to equations 1.1 and 1.2 was carried out using a computer program. The program uses a non-linear least-squares fitting method to determine the optimum values for the parameters presented in each equation (Ford et al, 1991). For the purpose of comparison, the data in this study were also fitted to equation 1.3, which is a simplified form of an equation produced by Higuchi (1963). Data were fitted to equation 1.3 by

linear regression. These equations are summarized below:

$$Q = K_1 t^n \quad \text{Equation 1.1}$$

$$Q = K_2 (t-l)^n \quad \text{Equation 1.2}$$

$$Q = K_3 t^{0.5} + C \quad \text{Equation 1.3}$$

All the terms in these equations, have been discussed thoroughly in section 1.4.1. However, there is a difference between the values of  $n$  from equation 1.1 and 1.2. Equation 1.1 is based on the assumption that release occurs as soon as the matrix is placed in contact with fluid and thus predicts an intercept at the origin (Ford et al, 1991) whereas, equation 1.2 includes a value of lag time and thus the plot would not pass through the origin. Therefore the value of  $n$  from equation 1.2 is defined as "lag time corrected".

The release rates from all matrices were calculated from linear regression of the data corresponding to 5 to 60% propranolol hydrochloride release on the basis of the square root of time. This was initially attempted irrespective of curve shape. Therefore, the release rates from matrices containing low polymer content, especially for NaCMC, are approximate values (due to the few data points obtained between 5 and 60% release). As the polymer content in the matrices increased, the value of release rates could be obtained more accurately. The values of  $T_{50\%}$  (time for 50% drug released) were calculated from the time for 50% of drug to be released as minutes.

## 3.2 RESULTS AND DISCUSSION

### **3.2.1 Release of propranolol hydrochloride from matrices containing HPMC K4M**

The release profiles, of propranolol hydrochloride from tablets containing different quantities of HPMC are shown in figure 3.1. All dissolution data were plotted as a function of the square root of time. An increase in HPMC content resulted in a decrease in the release rates. A similar dependence of the release rates on the drug : HPMC ratio in the matrices has been observed for HPMC matrices containing propranolol hydrochloride (Ford et al, 1985b; Mitchell et al, 1993d). The release rates, on the basis of the square root of time, are given in table 3.1.

The values of  $K_1$  and  $n$  based on equation 1.1 and  $K_2$ ,  $n$  and  $l$  based on equation 1.2 are presented in the table 3.2. It is seen that the value of  $n$  is about 0.6, indicating diffusion control (Ford et al, 1991). Similar values of  $n$  of 0.64 (Ford et al, 1987) and 0.63 (Ranga Rao et al, 1990) were found for propranolol hydrochloride release from matrices containing HPMC K15M and HPMC K4M matrices, respectively. Perez-Marcos et al (1994), using HPMC K4M and carbopol, reported values of 0.698, 0.646 and 0.608 for propranolol hydrochloride release kinetics from matrices containing 40, 90 and 140 mg HPMC K4M respectively.

The data in table 3.2 gave an estimate of the value of  $n$  based on equations



Figure 3.1: Release of propranolol hydrochloride from matrices containing different amounts of HPMC K4M (results are the means  $\pm$  SD of 6 determinations) plotted as a function of the square root of time

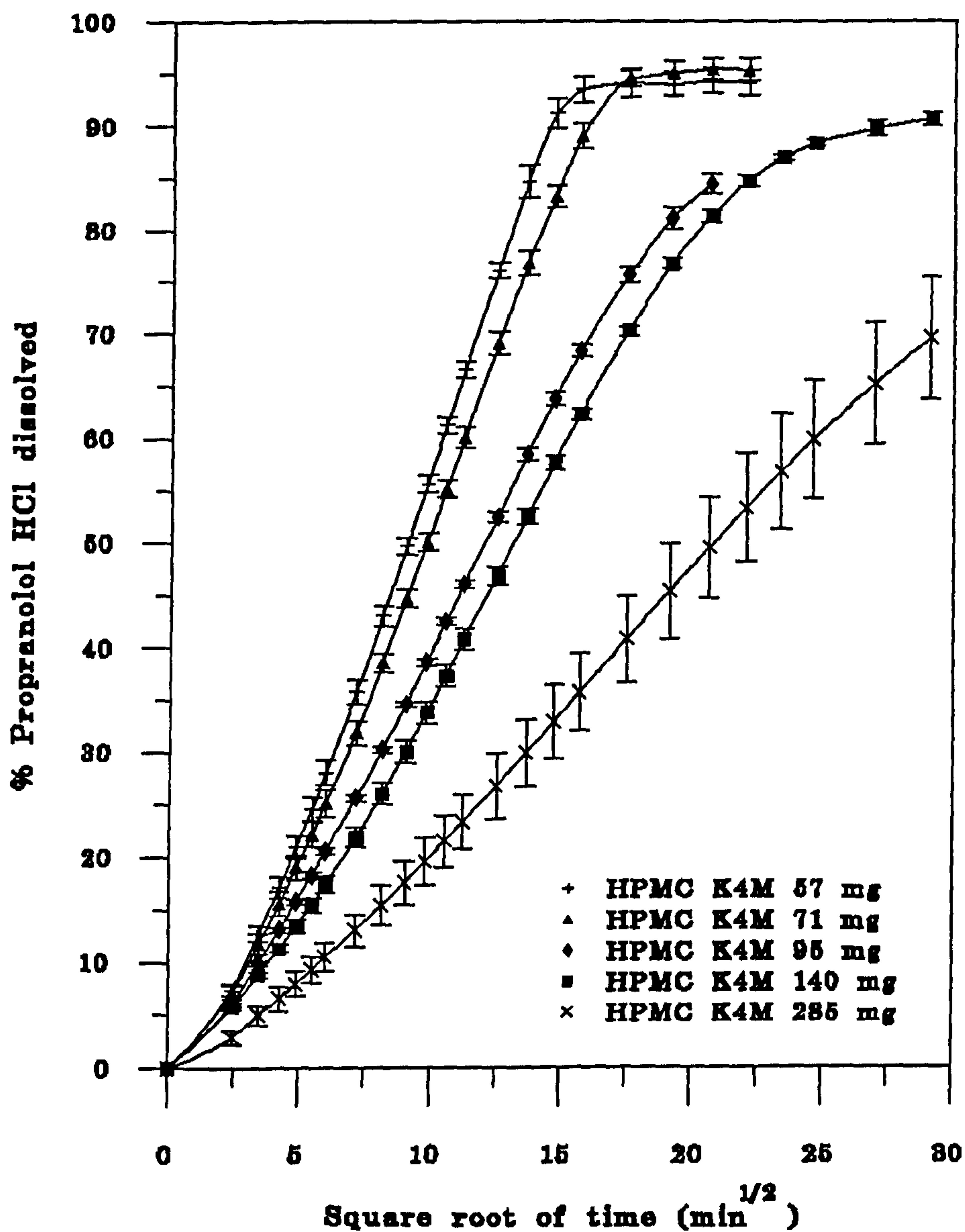


Table 3.1: Dissolution rates ( $\% \text{min}^{-1/2}$ ) of propranolol hydrochloride from matrices containing HPMC and NaCMC (Blanose)

calculated from data equivalent to 5-60% release. Results are the means  $\pm$  SD of 6 determinations.

Ratio HPMC:NaCMC	Total Polymer (mg)				
	57	71	95	140	285
1 : 0	6.7 $\pm$ 0.1	6.0 $\pm$ 0.1	4.7 $\pm$ 0.1	4.2 $\pm$ 0.0	2.6 $\pm$ 0.2
3 : 1	6.8 $\pm$ 0.2	5.7 $\pm$ 0.1	5.4 $\pm$ 0.1	4.1 $\pm$ 0.1	2.7 $\pm$ 0.0
1 : 1	9.3 $\pm$ 0.1	6.3 $\pm$ 0.4	5.0 $\pm$ 0.7	3.2 $\pm$ 0.0	1.3 $\pm$ 0.1
1 : 3	11.1 $\pm$ 2.9	6.1 $\pm$ 2.1	5.2 $\pm$ 0.5	2.2 $\pm$ 0.0	2.1 $\pm$ 0.1
0 : 1	27.1*	10.6*	4.6 $\pm$ 2.3	3.8 $\pm$ 0.2	3.1 $\pm$ 0.1

\* These values are only estimates of the release rates because propranolol hydrochloride was released very quickly.

Table 3.2: The values of  $K_1$ ,  $n$ ,  $ss$  (sums of squares) and Schwartz criterion based on equation 1.1,  $K_2$ ,  $n$ ,  $l$ ,  $ss$  and Schwartz criterion based on equation 1.2 calculated in the range of 5- 60% propranolol hydrochloride release, from matrices containing HPMC K4M

HPMC K4M content (mg)	Equation 1.1					Equation 1.2				
	$K_1$	$n$	$ss$	Schwartz	$K_2$	$n$	$l$	$ss$	Schwartz	
57	2.26	0.70	0.776	2.00	2.52	0.68	1.19	0.168	-12.417	
71	2.09	0.70	0.344	-7.85	2.17	0.69	0.41	0.283	-7.698	
95	2.09	0.64	0.686	0.008	2.26	0.62	1.20	0.187	-15.554	
140	1.66	0.66	0.762	1.338	1.59	0.67	-0.75	0.628	1.145	
285	1.23	0.61	3.720	32.252	1.42	0.59	5.39	1.52	17.396	



1.1 and 1.2. It was observed that, although the values of  $n$  from both equations were similar, equation 1.2 gave the lowest sums of squares of errors (ss). Previously, Ford et al (1991) reported that the sums of squares of errors, are a measure of the discrepancies between the observed data and the values which were predicted by a particular model. Therefore, this value gives an initial guide to the quality of a model; the greater the sum of squares, the poorer the model (Ford et al, 1991). However, due to the lower values of the sum of squares, equation 1.2 gave the best fits for the data from matrices containing HPMC K4M. Several authors have published methods for assessing changes in the sums of squares with increased number of variables, e.g., Schwartz, (1978) introduced an information criterion. The lowest value for the information criterion is the most appropriate for each set of data and therefore equation 1.2 was generally more appropriate than equation 1.1.

### **3.2.2 Release of propranolol hydrochloride from matrices containing NaCMC**

Figures 3.2, 3.3 or 3.4 show the release profiles of propranolol hydrochloride from matrices containing different amounts of NaCMC (Blanose), NaCMC P 800 or NaCMC P 350 respectively. Since matrices containing NaCMC tended to release the drug as a function of time rather than square root of time, the release data are plotted as a function of time. The release rates, based on the square root of time and irrespective of the curve shape, are given in table 3.3. Since the data could not be fitted to equation 1.2 for some of the matrices containing NaCMC, equation 1.1 was used. The values of  $K_1$  and  $n$  based on

this equation are also presented in the table 3.3. As mentioned in section 3.1.2.4, due to fast release of matrices with low polymer content, the release rates from NaCMC are approximate estimates.

In matrices containing NaCMC (Blanose), the dissolution rates increased from 3.1 to 27.1%  $\text{min}^{-1/2}$  as the content of NaCMC (Blanose) was lowered from 285 to 57 mg. Similarly the dissolution rate from matrices containing NaCMC P 800, increased from 3.9 to 28.8%  $\text{min}^{-1/2}$  (table 3.3). The largest differences observed in release rates were from matrices containing 95 mg of different kinds of NaCMC. Matrices containing 95 mg of NaCMC P 800 or NaCMC P 350 showed similar release rate ( $> 26\% \text{min}^{-1/2}$ ) whereas the rates from matrices containing 95 mg NaCMC (Blanose) were 4.6%  $\text{min}^{-1/2}$ . However, it is seen that the release rates from matrices containing NaCMC (Blanose) are slower than other kinds of NaCMC at similar concentrations. The rank order of release rate was NaCMC (Blanose)  $<$  NaCMC P 800  $<$  NaCMC P 350, which was dependent on their viscosity grades.

Since matrices containing 71 mg of NaCMC (Blanose) showed very fast release, matrices containing 71 mg of NaCMC P 800 or NaCMC P 350 were not investigated. The release profiles were considerably different to those from matrices containing HPMC. The amount of drug released at any time decreased as the proportion of any of the kinds of NaCMC in the matrices increased. A similar dependence of release rates on the drug : NaCMC ratio has been observed for NaCMC matrices containing propranolol hydrochloride

Figure 3.2: Release of propranolol hydrochloride from matrices containing different amounts of NaCMC (Blanose) plotted as a function of time. Results are the means  $\pm$  SD of 6 determinations.

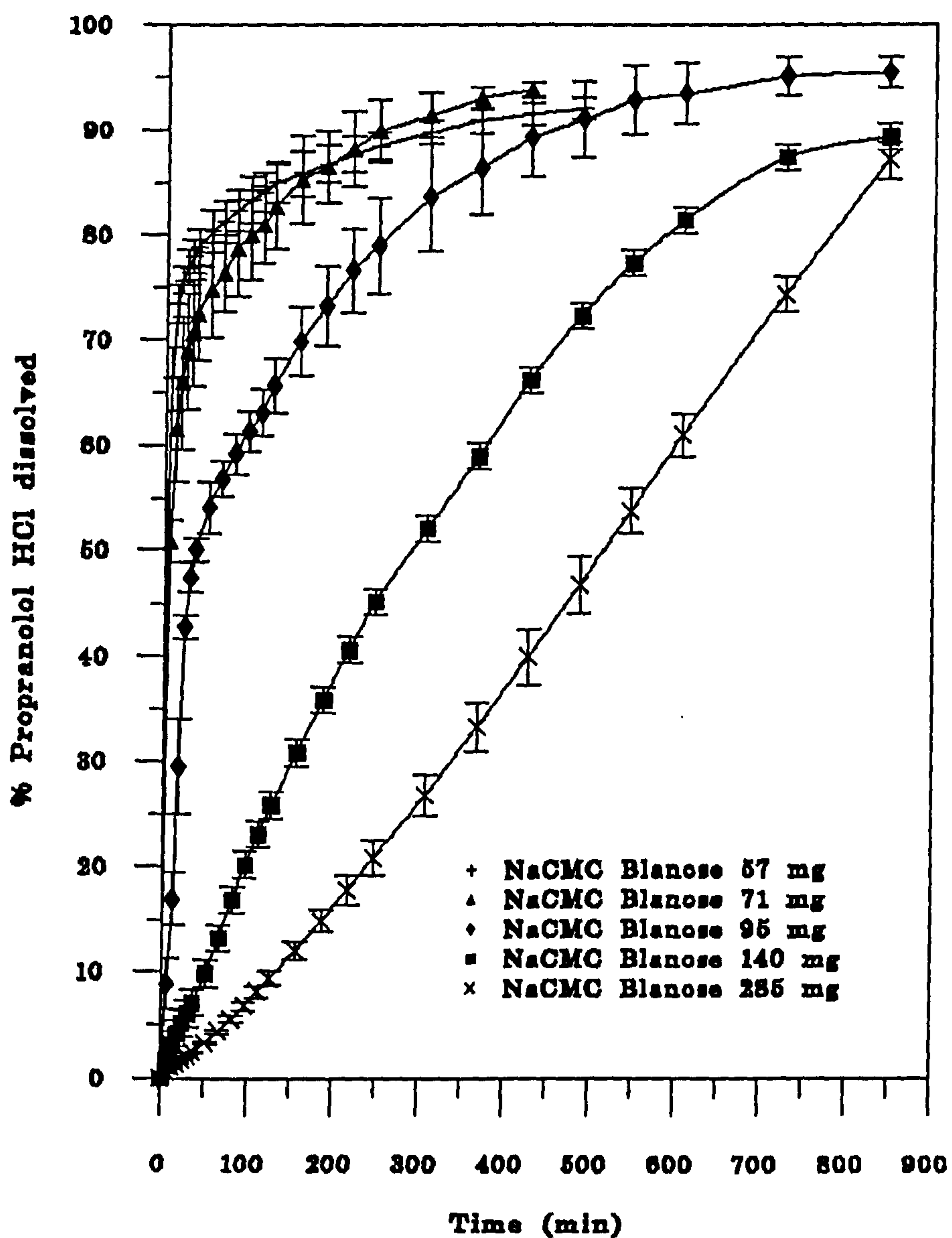




Figure 3.3: Release of propranolol hydrochloride from matrices containing different amounts of NaCMC P 800 plotted as a function of time. Results are the means  $\pm$  SD of 6 determinations.

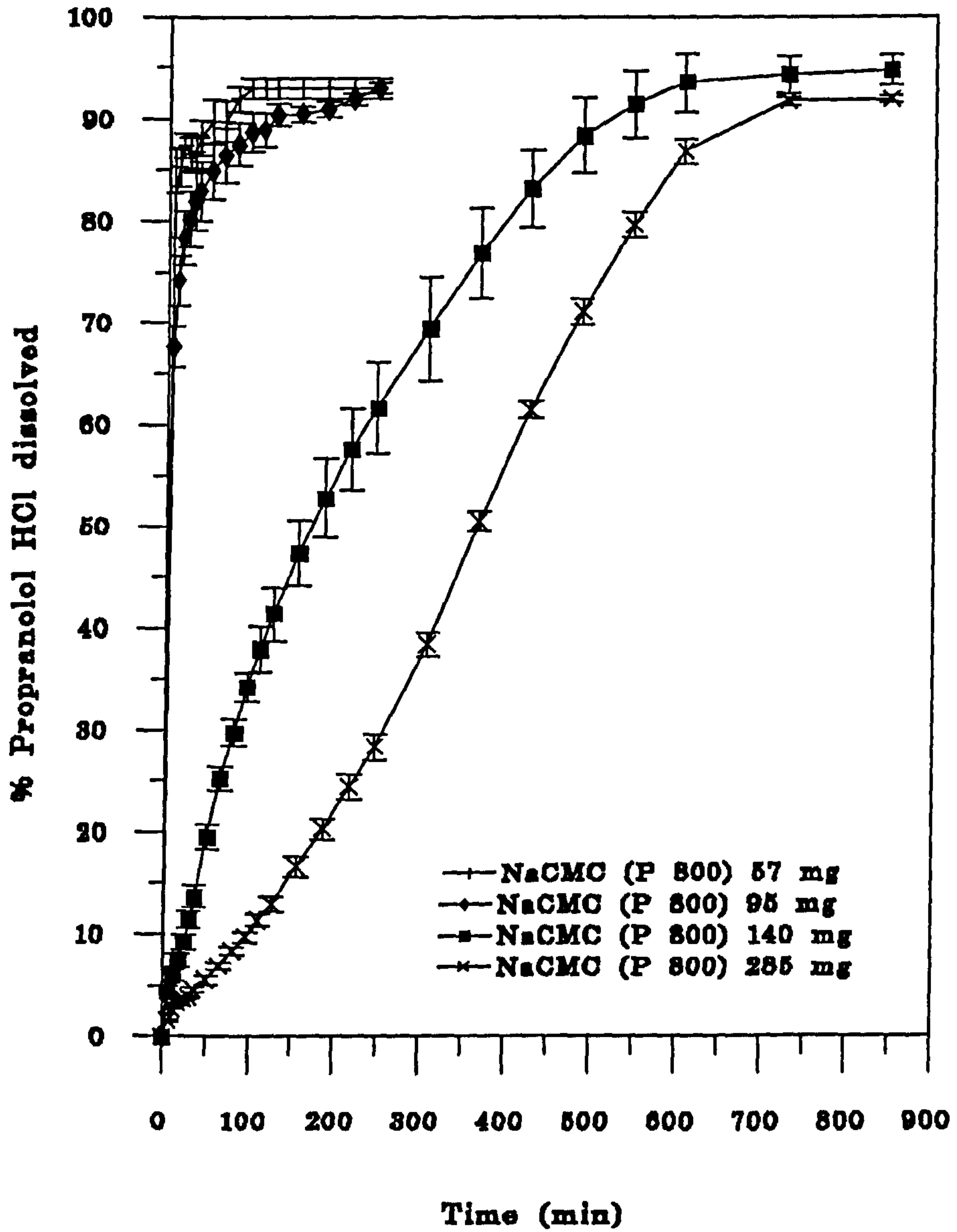


Figure 3.4: Release of propranolol hydrochloride from matrices containing different amounts of NaCMC P 350 plotted as a function of time. Results are the means  $\pm$  SD of 6 determinations.

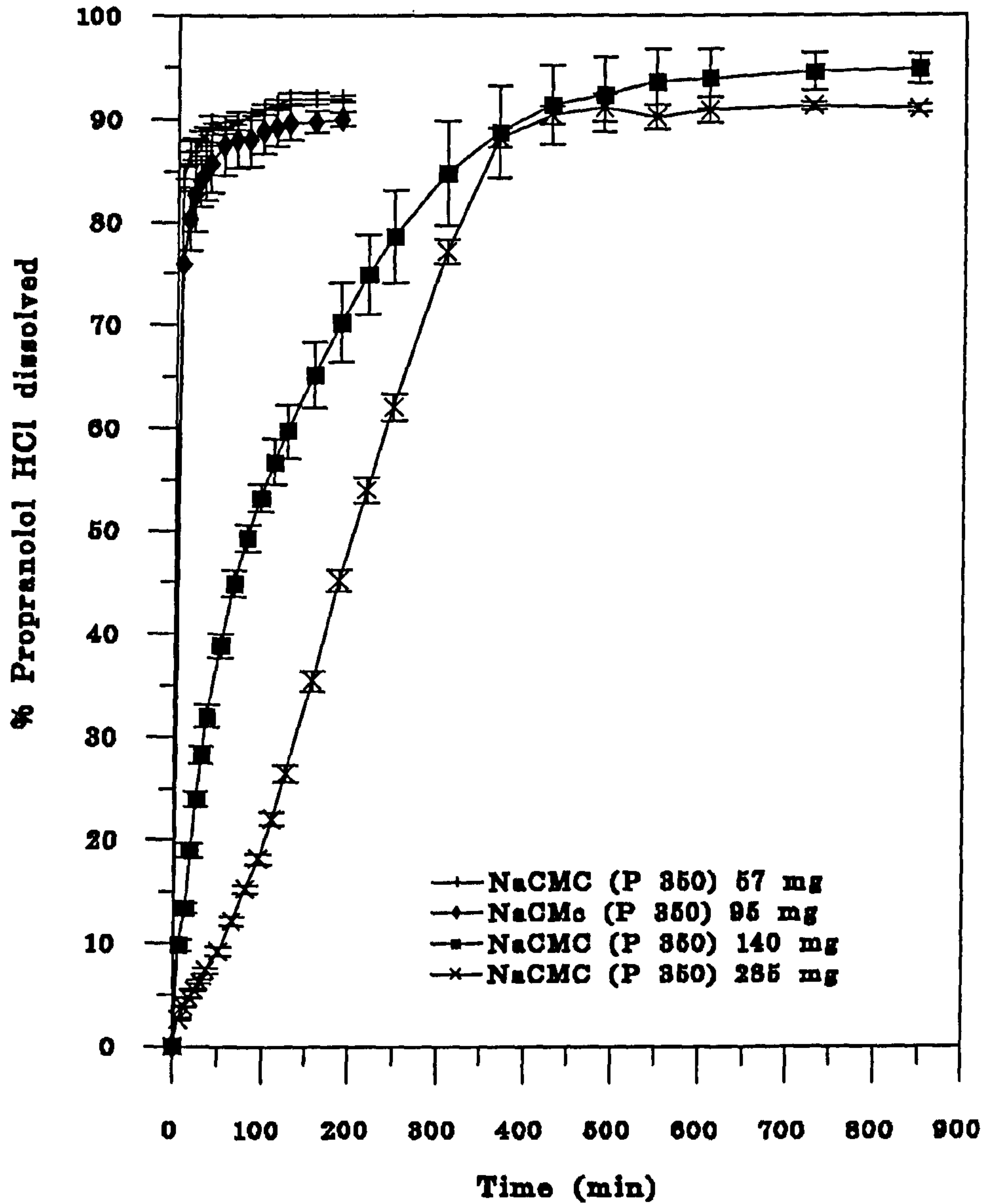


Table 3.3: Estimated values of release rates ( $\text{min}^{-1/2}$ ),  $T_{50\%}$  (minute),  $K_1$  ( $\text{minute}^{-n}$ ),  $n$  and  $ss$  (sums of squares) based on equation 1.1 in the range of 5-60% drug release from matrices containing different kinds of NaCMC. Results are the means  $\pm$  SD of 6 determinations.

Polymer content ( mg)	Parameters					
	$T_{50\%}$ minute $\pm$ SD	Release rate $\text{min}^{-1/2} \pm$ SD	$K_1$ ( $\text{minute}^{-n}$ )	$n$	$ss$	
Blanose	57	4.5 $\pm$ 0.4	27.1*	-	-	
	71	7.2 $\pm$ 0.5	10.6 $\pm$ 4.6	0.33	2.12	
	95	41.6 $\pm$ 15.1	4.6 $\pm$ 2.3	8.29	0.46	453
	140	289.7 $\pm$ 25.4	3.8 $\pm$ 0.2	0.42	0.84	15
	285	512.9 $\pm$ 18.5	3.1 $\pm$ 0.1	0.04	1.16	3.56
P 800	57	3.6 $\pm$ 0.2	28.8*	-	-	
	95	4.4 $\pm$ 0.2	26.0*	-	-	
	140	173.0 $\pm$ 28.4	4.5 $\pm$ 0.3	1.20	0.74	45
	285	385.9 $\pm$ 8.0	3.9 $\pm$ 0.4	0.12	1.05	0.05
P 350	57	3.6 $\pm$ 0.1	29.0*	-	-	
	95	4.0 $\pm$ 0.4	27.5*	-	-	
	140	77.4 $\pm$ 9.8	6.1 $\pm$ 0.5	1.05	0.61	28
	285	201.9 $\pm$ 36.2	5.2 $\pm$ 0.4	0.09	1.18	1.43

\* These values are only estimates of the release rates because propranolol hydrochloride was released very quickly.

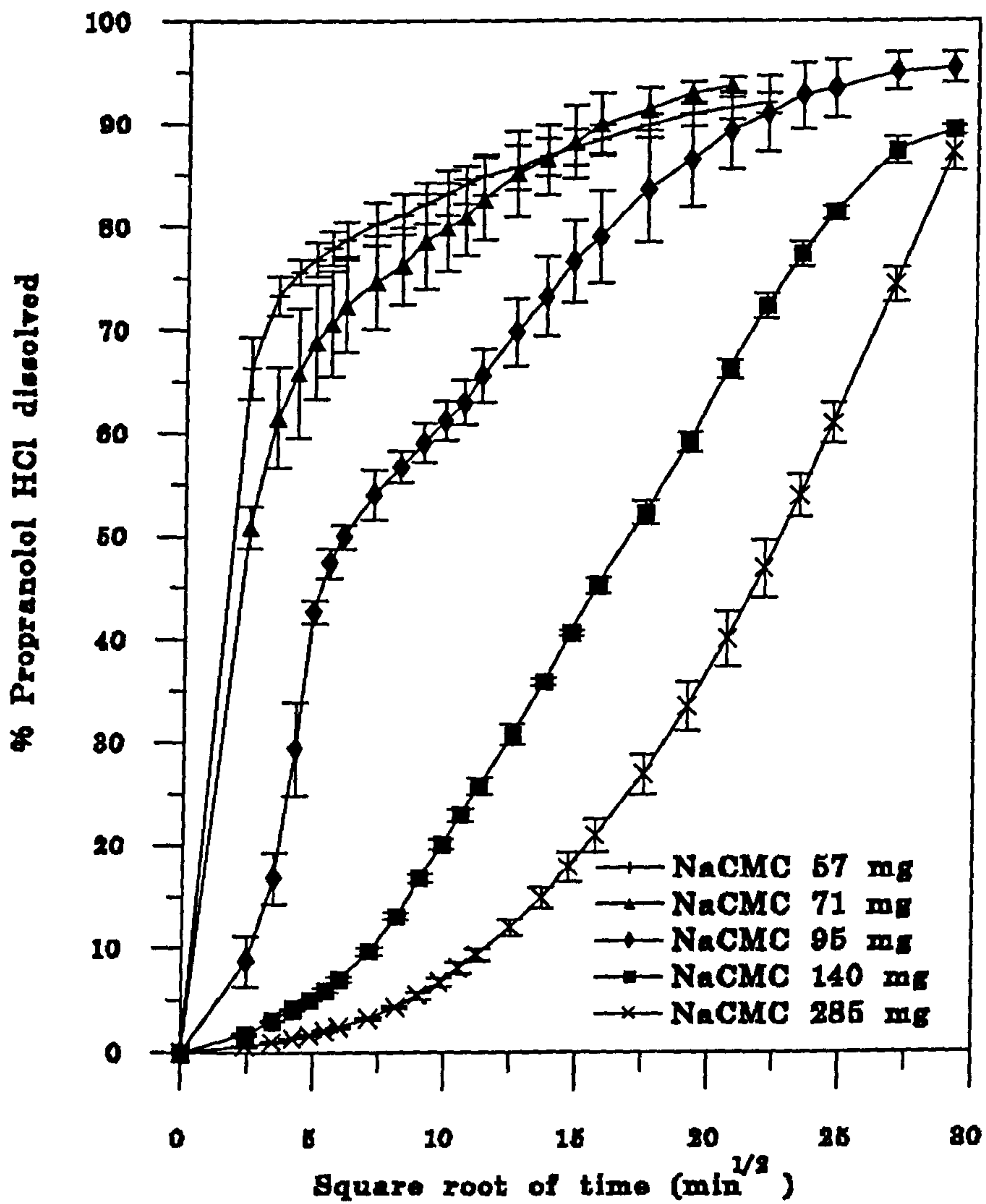


(Baveja et al, 1987) or pseudoephedrine hydrochloride (Baveja et al, 1989).

However, the matrices containing 57 or 71 mg NaCMC showed a fast release of propranolol hydrochloride, due to their disintegration. More than 65% of the drug in the matrices was released during the initial 6 minutes of contact with dissolution media. The data indicate that the matrices containing NaCMC released their drug by one of two release mechanisms depending on the polymer content. Matrices containing 57, 71 or 95 mg NaCMC were probably unable to provide a protective gel layer around themselves; matrices containing more than 95 mg were able to do so and therefore showed controlled drug delivery. It seems that a NaCMC content of about 95 mg was required before even some control of drug release was accomplished. The values of  $n$  based on equation 1.1 from matrices containing 95 mg NaCMC (Blanose) were 0.94 between 5-40% and 0.24 between 40-60% release, indicating a significant difference in drug release mechanism during the two periods from these matrices.

When the release data from matrices containing 285 mg NaCMC (Blanose) were plotted against time (figure 3.2) instead of square root of time (figure 3.5), the data between the range of 5-80% could be regarded as linear ( $r=0.999$ ). This indicates that square root of time kinetics did not accurately describe the propranolol hydrochloride release from matrices containing 285 mg NaCMC. The values  $n$  for matrices containing 285 mg NaCMC were near 1 confirming the near zero-order release from these matrices. In contrast,

Figure 3.5: Release of propranolol hydrochloride from matrices containing different amounts of NaCMC (Blanose) plotted as a function of time. Results are the means  $\pm$  SD of 6 determinations.



matrices containing 140 mg tended to release their drug by anomalous release. The lowest value for n (0.33) was obtained for matrices containing 71 mg NaCMC (Blanose) which showed fast release of propranolol hydrochloride due to disintegration of these matrices.

For further comparison of release data from matrices containing the different kinds of NaCMC, equation 1.3 was used to give estimates of release rates and intercepts from matrices containing 140 or 285 mg NaCMC. Low polymer content (57, 71 and 95 mg) of NaCMC P 800 or NaCMC P 350 showed fast release (more than 80% during 6 minutes) and therefore it was impossible to accurately estimate values of  $K_3$ . From the data in table 3.4, it was observed that as the polymer content or its viscosity grade increased, the release rates decreased and so did the intercept, indicating a lag time before drug release.

Table 3.4: Estimated values of release rate ( $K_3$ ) and intercept (%) from matrices containing 140 or 285 mg different kinds of NaCMC based on equation 1.3.

Parameters	Blanose (mg)		P 800 (mg)		P 350 (mg)	
	140	285	140	285	140	285
Slope ( $K_3$ )	3.83	3.10	4.47	3.90	6.10	5.21
Intercept (%)	-16.5	-30.2	-12.6	-25.6	-4.93	-24.10
$r^*$	0.993	0.999	0.986	0.991	0.975	0.993

$r^*$  Regression coefficient between 5-60% drug release, based on time



### **3.2.3 Release of propranolol hydrochloride from matrices containing HPMC and NaCMC**

#### **3.2.3.1 The effect of HPMC and NaCMC (Blanose) on drug release**

The release profiles of propranolol hydrochloride from matrices containing 57, 71 or 95 mg polymer and different ratios of HPMC and NaCMC (Blanose) are shown in figures 3.6, 3.7 and 3.8 respectively. The values of the release rates for all matrices consist of different ratios of HPMC and NaCMC (Blanose) are presented in table 3.1. It was observed that from these matrices, the dissolution rates increased as the proportion of NaCMC increased. This might be potentially due to a higher erosion rate of these matrices compared to matrices containing HPMC alone (Ranga Rao et al, 1990). Ranga Rao et al (1990) reported that the erosion rates of matrices containing 50% drug (metoprolol tartrate or alprenolol hydrochloride) and 50% of 1:1 HPMC : NaCMC or 1:1 hydroxypropylcellulose : NaCMC were much higher compared to matrices containing HPMC or hydroxypropylcellulose alone.

The release profiles of propranolol hydrochloride from matrices containing 140 or 285 mg polymer are shown in figures 3.9 and 3.10 respectively. In matrices containing 140 mg polymer, the dissolution rates decreased as the NaCMC content increased to 75% of the total polymer (1:3 HPMC : NaCMC). In matrices containing 285 mg total polymer, a minimum in rates ( $1.3 \pm 0.1$ ) occurred for matrices containing 1:1 HPMC : NaCMC (Blanose). This decrease in release rate might have been due to the formation of a complex

Figure 3.6: The effect of HPMC : NaCMC (Blanose) ratio on the release of propranolol hydrochloride from matrices containing 57 mg polymer. Results are the means  $\pm$  SD of 6 determinations.

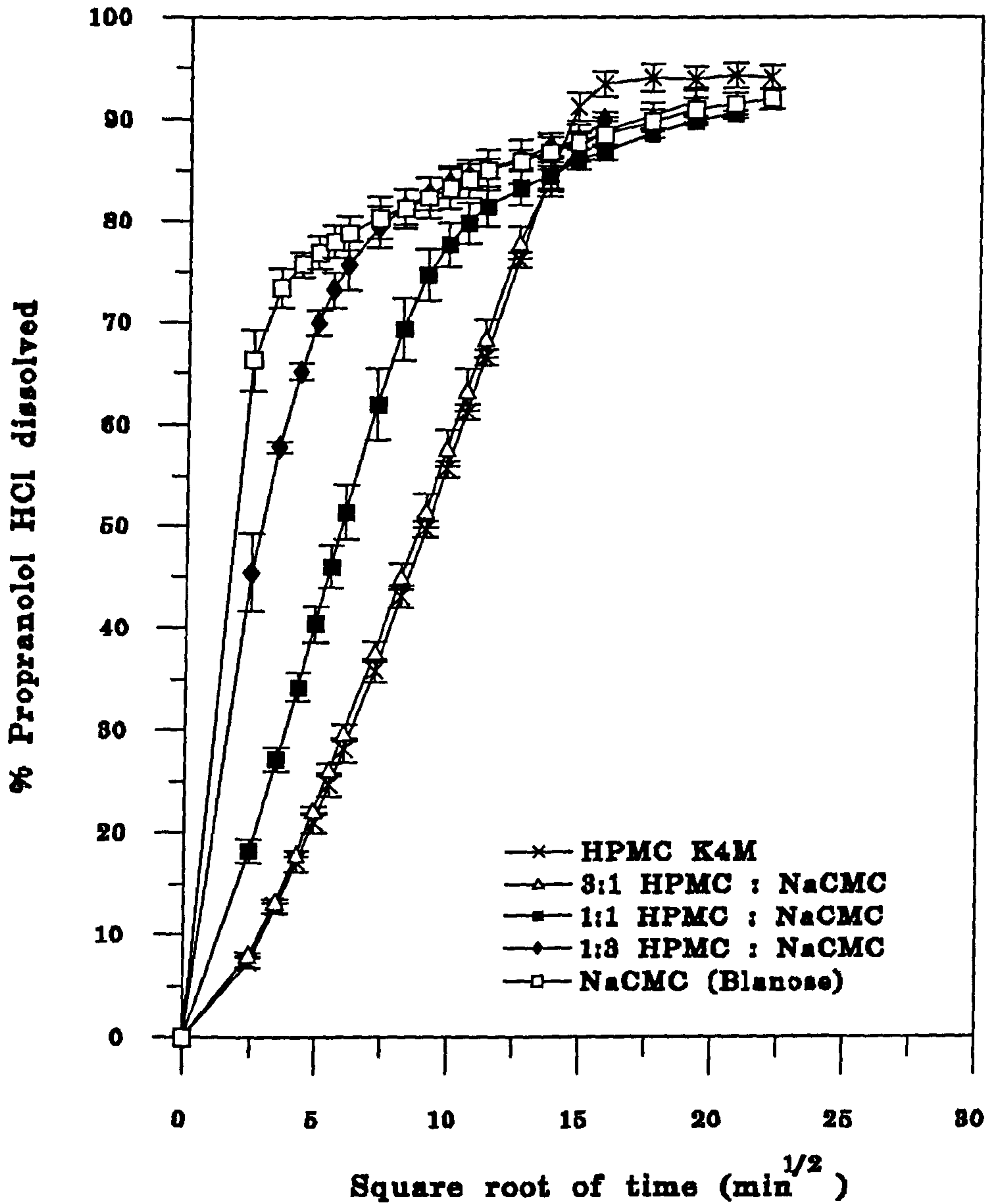


Figure 3.7: The effect of HPMC : NaCMC (Blanose) ratio on the release of propranolol hydrochloride from matrices containing 71 mg polymer. Results are the means  $\pm$  SD of 6 determinations.

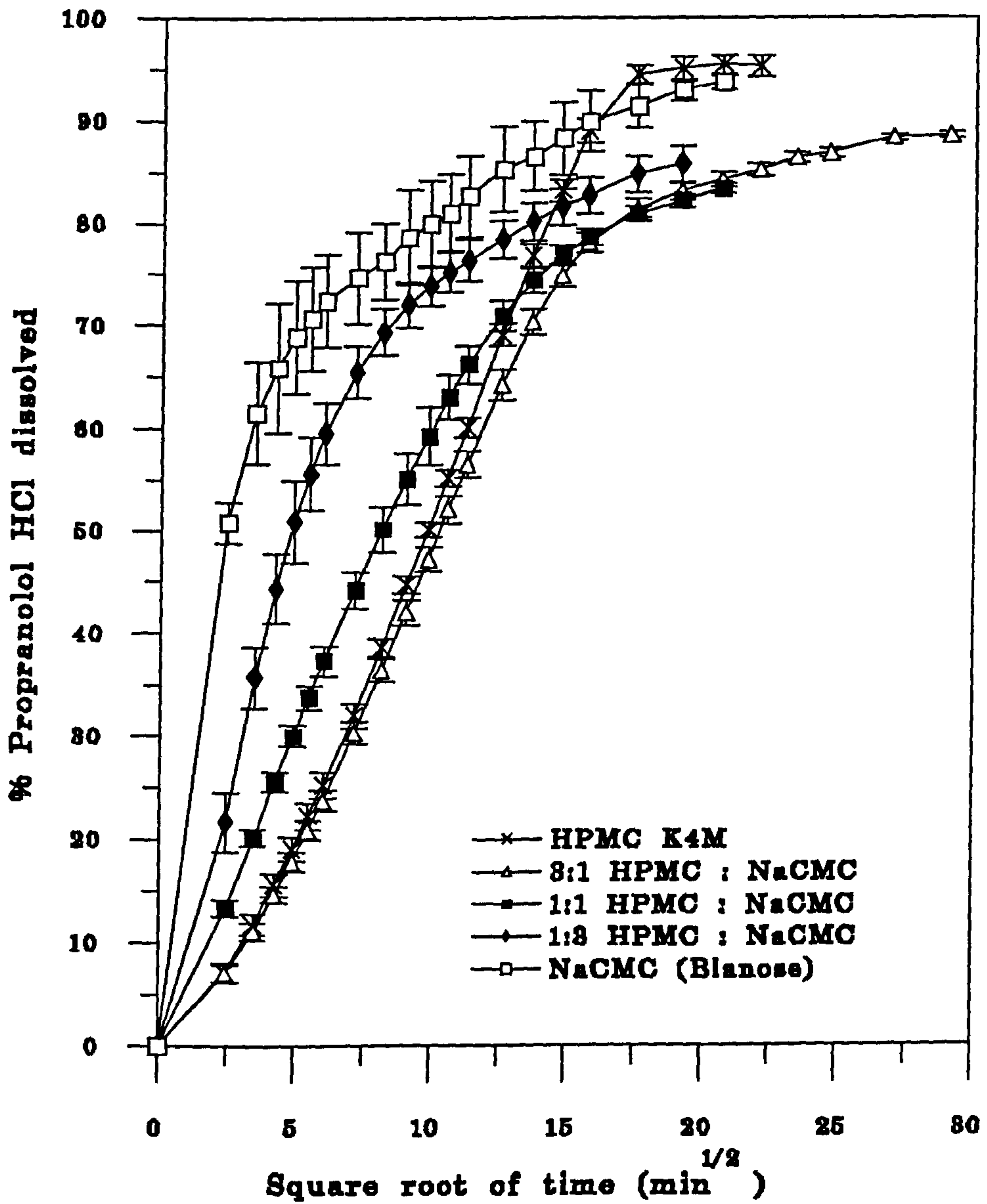




Figure 3.8: The effect of HPMC : NaCMC (Blanose) ratio on the release of propranolol hydrochloride from matrices containing 95 mg polymer. Results are the means  $\pm$  SD of 6 determinations.

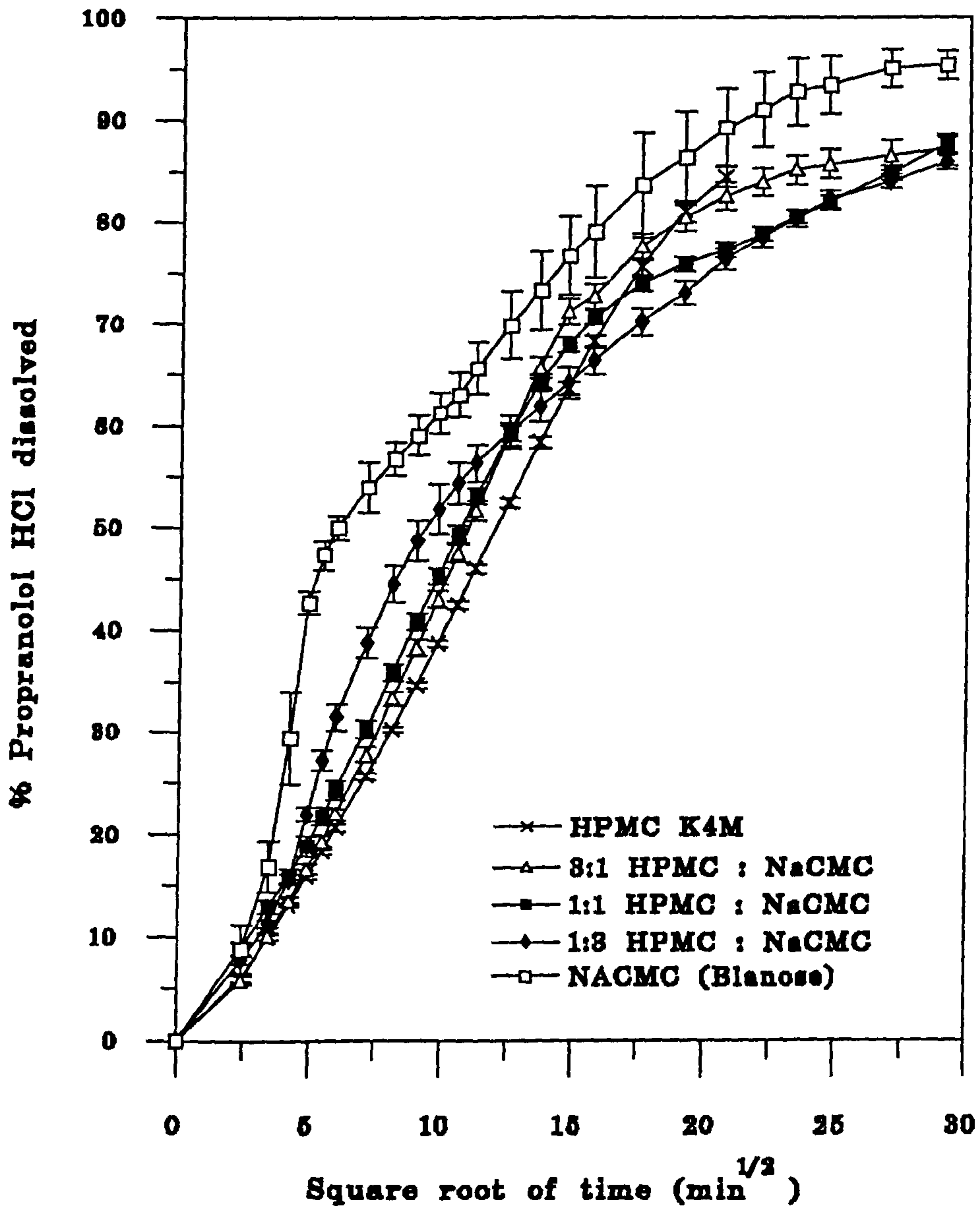


Figure 3.9: The effect of HPMC : NaCMC (Blanose) ratio on the release of propranolol hydrochloride from matrices containing 140 mg polymer. Results are the means  $\pm$  SD of 6 determinations.

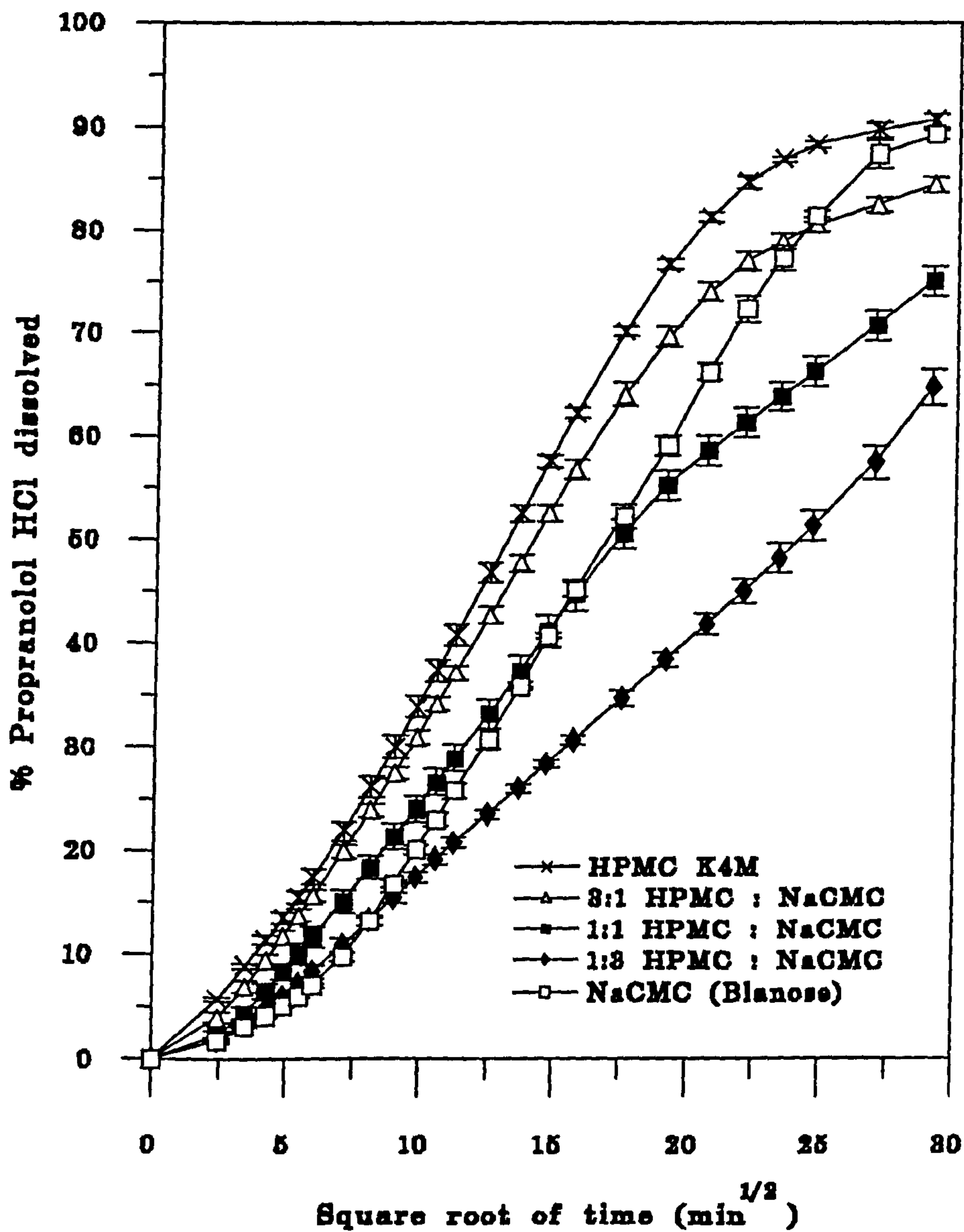
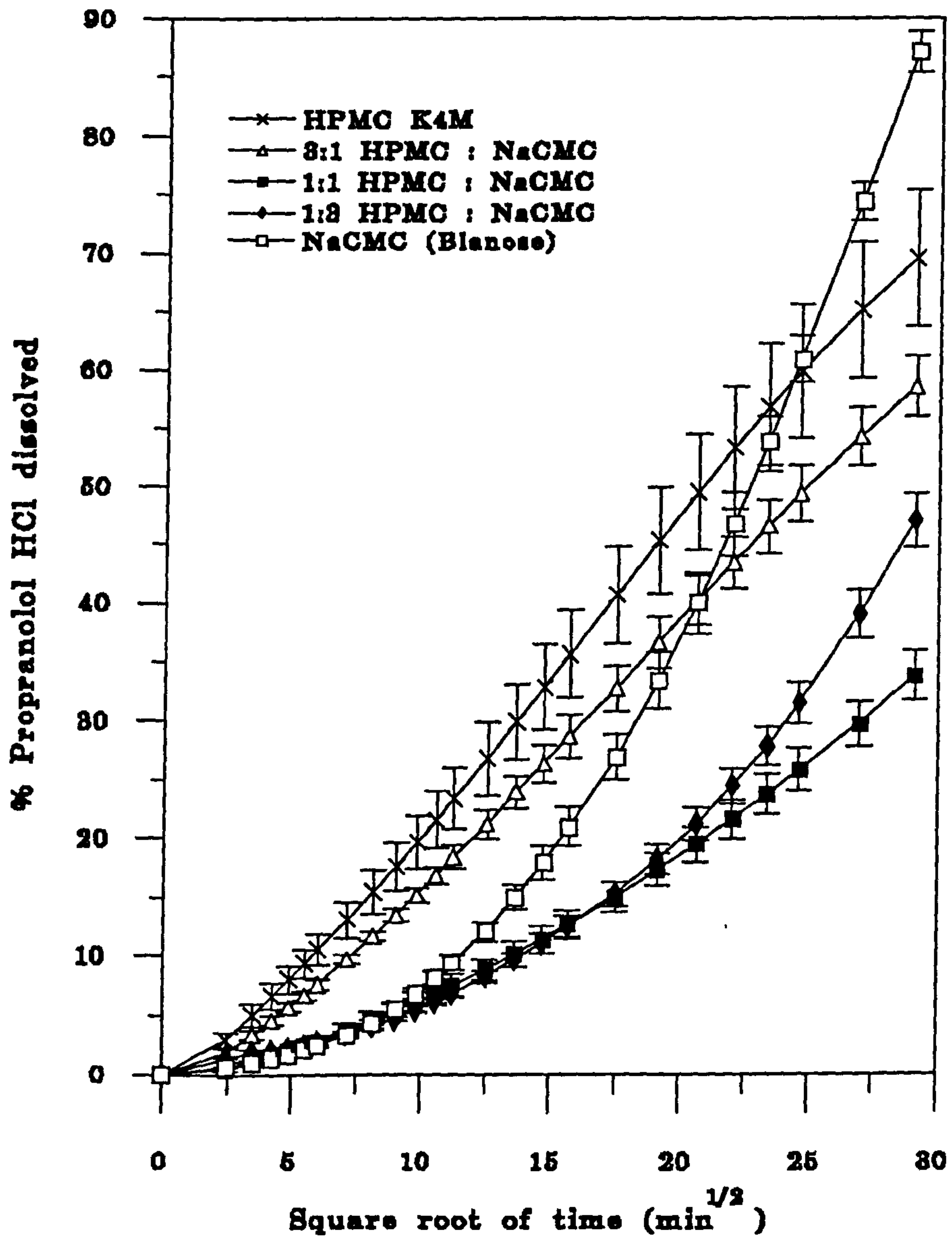


Figure 3.10: The effect of HPMC : NaCMC (Blanose) ratio on the release of propranolol hydrochloride from matrices containing 285 mg polymer. Results are the means  $\pm$  SD of 6 determinations.





between the cationic drug (propranolol hydrochloride) and the anionic NaCMC (Ranga Rao et al, 1990). A similar theory was proposed for the release of chlorpheniramine maleate from matrices containing NaCMC (Feely and Davis, 1988). Ranga Rao et al (1990), using propranolol hydrochloride (100 mg) incorporated in matrices containing HPMC and NaCMC (50 mg: 50 mg), reported that the release rate was much slower than matrices containing drug : HPMC (in ratio 1:1). This was attributed to a complex between propranolol hydrochloride and NaCMC.

Table 3.5 shows the values of  $K_1$  and  $n$ , from matrices containing different ratios of HPMC : NaCMC, calculated from the range of 5-60% drug release and based on equation 1.1. It can be seen in the table 3.5, the value of the release exponent ( $n$ ) is not related to the polymer content. The lowest value (0.33) was obtained for matrices containing 57 mg total polymer at the ratio of 1:3 HPMC : NaCMC. For other formulations, the value of  $n$  was greater than 0.52 indicating predominately diffusional release mechanisms (Ford et al, 1991). It is clearly apparent that by further increasing the proportion of the NaCMC, the value of  $n$  increased, a value of 1.07 being attained for HPMC : NaCMC (in the ratio 1:3) indicating near zero-order release. Ranga Rao et al (1990) reported a value of 0.2522 for matrices containing 100 mg propranolol and 100 mg polymer (1:1 HPMC : NaCMC).

Research efforts during recent years have focused on the design of zero-order delivery systems which will release drug at a constant, predetermined rate.

Table 3.5: Values of kinetic constants ( $K_1$ ), release exponents (n) for drug release between 5-60% release determined irrespective of curve shape, from matrices containing different ratios and different contents of HPMC and NaCMC (Blanose) based on equation 1.1

HPMC:NaCMC ratio	$K_1$	n
<u>75% HPMC:25% NaCMC</u>		
57 mg	2.45	0.69
71 mg	2.12	0.68
95 mg	1.90	0.68
140 mg	1.44	0.67
285 mg	0.91	0.62
<u>50% HPMC:50% NaCMC</u>		
57 mg	5.73	0.61
71 mg	5.48	0.53
95 mg	2.80	0.61
140 mg	1.39	0.62
285 mg	0.16	0.79
<u>25% HPMC:75% NaCMC</u>		
57 mg	25.30*	0.33*
71 mg	9.61	0.52
95 mg	4.14	0.55
140 mg	1.07	0.59
285 mg	0.035	1.07

\* This value is an approximation, due to the low number of data points.

In order to ascertain the zero-order release from matrices containing 285 mg of HPMC : NaCMC (Blanose), the drug release was alternatively evaluated by calculating the instantaneous release rate and plotting it as a function of time (figure 3.11). The matrix tablets containing HPMC alone had an initial burst release, whereas the release rates from those consisting of 1:3 HPMC : NaCMC (Blanose) did not change, confirming near zero-order release kinetics. Colombo et al (1992), using similar plots, interpreted the kinetics of drug release from matrices of different surface areas. They suggested that the least variable release rate indicated zero-order or near zero-order release.

Figure 3.12 is a three dimensional graph, for data based on equation 1.1, to illustrate the inter-relationships between the value of  $n$  (tables 3.2 and 3.3), HPMC and NaCMC (Blanose) content. As the NaCMC (Blanose) content increased, the value of  $n$  tended to increase. However, as the HPMC content increased, the value of  $n$  increased until a content of 95 mg after which increasing HPMC content did not affect its release exponent ( $n$ ).

Since matrices containing 285 mg of 1:1 HPMC and NaCMC (Blanose) gave the minimum release rate (table 3.1) and a high value of  $n$  (0.79) (table 3.5), the effects of NaCMC types on the release of propranolol hydrochloride from matrices containing HPMC : NaCMC P 800 and HPMC : NaCMC P 350 were investigated.



Figure 3.11: Instantaneous propranolol hydrochloride release rates versus time from matrices containing 285 mg different ratios of HPMC : NaCMC (Blanose). Results are the means  $\pm$  SD of 6 determinations.

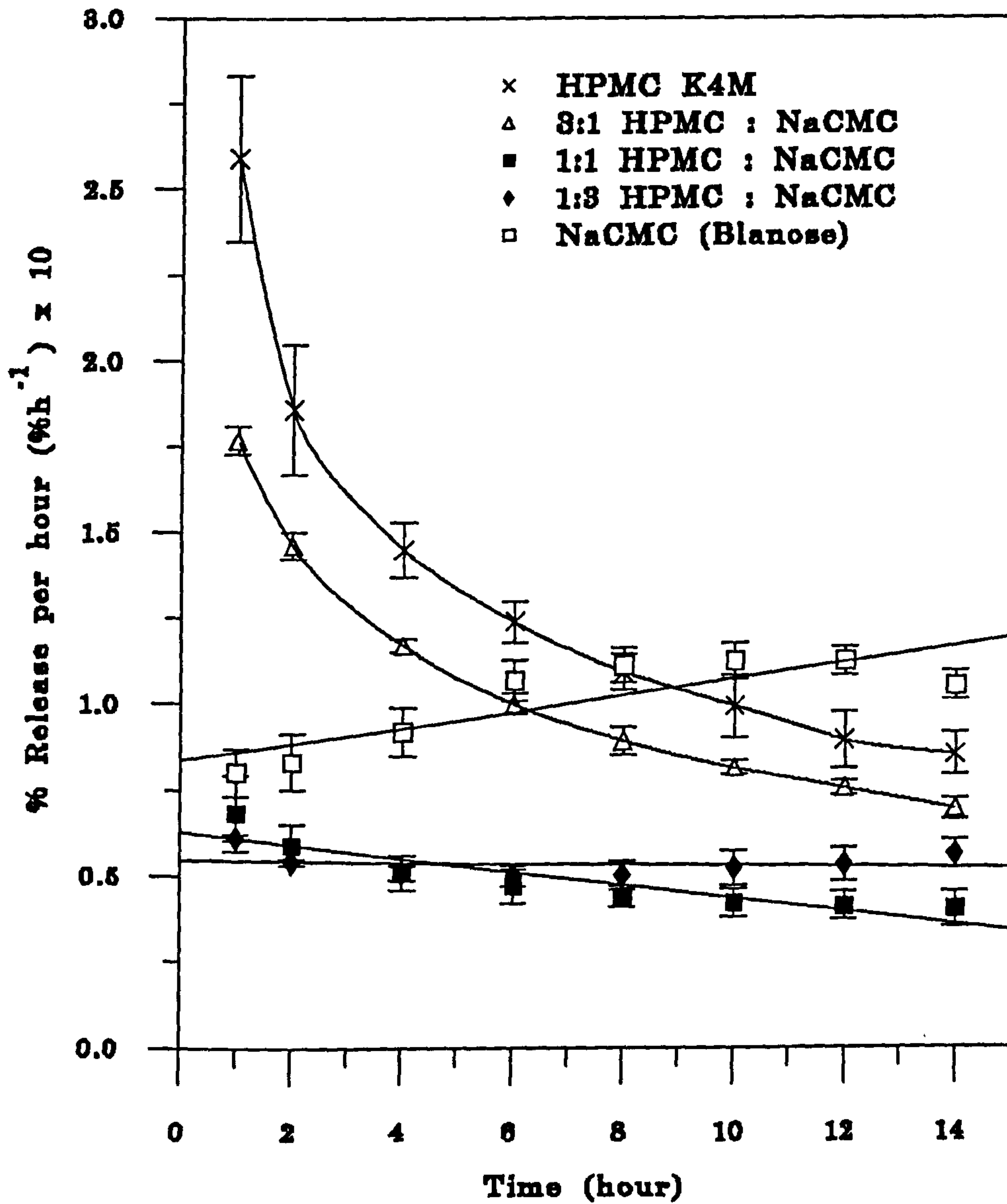
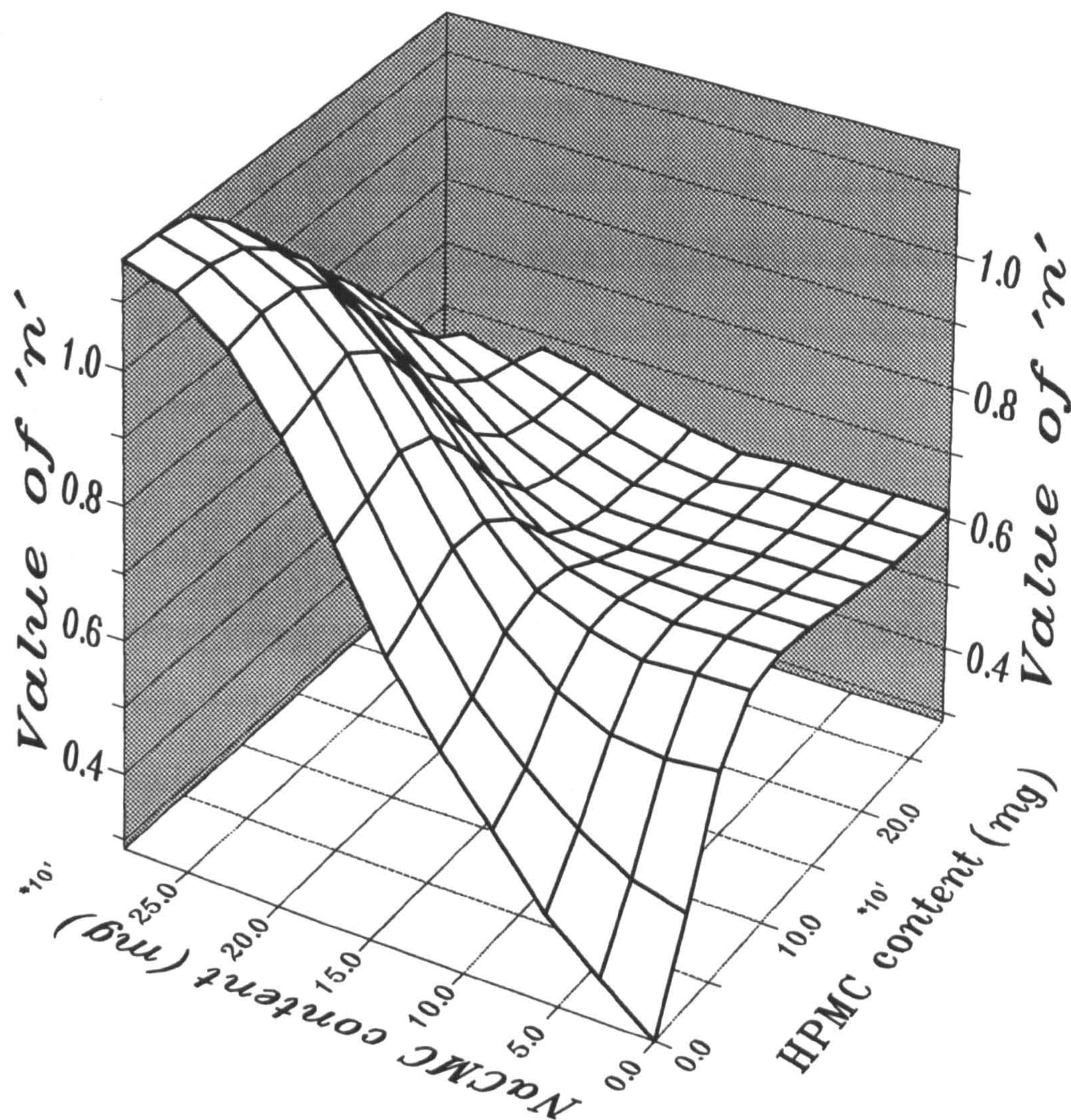




Figure 3.12: Three dimensional graph from values of release exponent ( $n$ ) based on equation 1.1, showing the relationship between HPMC and NaCMC (Blanose) content in the matrices





### 3.2.3.2 The effect of mixture of HPMC and different kinds of NaCMC on drug release

Figures 3.13, 3.14 and 3.15 show the release of propranolol hydrochloride from matrices containing 95 mg, 140 mg and 285 mg total polymer consisting of 1:1 HPMC : NaCMC (Blanose), HPMC : NaCMC P 800 or HPMC : NaCMC P 350 respectively. The release rates of all formulations and also the release kinetics and  $T_{50\%}$ s are shown in table 3.6. A comparison of figures 3.13, 3.14 and 3.15 indicates that as the polymer content increased the linearity of the curves for whole period of drug release increased and matrices tended to release their drug more slowly. For instance, the regression coefficients from 1:1 HPMC K4M : NaCMC (Blanose) were 0.865, 0.950 or 0.999 for matrices containing 95, 140 or 285 mg polymer respectively, by treating the data as a function of time.

The data in table 3.6 indicate that as the viscosity of NaCMC decreased the value of release exponent from matrices containing 285 mg total polymer decreased from 0.81 to 0.72, whereas this relationship between the viscosity of NaCMC and the release exponent was not observed for matrices containing less than 285 mg polymer content (57, 95 or 140 mg).

### 3.3 CONCLUDING REMARKS

The dissolution profiles of propranolol hydrochloride from HPMC-NaCMC matrices were very complicated. The results confirmed that the use of either HPMC or NaCMC alone could not provide a zero-order release of propranolol



Figure 3.13: Release of propranolol hydrochloride from matrices containing 95 mg total polymer consist of 1:1 HPMC K4M : different kinds of NaCMC as function of time. Results are the means  $\pm$  SD of 6 determinations.

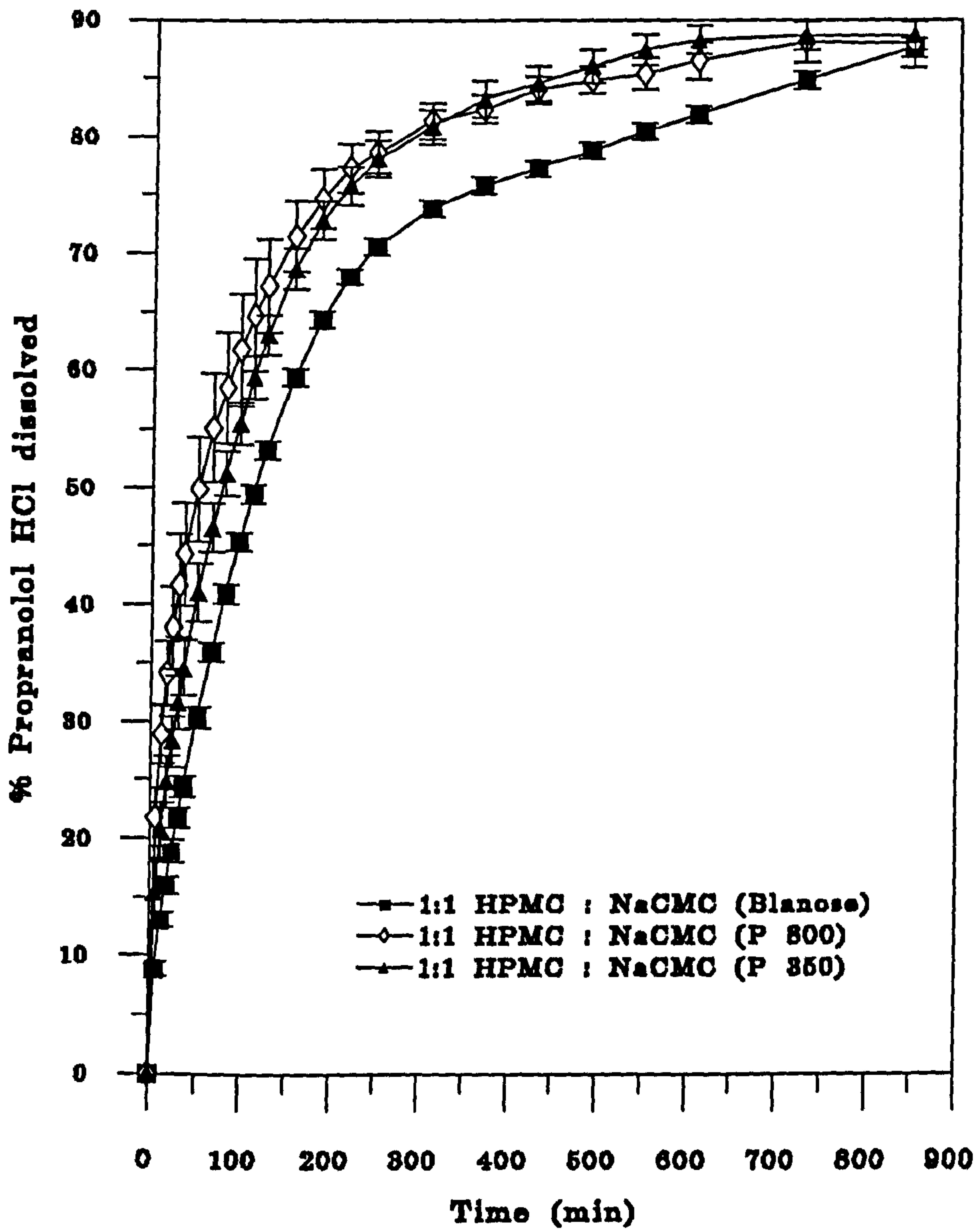


Figure 3.14: Release of propranolol hydrochloride from matrices containing 140 mg total polymer consist of 1:1 HPMC K4M : different kinds of NaCMC as function of time. Results are the means  $\pm$  SD of 6 determinations.

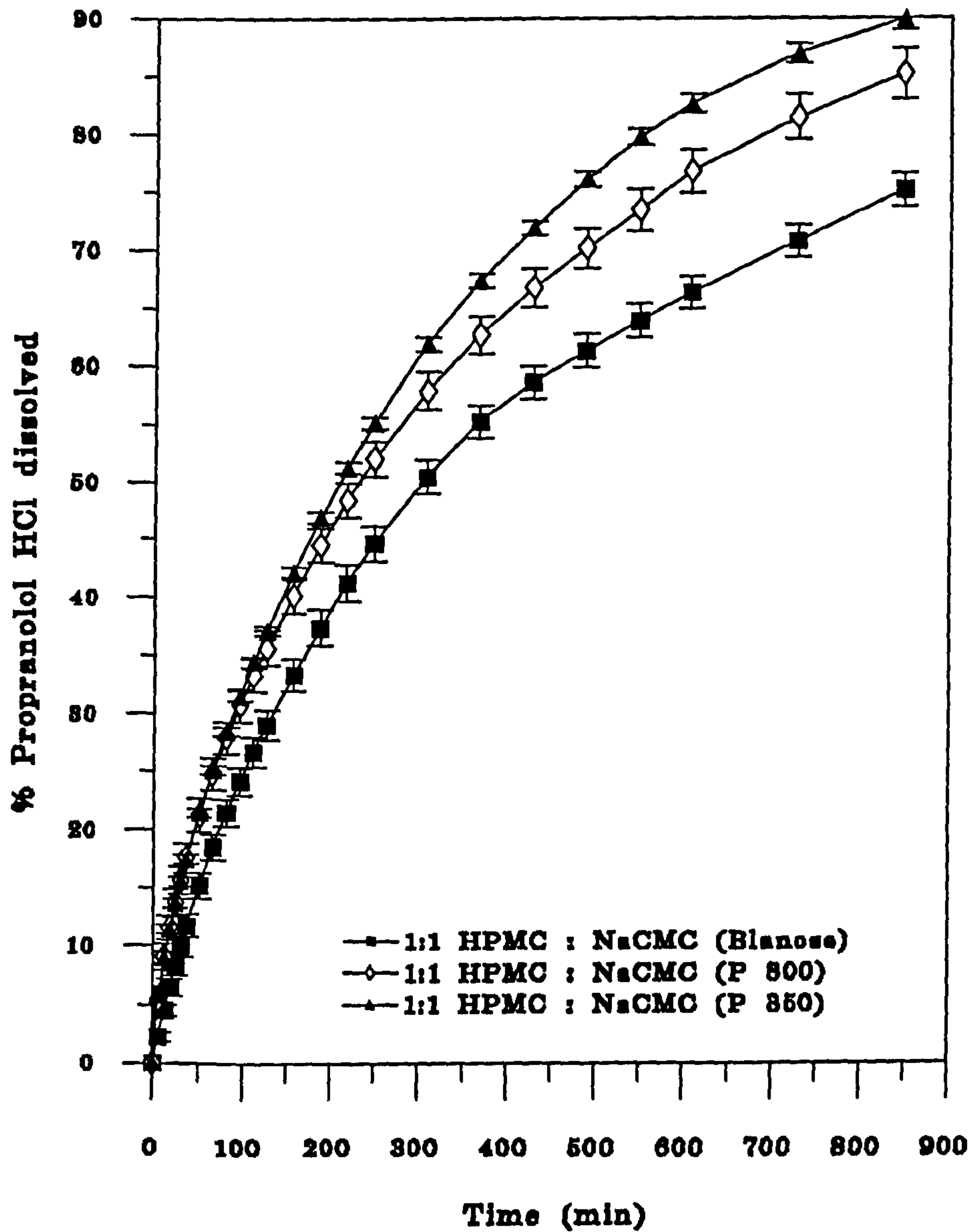


Figure 3.15: Release of propranolol hydrochloride from matrices containing 285 mg total polymer consist of 1:1 HPMC K4M : different kinds of NaCMC as function of time. Results are the means  $\pm$  SD of 6 determinations.

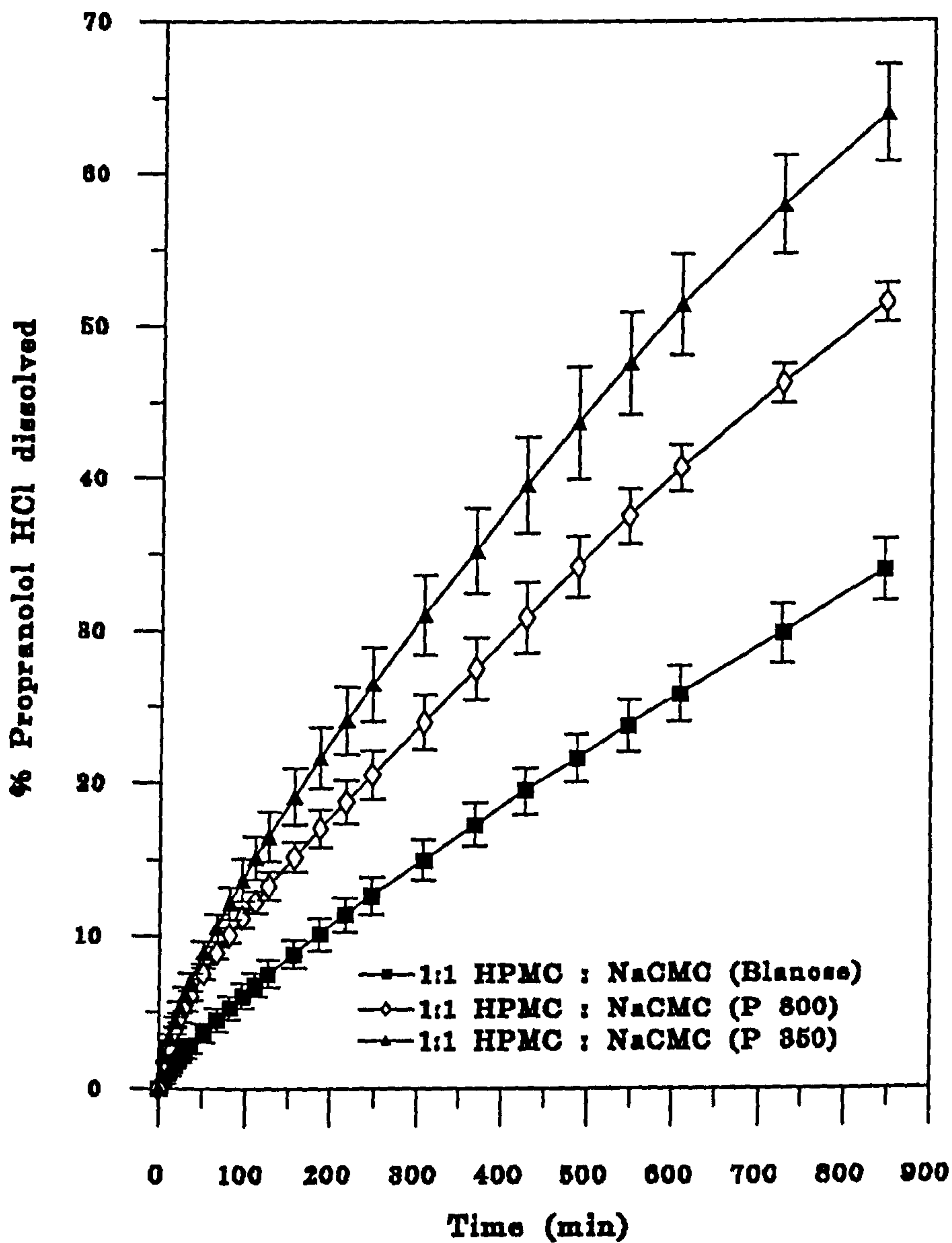




Table 3.6: Estimated values of release rates ( $\text{min}^{-1/2}$ ),  $T_{50\%}$  (minute),  $K_2$ , release exponent (n), I and ss (sums of squares) based on equation 1.2 for data corresponding to 5-60% drug release from matrices containing 1:1 HPMC K4M : different kinds of NaCMC. Results are the means  $\pm$  SD of 6 determinations

1:1 HPMC:NaCMC's ( mg)		Parameters						
		$T_{50\%}$ minute $\pm$ SD	Release rate $\text{min}^{-1/2} \pm$ SD	$K_2$	n	I	ss	
HPMC:Blanose	57	34.6 $\pm$ 3.5	9.7 $\pm$ 0.1	6.70	0.57	0.18	0.08	
	95	113.0 $\pm$ 3.1	5.1 $\pm$ 0.1	2.75	0.61	-0.37	2.38	
	140	300.7 $\pm$ 13.6	3.1 $\pm$ 0.0	1.76	0.58	8.67	7.07	
	285	1089.3 $\pm$ 66.1*	1.3 $\pm$ 0.1*	0.14	0.81	-6.37	0.04	
HPMC:P 800	57	11.6 $\pm$ 2.2	17.1 $\pm$ 2.4	20.70	0.39	1.60	0.08	
	95	59.6 $\pm$ 15.9	8.6 $\pm$ 1.1	13.50	0.34	1.92	0.68	
	140	229.1 $\pm$ 14.5	3.5 $\pm$ 0.1	2.66	0.54	2.64	1.34	
	285	752.1 $\pm$ 63.8	2.0 $\pm$ 0.1	0.28	0.77	-2.10	0.82	
HPMC:P 350	57	3.6 $\pm$ 0.1	15.5 $\pm$ 1.9	13.80	0.49	-0.46	0.26	
	95	4.0 $\pm$ 0.4	6.0 $\pm$ 0.2	5.83	0.49	-1.07	0.22	
	140	77.4 $\pm$ 9.8	3.7 $\pm$ 0.0	2.22	0.58	1.61	0.51	
	285	201.9 $\pm$ 36.2	2.2 $\pm$ 0.1	0.50	0.72	-2.07	1.07	

\* based on 5-35% released, because these matrices released 35% of drug during 14 hours.

hydrochloride and showed clearly that near zero-order release was only achievable within a narrow range of HPMC : NaCMC ratios.

The release rates from matrices consisting of NaCMC P 800 were slightly faster than Blanose and slower than P 350, indicating that the release rates were dependent on the viscosity grades of NaCMC. The rank order of drug release was NaCMC (Blanose) < NaCMC P 800 < NaCMC P 350. Admixture of HPMC with the different viscosity grades of NaCMC caused a decrease in the total release of propranolol hydrochloride. The effect of viscosity grade of NaCMC on drug release was clearly seen in figure 3.15.

Since the mechanisms of drug release from matrices consisting of HPMC and NaCMC appeared to be very complicated, it was necessary to characterize the properties of HPMC, NaCMC and their mixtures. This will be discussed in the next chapter.

# **CHAPTER 4 CHARACTERIZATION OF HYDROXYPROPYLMETHYLCELLULOSE, SODIUM CARBOXYMETHYLCELLULOSE AND THEIR MIXTURES**

## **4.1 INTRODUCTION**

As discussed in chapter 3, the release profiles from matrices containing HPMC, NaCMC or their mixtures were very complicated. Matrices containing HPMC showed Higuchian release; their release rates were linear with the square root of time. Matrices containing NaCMC gave different behaviour to HPMC. Although it is accepted that the viscosity grade of HPMC does not effect the release of soluble drugs (Ford et al, 1985a, b; Chenog et al, 1992), the viscosity grade of NaCMC had a pronounced effect on drug release. Since drug release from hydrophilic matrices, especially HPMC, is controlled by factors including the water distribution into the polymer (Ford and Mitchell, 1995), the extent of swelling (Rajabi-Siahboomi et al, 1993), the cloud point (Mitchell et al, 1993c) and the hydration process (Ford and Mitchell, 1995), it was considered necessary to study these parameters for HPMC, NaCMC and their mixtures.

### **4.1.1 Aims and objectives**

The purpose of the studies described in this chapter was to characterize HPMC, NaCMC and their mixtures by examining the viscosity of their aqueous solutions, the cloud points of their solutions, the water distribution



of their gels and the water uptake into their compressed wafers.

## 4.2 VISCOSITY

Viscosity is an expression of the resistance to flow of a system under an applied stress (Martin et al, 1983). The more viscous a liquid, the greater the applied force required to make it flow at a particular rate. Aqueous solutions of cellulose ethers display non-Newtonian behaviour and give rheological behaviour typical of linear polymers, i.e. the viscosity increases drastically with increase in the polymer concentration (Doelker, 1987). The viscosity of polymer solutions also depends on the molecular weight of the polymer (Alfrey, 1947; Doelker, 1987). The viscosity data from an aqueous solution can be used to obtain the molecular weight of material comprising the disperse phase (Martin et al, 1983) and also they provide a measure of the size or extension in space of the polymer molecules (Alfrey, 1947). However, due to the entanglement and association of polymer chains, aqueous solutions of high molecular weight cellulose ethers are shear-thinning, that is their apparent viscosities decrease with increase in rate of shear (Greminger and Krumel, 1980).

Viscosity is one of the most widely utilized characteristics for characterization of polymers and it is important to the design of many oral controlled release dosage forms (Doelker, 1987). Many types of viscometers have been discussed in detail by Martin et al (1983). Amongst them, the United States Pharmacopoeia / National Formulary (USP 23/NF 18, 1995) suggested a

capillary apparatus for determining the viscosity of solutions of methylcellulose or polymers.

## **4.2.1 Theoretical background**

### **4.2.1.1 Definitions and symbols**

Several coefficients of viscosity may be defined including dynamic viscosity, kinematic viscosity, specific viscosity, intrinsic viscosity and reduced viscosity.

The dynamic viscosity ( $\eta$ ) of a liquid is the tangential force on unit area of either of two parallel planes at unit distance apart when the space between the planes is filled with the fluid and one of the planes moves relatively to the other with unit velocity in its own plane (British Standard 188; 1975). Its Standard International (SI) unit is Poise (Pa.s.). The kinematic viscosity ( $\nu$ ) of a liquid may be defined as the dynamic viscosity divided by the density of the fluid ( $\rho$ ). Its SI unit is Stokes (St). The smaller units of dynamic and kinematic viscosities are centipoise (cP) and centistokes (cSt) respectively (Marriott, 1988).

By determining the viscosity at various concentrations ( $c$ ) and knowing the viscosity of the medium ( $\eta_0$ ), the specific viscosity ( $\eta_{sp}$ ), reduced viscosity (symbol  $\eta_{sp}/c$ ) and intrinsic viscosity ( $[\eta]$ ) (dL/g) of a polymer solution may be determined. Specific viscosities, may be calculated using equation 4.3 and the obtained results may be used to determine the other viscosities.

#### 4.2.1.2 Equations describing viscosity

The dynamic viscosity of a solution may be determined using equation 4.1 and U-tube viscometry (British Standard 188; 1975).

$$\eta = Ct \qquad \text{Equation 4.1}$$

where:  $\eta$  = the dynamic viscosity of the sample (cP),  $C$  = the viscometer constant and  $t$  = the flow time (seconds).

The specific viscosities,  $\eta_{sp}$ , may be calculated at any given polymer concentration using equation 4.2 (Arwidsson and Nicklasson, 1989; 1990):

$$\eta_{sp} = \frac{\eta}{\eta_o} - 1 = \frac{\eta - \eta_o}{\eta_o} \qquad \text{Equation 4.2}$$

Where:  $\eta$  = the dynamic viscosity of the polymer solution and  $\eta_o$  = the dynamic viscosity of solvent.

The reduced viscosity ( $\eta_{sp}/c$  or  $\eta_{red}$ ) can be calculated by dividing the specific viscosity by concentration. Extrapolation of reduced viscosities to zero concentration, gives the intrinsic viscosity which eliminates the effect of the buildup of the reduced viscosity due to intermolecular entanglements (Martin et al, 1983).

Alfrey (1947) suggested that the specific viscosity of a polymer solution can



be satisfactorily related to its concentration by the first two terms of a power series (Equation 4.3).

$$\eta_{sp} = a_1.c + a_2.c^2 \quad \text{Equation 4.3}$$

where the first coefficient,  $a_1$ , is ordinarily called the "intrinsic viscosity" and represented by the symbol  $[\eta]$ . The second coefficient,  $a_2$ , reflects the interaction among solute molecules and is related to the equation 4.4.

$$a_2 = k' [\eta]^2 \quad \text{Equation 4.4}$$

$k'$  is a Huggins interactions constant for a given chemical species of polymer in a given solvent and is independent of the molecular weight of the polymer.

The application of intrinsic viscosity ( $[\eta]$ ) and interaction constant  $k'$  has been suggested as a tool for selecting appropriate solvent mixtures for different polymers (Arwidsson and Nicklasson, 1989; 1990). The two parameters  $[\eta]$  and  $k'$  are both indirect means of measuring the ability of a solvent system to dissolve a polymer. Therefore, the intrinsic viscosity is high in "good" solvents and low in "poor" solvents (Alfrey, 1947). The value of  $k'$  gives an indication of the polymer-polymer and polymer-solvent interactions, such that a positive slope is produced for a polymer which interacts weakly with a solvent. The slope becomes less positive or sometimes negative with increase in interaction (Huggins, 1942; Mitchell et al, 1993c).

The intrinsic viscosity  $[\eta]$  and the interaction constant  $k'$  may be calculated by means of linear regression analysis of the data in a plot of reduced viscosity ( $\eta_{sp}/c$ ) versus polymer concentration according to equation 4.5, which is a modified form of equation 4.3 (Arwidsson and Nicklasson, 1989; 1990).

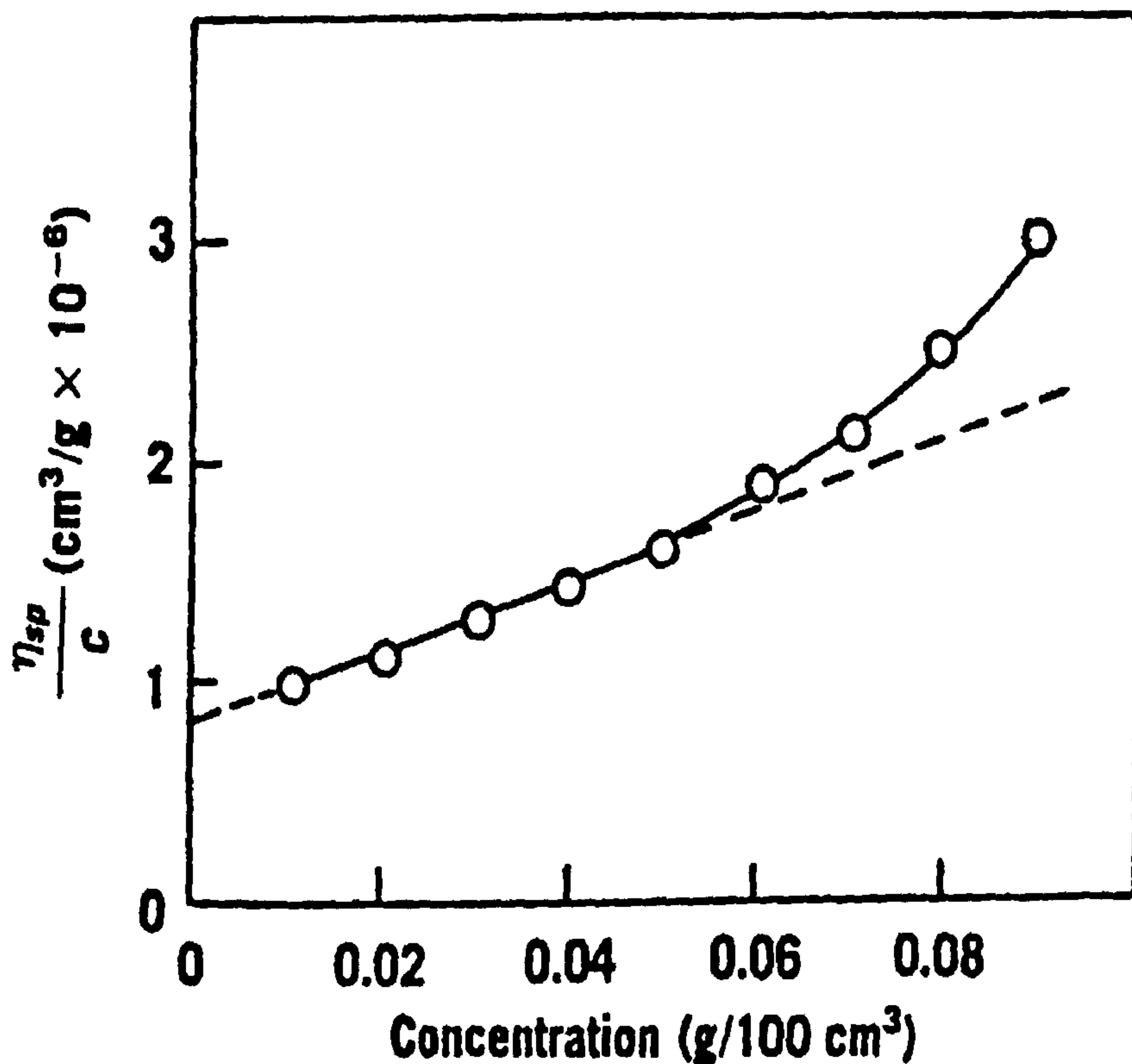
$$\eta_{sp}/c = \eta_{red} = [\eta] + k' [\eta]^2 c \quad \text{Equation 4.5}$$

In this equation,  $\eta_{sp}$  = specific viscosity,  $c$  = concentration (g/dL),  $[\eta]$  = intrinsic viscosity (dL/g) and  $k'$  = Huggins interactions constant.

Figure 4.1 shows a theoretical plot of reduced viscosity versus polymer concentration. Extrapolation of the plot to the ordinate-axis gives the intrinsic viscosity  $[\eta]$  and the Huggins interaction constant can be calculated by dividing the gradient by the square of the value obtained for the intrinsic viscosity (equation 4.4).  $k'$  and  $[\eta]$  are obtained on the understanding that this equation is valid at low concentrations only. The reduced viscosity can be represented by equation 4.6.

$$\frac{\eta_{sp}}{c} = \frac{\left(\frac{\eta}{\eta_0} - 1\right)}{c} \quad \text{Equation 4.6}$$

Figure 4.1: Typical plot of reduced viscosity versus concentration, showing that extrapolation to the ordinate-axis, gives the intrinsic viscosity of the polymer solution (after Martin et al, 1983).



## 4.2.2 Experimental

### 4.2.2.1 Solution preparation

The following gels were prepared and tested according to the methods described in section 2.2.1.1:

- low concentration gels containing 0.01, 0.02, 0.025, 0.03, 0.04 or 0.05% w/w of HPMC K4M, NaCMC or their 1:1 mixture,



- gels containing HPMC : NaCMC at ratios of 0.4 : 0.1, 0.3 : 0.2, 0.25 : 0.25, 0.2 : 0.3 or 0.1 : 0.4 (% w/w).

#### 4.2.2.2 Method of viscosity determination

The method described in section 2.2.1.2 for the determination of viscosity was used. The value of the kinematic viscosity of water, experimentally determined at 37°C using a U-tube grade A viscometer, was 0.710 cS. The dynamic and kinematic viscosities of water at 20°C were taken to be 1.0020 cP and 1.0038 cSt respectively (British standard 188, 1975).

### **4.2.3 Results and discussion**

#### 4.2.3.1 Viscosity of hydroxypropylmethylcellulose and sodium carboxymethylcellulose

Figure 4.2 shows the results of the kinematic, specific and reduced viscosities of HPMC gels. Figure 4.3 shows the reduced viscosities of gels containing NaCMC (Blanose), NaCMC (P 800) or NaCMC (P 350). The corresponding values and data obtained for kinematic and specific viscosities are presented in the table 4.1. As the concentration of HPMC or NaCMC increased, their kinematic and specific viscosities increased, whereas in the case of NaCMC gels the reduced viscosities showed different behaviour. The results of kinematic, specific and reduced viscosities of the different grades of NaCMC (Blanose, NaCMC P 800 and NaCMC P 350) showed that the viscosity ranked as Blanose > P 800 > P 350 which probably was due to differences in their

molecular weights. In contrast to HPMC gels, NaCMC gels, especially those containing NaCMC P 350, did not obey equation 4.5.

The deviation from linearity for the reduced viscosities of NaCMCs in figure 4.3 is probably due to the pseudoplastic nature of their gels (Kumar and Bankar, 1993; Doelker, 1987). Doelker (1987) reported that, because of entanglement and association of the polymer chains, aqueous solutions of cellulose ethers are pseudoplastic and their apparent viscosities decrease with increased rate of shear. This phenomenon is generally more pronounced at higher shear-rate conditions and for higher viscosity type materials (Doelker, 1987). However, solutions of the low-molecular-weight NaCMCs, have low viscosities and are less pseudoplastic than the solutions of high-molecular weight NaCMCs (Batdorf and Rossman, 1973).

The determination of the reduced viscosities of polymers is valid at low concentrations of polymer (Martin et al, 1983; Alfrey, 1947). This fact is clearly seen in table 4.1 in which the reduced viscosities of NaCMC (Blanose) at 0.03 and 0.04% w/w are similar, whereas their kinematic and specific viscosities have increased. The reduced viscosity of NaCMC P 350 decreased as the concentration increased above 0.03% w/w. Similar findings for gelatin were reported by Gautam and Schott (1994) who investigated the physicochemical properties of gelatin and reported that its reduced viscosity decreased as the concentration of polymer increased.

Figure 4.2: The effect of concentration on the kinematic, specific and reduced viscosities of HPMC K4M gels (results are the means  $\pm$  SD of three determinations)

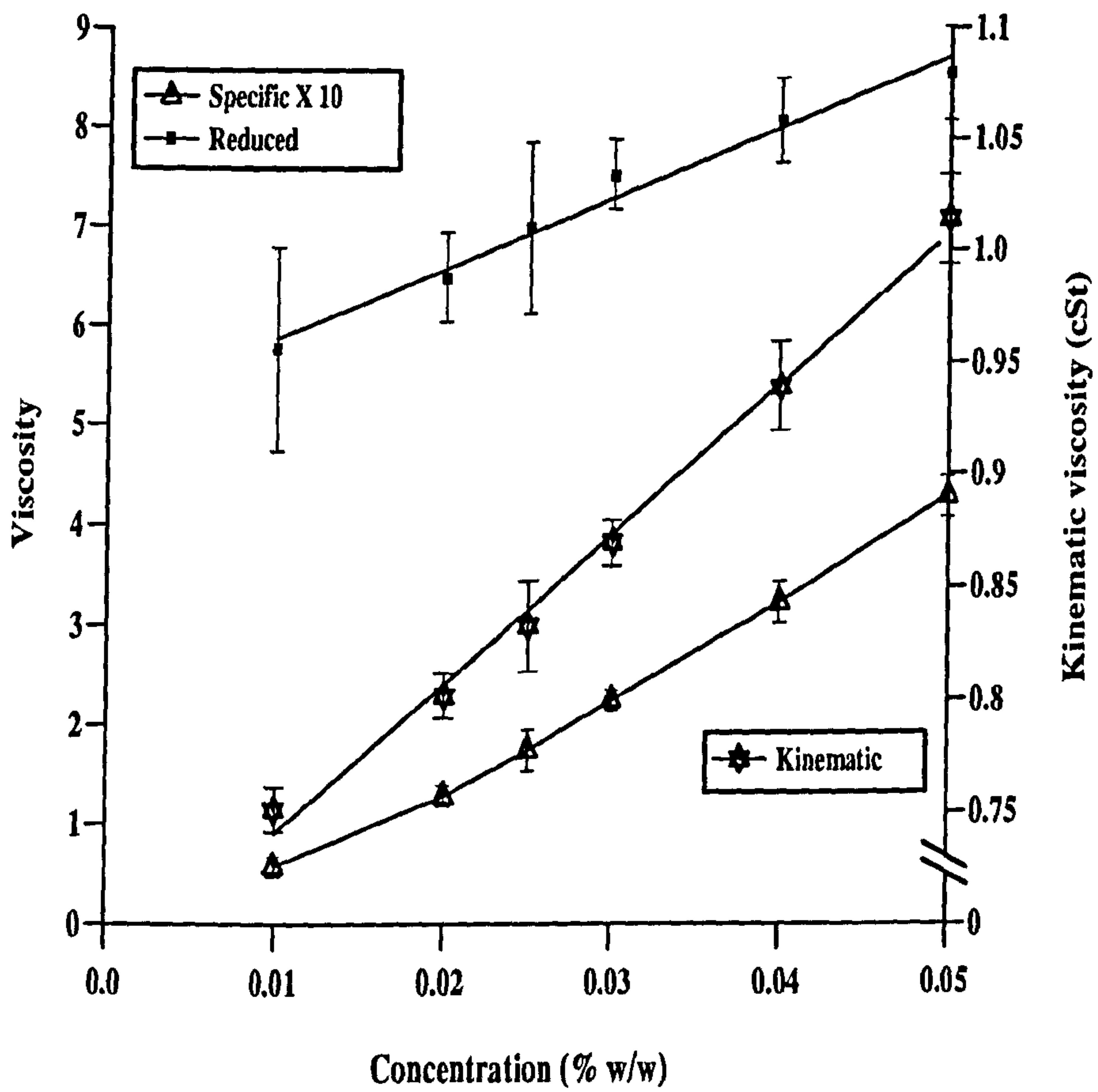




Figure 4.3: The effect of concentration on the reduced viscosities of gels containing NaCMC (Blanose), NaCMC (P 800) or NaCMC (P 350) obtained at 37°C (results are the means  $\pm$  SD of three determinations)

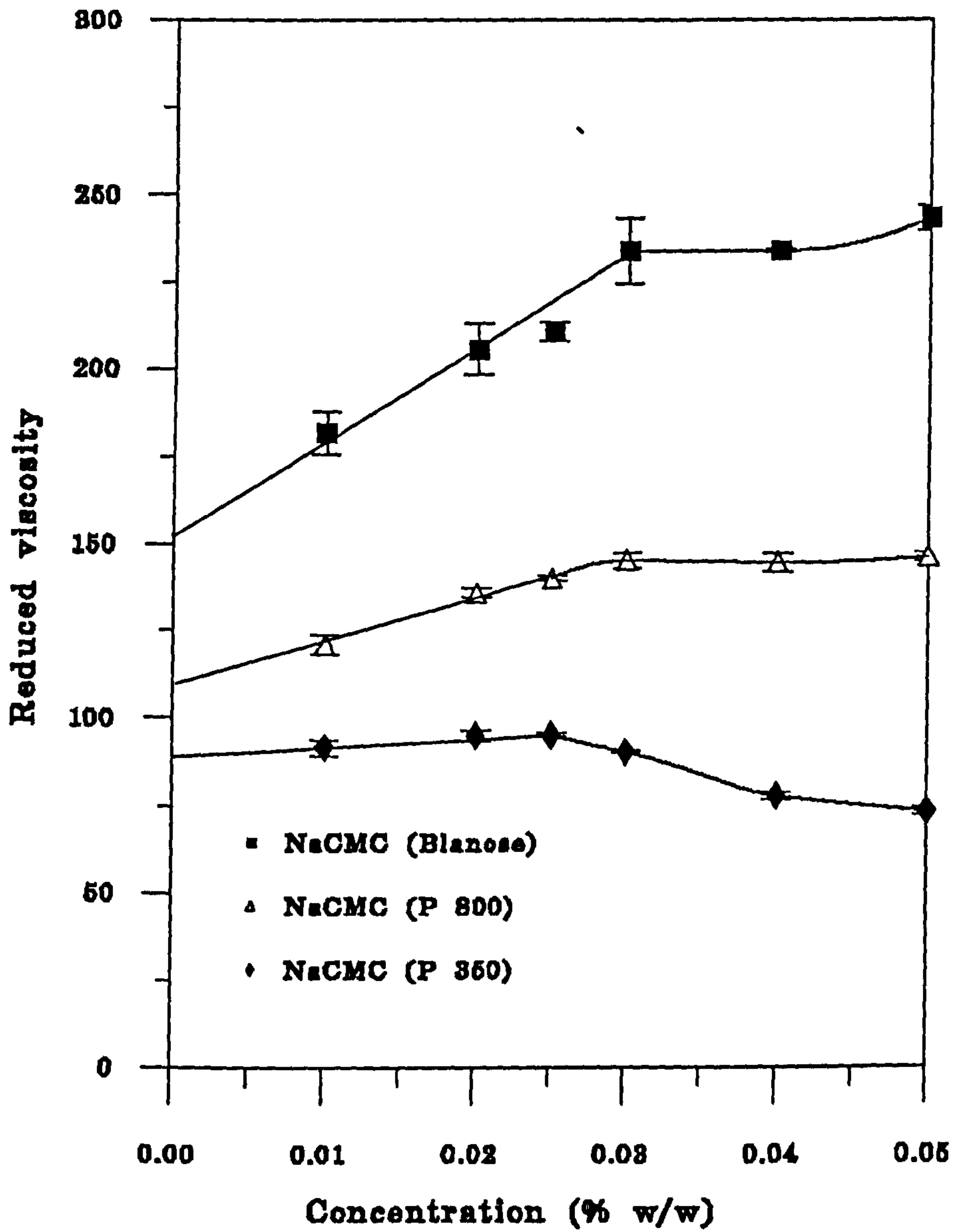


Table 4.1: The effect of concentration on the kinematic ( $\eta$ ), specific ( $\eta_{sp}$ ) and reduced viscosities ( $\eta_{sp}/c$ ) of NaCMC (Blanose), NaCMC (P 800) and NaCMC (P 350) obtained at 37°C (results are the means  $\pm$  SD of three determinations)

Con. % w/w	NaCMC (Blanose)			NaCMC (P 800)			NaCMC (P 350)		
	$\eta$ (cSt)	$\eta_{sp}$	$\eta_{sp}/c$	$\eta$ (cSt)	$\eta_{sp}$	$\eta_{sp}/c$	$\eta$ (cSt)	$\eta_{sp}$	$\eta_{sp}/c$
0.01	2.00 $\pm$ 0.04	1.8 $\pm$ 0.1	181.7 $\pm$ 6.2	1.57 $\pm$ 0.02	1.2 $\pm$ 0.2	121.1 $\pm$ 2.7	1.36 $\pm$ 0.02	0.9 $\pm$ 0.02	91.5 $\pm$ 2.3
0.02	3.63 $\pm$ 0.10	4.1 $\pm$ 0.1	205.6 $\pm$ 7.3	2.64 $\pm$ 0.02	2.7 $\pm$ 0.0	135.9 $\pm$ 1.3	2.06 $\pm$ 0.02	1.9 $\pm$ 0.03	95.1 $\pm$ 1.4
0.025	4.45 $\pm$ 0.05	5.3 $\pm$ 0.1	210.7 $\pm$ 2.8	3.20 $\pm$ 0.01	3.5 $\pm$ 0.1	140.3 $\pm$ 0.7	2.40 $\pm$ 0.01	2.4 $\pm$ 0.01	95.2 $\pm$ 0.6
0.03	5.69 $\pm$ 0.27	7.0 $\pm$ 0.4	233.8 $\pm$ 9.3	3.80 $\pm$ 0.04	4.4 $\pm$ 0.1	145.1 $\pm$ 2.1	2.63 $\pm$ 0.01	2.7 $\pm$ 0.01	90.1 $\pm$ 0.3
0.04	7.35 $\pm$ 0.02	9.4 $\pm$ 0.1	233.8 $\pm$ 0.7	4.82 $\pm$ 0.07	5.8 $\pm$ 0.1	144.4 $\pm$ 2.5	2.91 $\pm$ 0.03	3.1 $\pm$ 0.04	77.4 $\pm$ 1.0
0.05	9.19 $\pm$ 0.24	12.0 $\pm$ 0.3	243.1 $\pm$ 3.7	5.89 $\pm$ 0.05	7.3 $\pm$ 0.1	145.9 $\pm$ 1.3	3.30 $\pm$ 0.03	3.6 $\pm$ 0.05	73.0 $\pm$ 1.0

#### 4.2.3.2 Viscosity of mixed HPMC and NaCMC

Figure 4.4 shows the results of reduced viscosities of HPMC, NaCMC (Blanose) or their 1:1 mixture at low concentrations ( $\leq 0.05\%$  w/w). The results for the kinematic, specific and reduced viscosities of their 1:1 mixtures are presented in table 4.2. The estimates of the intrinsic viscosities and Huggins constants from gels containing HPMC K4M, the three kinds of NaCMC and the mixture of 1:1 HPMC and NaCMC (Blanose), which were calculated from the linear portions of figures 4.3 and 4.4 can be seen in table 4.3.

The data in table 4.3 indicate that the value of  $k'$  for the 1:1 mixture was intermediate between HPMC and NaCMC. Arwidsson and Nicklasson (1989) reported that the low values for interaction constant,  $k'$ , indicate that a low interaction between polymer and solvent. So, these data confirm that the NaCMC could absorb water more readily than HPMC, or in other words, it would appear that water is a better solvent for NaCMC than HPMC K4M or their 1:1 mixture. Alternatively Marriott (1988) reported that a positive slope was produced for a polymer which interacted weakly with the solvent. Therefore, the high value for the NaCMC slope in table 4.3 again implies that water is a desirable solvent for NaCMC. Amongst three different kinds of NaCMC, NaCMC P 350 gave the lowest value of  $k'$  (0.033) calculated from linear portion of its curve (figure 4.3).

At low concentrations ( $\leq 0.05\%$  w/w) of the polymers (figure 4.4), the reduced viscosities of the 1:1 mixtures were intermediate between the reduced



Figure 4.4: The effect of concentration on the reduced viscosities of gels containing HPMC K4M, NaCMC (Blanose) or their 1:1 mixture obtained at 37°C (results are the means  $\pm$  SD of three determinations)

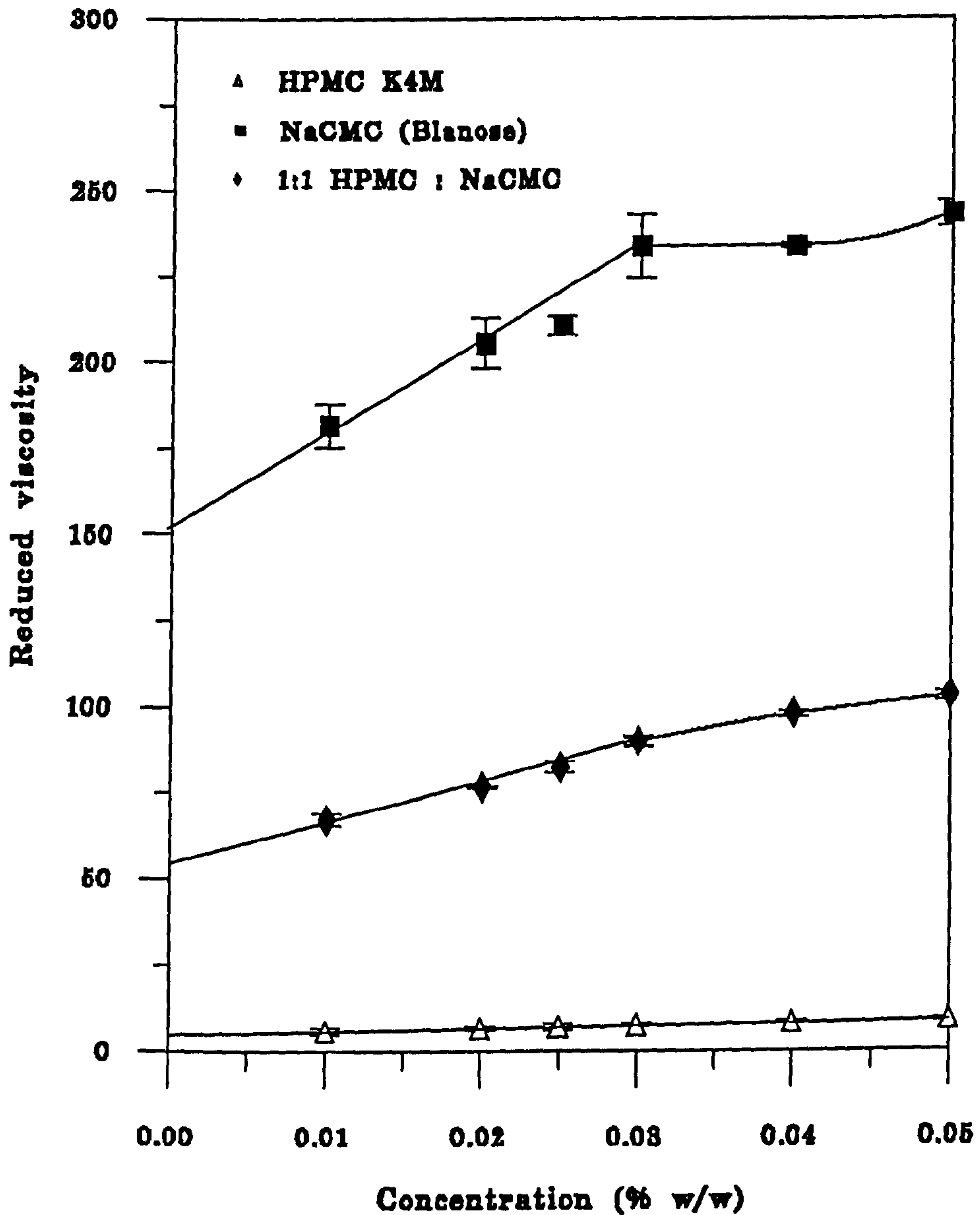


Table 4.2: The kinematic ( $\eta$ ), specific ( $\eta_{sp}$ ) and reduced viscosity ( $\eta_{sp}/c$ ) of the 1:1 HPMC : NaCMC (Blanose) mixture at 37°C (results are the means  $\pm$  SD of three determinations)

1:1 HPMC : NaCMC Concentration (% w/w)	$\eta$ (Centistoke)	$\eta_{sp}$	$\eta_{sp}/c$
0.01	1.19 $\pm$ 0.01	0.67 $\pm$ 0.02	67.10 $\pm$ 1.56
0.02	1.80 $\pm$ 0.01	1.53 $\pm$ 0.01	76.53 $\pm$ 0.33
0.025	2.17 $\pm$ 0.03	2.06 $\pm$ 0.04	82.25 $\pm$ 1.59
0.03	2.62 $\pm$ 0.02	2.69 $\pm$ 0.04	89.57 $\pm$ 1.07
0.04	3.48 $\pm$ 0.03	3.90 $\pm$ 0.04	97.53 $\pm$ 1.00
0.05	4.35 $\pm$ 0.05	5.13 $\pm$ 0.07	102.63 $\pm$ 1.46

viscosities of the individual polymers. This would tend to indicate a lack of interaction between the polymer molecules in dilute solutions, because both polymers, in solution, are separated and are unable to interact together.

When the concentrations of polymers were increased, between 0.1 - 0.5% w/w, the 1:1 mixtures had higher reduced viscosities than either of the pure polymers. The reason for the increase in reduced viscosity might be due to

**Table 4.3: The intrinsic viscosity  $[\eta]$ , gradient and interaction constant,  $k'$ , for HPMC K4M, NaCMC (Blanose) and their 1:1 mixture and also NaCMC P 800 or NaCMC P 350 at 37°C**

Polymer	$[\eta]$ (dL/g)	gradient	$k'$
HPMC K4M	5.16	70.9	2.663
NaCMC (Blanose)	156.00	2445.0	0.100*
1:1 HPMC:Blanose	59.10	920.0	0.263
NaCMC P 800	108.00	1309.0	0.112*
NaCMC P 350	89.10	263.0	0.033*

\* From linear portions of plots in figure 4.3 (0.01 to 0.03% w/w)

interaction between the two polymers, especially since the carboxyl groups of CMC may promote stronger hydrogen bonding between the carboxyl groups on NaCMC and the hydroxyl groups on the HPMC (Walker and Wells, 1982). The data in table 4.4, show the increase in viscosity when admixtures of the two polymers were examined at higher concentrations. As the NaCMC concentrations in gels containing admixtures with HPMC increased, the viscosities increased more than anticipated, indicating a synergistic increase in viscosity. For instance, gels containing 0.1% w/w HPMC or 0.4% w/w NaCMC (Blanose) had reduced viscosities of 8.1 and 303.9 respectively



Table 4.4: The reduced viscosities of HPMC K4M, NaCMC (Blanose) and their mixtures at 37°C (results are the means  $\pm$  SD of three determinations)

Polymer	Concentration (% w/w)					
	0.1	0.2	0.25	0.3	0.4	0.5
HPMC K4M	8.1 $\pm$ 0.1	11.3 $\pm$ 0.1	12.9 $\pm$ 0.1	16.2 $\pm$ 0.1	22.1 $\pm$ 0.2	31.9 $\pm$ 0.1
NaCMC (Blanose)	105.3 $\pm$ 0.9	164.1 $\pm$ 1.1	201.1 $\pm$ 0.2	229.4 $\pm$ 0.3	303.9 $\pm$ 0.6	484.7 $\pm$ 0.2
	Ratio of HPMC:NaCMC (Blanose) % w/w					
Mixture of HPMC:NaCMC	0.4 : 0.1	0.3 : 0.2	0.25 : 0.25	0.2 : 0.3	0.1 : 0.4	
	137.3 $\pm$ 0.9	219.6 $\pm$ 1.2	303.8 $\pm$ 3.3	368.1 $\pm$ 1.6	483.6 $\pm$ 1.5	

whereas, their mixture had a reduced viscosity of 483.6 (table 4.4) which is about 55% higher than the sum of their individual viscosities.

Walker and Wells (1982) reported that when HPMC was blended with NaCMC a synergistic effect occurred whereby the resultant viscosity was considerably higher than anticipated. Doelker (1987) stated that although NaCMC was macroscopically compatible with nonionic cellulose ethers, it does interact with them, so that a synergistic effect on viscosity is observed. Mannion et al (1990), showed that there was good agreement between predicted and observed values of viscosities of aqueous solutions of HPMC and NaCMC. They considered that the enhanced viscosity observed in their mixtures might be explained in terms of coil expansion of the anionic polymer.

### 4.3 CLOUD POINTS OF GELS CONTAINING HYDROXYPROPYLMETHYLCELLULOSE, SODIUM CARBOXYMETHYLCELLULOSE OR THEIR MIXTURE

#### **4.3.1 Theoretical background**

Lapidus and Lordi (1968) reported that the hydration of cellulose ethers is affected by temperature. In solution at lower temperatures, molecules are hydrated and there is little polymer-polymer interaction other than simple entanglement (Sarker, 1979). As the temperature increases, the polymer loses its water of hydration and at the same time the relative viscosity decreases.

Eventually, when a sufficient but not complete dehydration of the polymer occurs, a polymer-polymer association takes place and the system approaches an infinite network structure reflected by a sharp rise in relative viscosity (Sarker, 1979). Gelation of methylcellulose or HPMC in solution is primarily caused by hydrophobic interactions between molecules containing methoxyl substitution. The temperature at which this occurs is known as the thermal gelation point (TGP) (Sarker, 1979). Another phenomenon observed in HPMC gels with increase in their temperature is a precipitation of the polymer molecules. This property may be measured by light transmission (Mitchell et al, 1990b).

Sarker (1979) showed that when the temperature of a methylcellulose solution increased, the light transmission remained at 100% until at some elevated temperature, it began to decrease with increasing temperature. Sarker (1979) defined the temperature at which light transmission reached 97.5% and 50% of its optimal value as incipient precipitation temperature (IPT) and cloud point (CP), respectively. The cloud point may also be defined as the lowest temperature at which turbidity is developed when a dilute solution of a polymer is heated slowly (Klug, 1971).

The thermal gelation of Methocel polymers is the most interesting of its unique properties and are due to the modifications made to the celluloses during their manufacturing (Van Coillie, 1989). The uniqueness of this property comes from the reversibility of the thermal gelation process when



aqueous solutions of either methylcellulose or HPMC are heated (Sarker, 1979). The reversibility of thermal gelation also has been called sol-gel transformation which would occur within a narrow range of temperature.

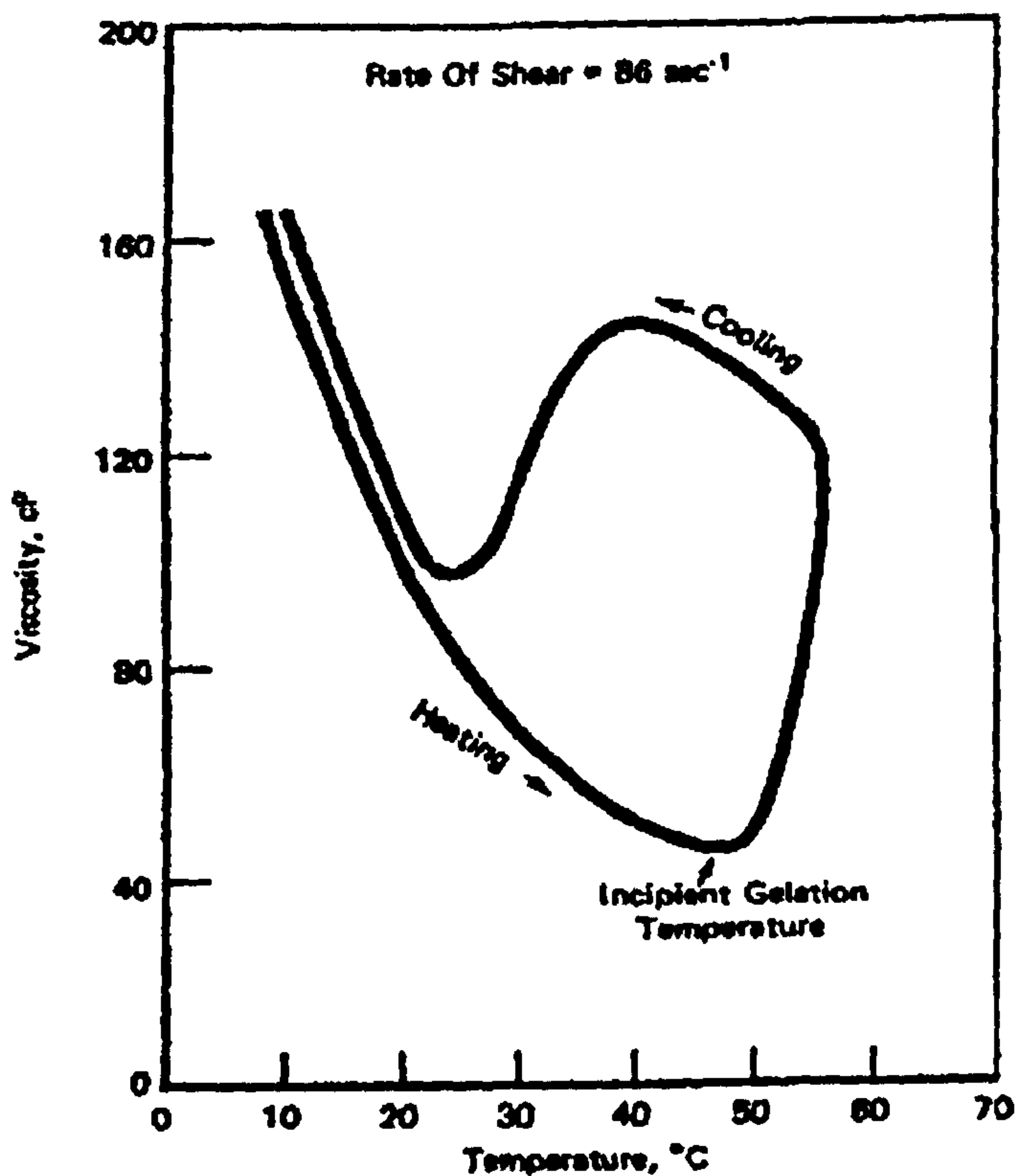
Figure 4.5 shows a typical relationship between viscosity and temperature for a methylcellulose solution during the sol-gel transformation. When the temperature is increased, the viscosity of the solution decreases until the temperature reaches the incipient gelation temperature (IPT) at which there is a sharp rise in viscosity, indicating gelation (Sarker, 1979). The gel remains as long as the temperature is kept high enough. On the other hand, the cooling curve looks quite different. Viscosity and other properties alternatively return to those of the starting solution. This process is reversible on cooling resulting in a solution with the original viscosity (Klug, 1971).

The mechanisms involved in this phase separation phenomenon are the emergence of interactions between polymeric chains and the weakening of hydrogen bonding between the water molecules and polymers (Doelker, 1987). Sarker (1979) confirmed that hydroxypropyl group in HPMC is responsible for producing the cloud point and reported that at low concentrations of HPMC it is possible to produce a turbid solution before gelation occurs whilst at higher concentrations a gel is produced before turbidity.

Mitchell et al (1990b) demonstrated that factors such as the cloud point of the

cellulose ether, the type of ether and gel strength, may influence the performance and properties of gels containing HPMC or methylcellulose. Additionally there are similar reports by Fagan et al (1989) and Klug (1971), but there are no published works, known to the author, which demonstrate the effect of temperature on gels containing HPMC and NaCMC. Therefore the aim of this part of work was to study the effect of temperature on the cloud points of gels containing HPMC and NaCMC and compare them.

Figure 4.5: Gelation behaviour of a 2% w/v aqueous solution of methylcellulose (Methocel A100) on heating at 0.25°C / minute as measured by changes in dynamic viscosity with temperature (after Sarker, 1979).



## **4.3.2 Experimental**

### **4.3.2.1 Gel preparation**

Gels containing 0.5, 1, 1.5, 2, 3, 4 and 5% (w/w) HPMC K4M, NaCMC (Blanose) or their 1:1 mixtures were prepared as described in section 2.2.1.1.

### **4.3.2.2 Cloud point determination**

The cloud points of the gels were determined by the methods described in section 2.2.1.3.

## **4.3.3 Results and Discussion**

### **4.3.3.1 Cloud points of HPMC K4M and NaCMC (Blanose)**

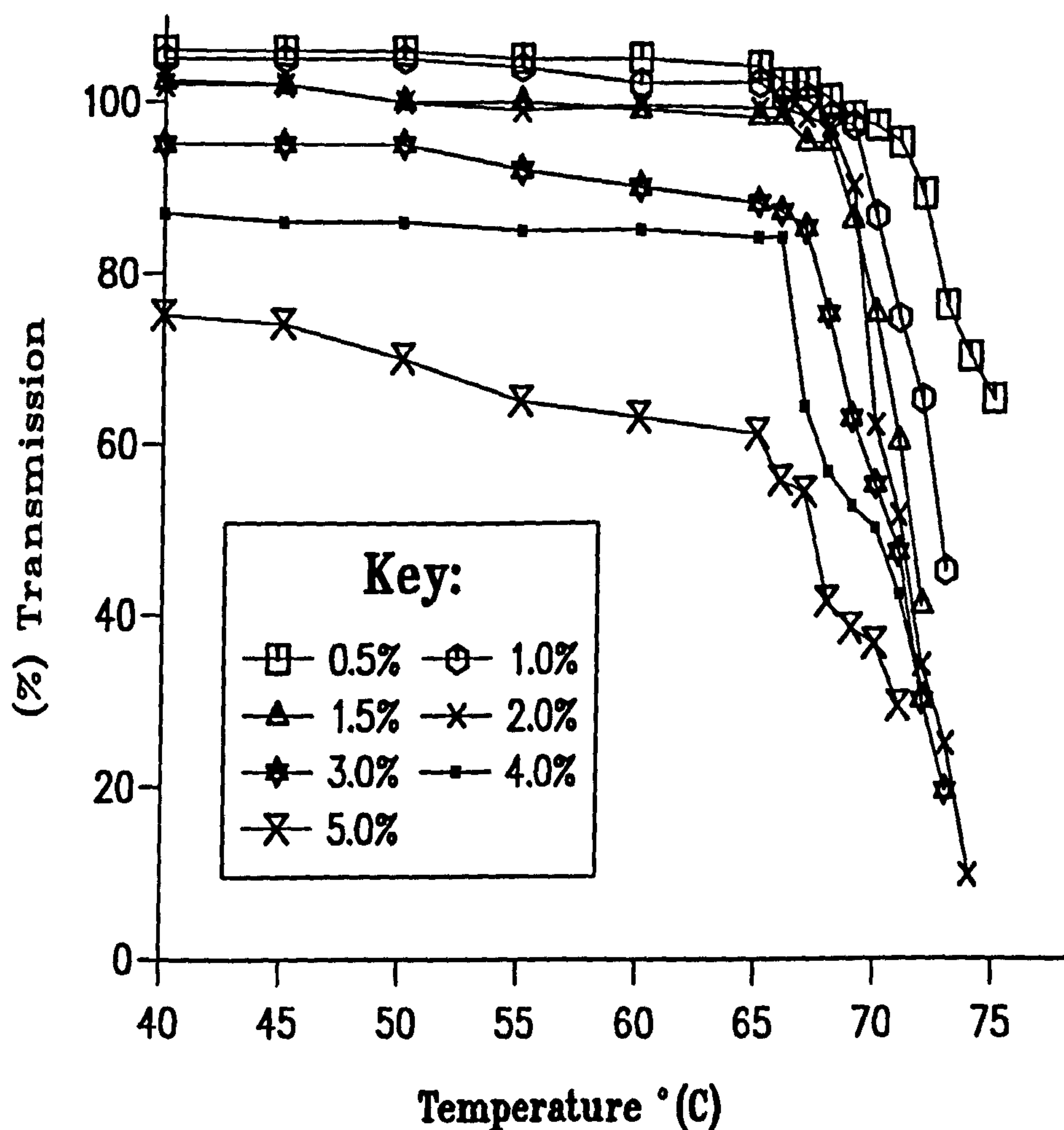
Figure 4.6 shows the effect of temperature on the light transmission of gels containing between 0.5 and 5% w/w HPMC K4M. When the temperature increased, the light transmission of HPMC gels decreased and a precipitation was observed. Table 4.5 shows the values of cloud point of the gels. As seen in table 4.5, there was a difference of more than 8°C between the cloud points of gels containing 0.5 and 5% w/w of HPMC.

The light transmission of gels containing up to 5% NaCMC (Blanose) remained unchanged with increase in the temperature up to 50°C. As the temperature increased above 50°C, in contrast to HPMC gels, the light transmission increased to in excess of 100%. As the concentration of NaCMC in the gels increased, the observed light transmission became lower. A



maximum light transmission of 132% was observed at 75°C, for gels containing 0.5% w/w. At this temperature the light transmission for gels containing 5% was 105%.

Figure 4.6: The effect of temperature on the light transmission of gels of different concentrations of HPMC K4M (results of at least 3 readings)



**Table 4.5: Effect of concentration on the cloud point temperatures of HPMC K4M gels (results are obtained from at least 3 tests)**

<b>Concentration (%w/w)</b>	<b>Cloud Point (°C)</b>
0.5%	> 75°C
1%	72 - 73
1.5%	71 - 72
2%	71 - 72
3%	70 - 71
4%	70
5%	67 - 68

The possible reason for the increase in light transmission is that the methoxyl substitution is responsible for gelation, and the hydroxypropyl substitution is also responsible for altering the gelation characteristics significantly (Sarker, 1979). For example, hydroxyethyl methylcellulose, which contains a high degree of methoxyl and a low degree of hydroxyethyl substitution, is known to exhibit gelation, but the polymer containing a high degree of hydroxyethyl and a low degree of methoxyl substitution does not gel (Sarker, 1979). Also, Sarker (1979) reported that the type of substitution is important in determining the gelation properties of cellulose ethers. For

example, carboxymethyl cellulose, sulfoethyl cellulose and hydroxyethyl cellulose are all non-gelling polymers. Klug (1971) reported a value of  $>100^{\circ}\text{C}$  for the cloud point of gels containing 1% w/w of NaCMC that is in accordance with the above findings.

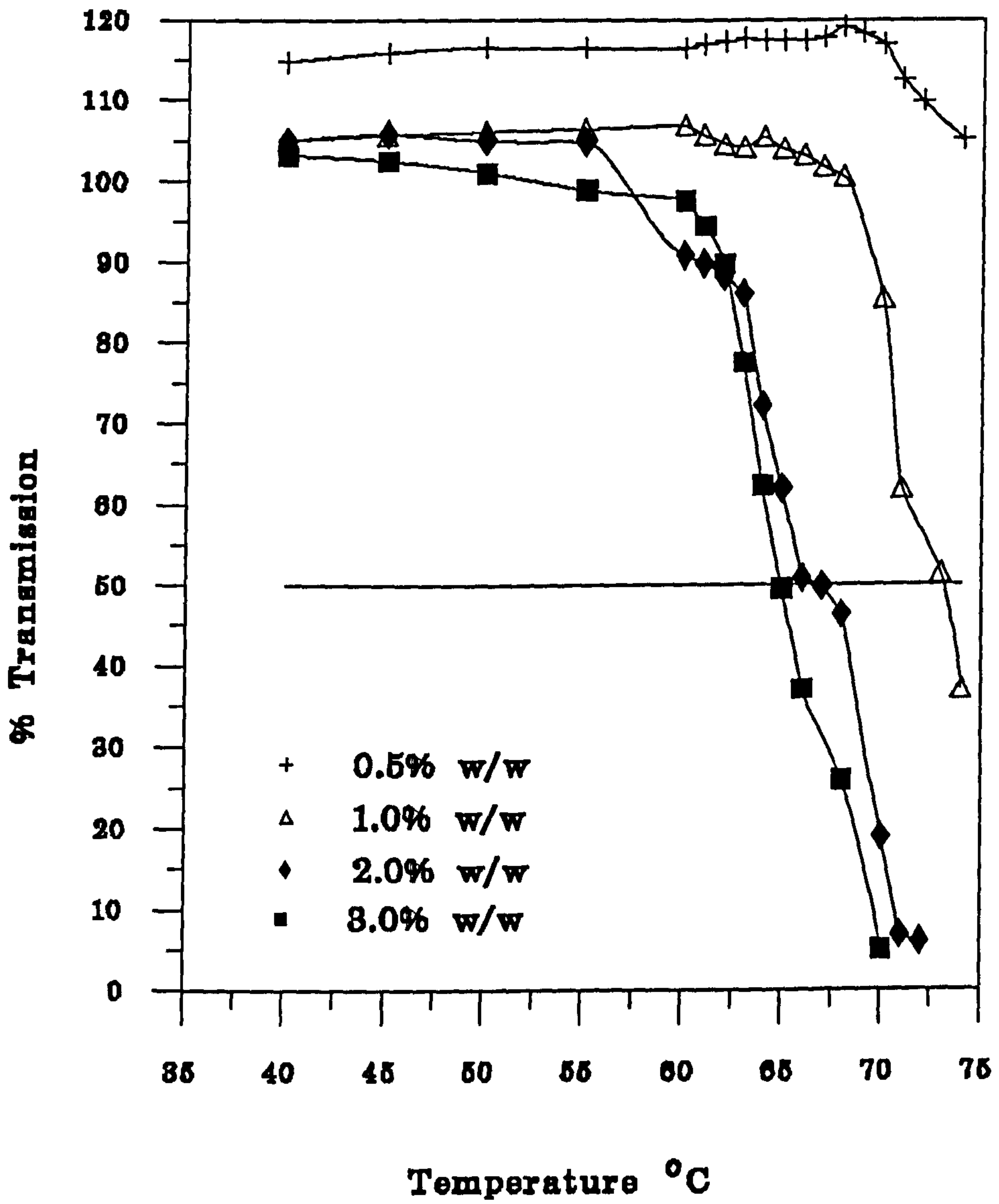
#### 4.3.3.2 Cloud points of gels containing 1:1 HPMC K4M : NaCMC (Blanose)

Although, NaCMC alone did not have a cloud point, its mixture with HPMC K4M showed a decrease in cloud point. Only gels containing 0.5, 1, 2 and 3% w/w polymer were tested. Gels containing more than 3% w/w were not examined due to their high viscosity that made it impossible to fill the cuvette.

Figure 4.7 shows the effect of temperature on the light transmission of gels containing 1:1 HPMC : NaCMC. Gels containing 1, 2 or 3% w/w polymer gave the cloud points of about 73, 66 or 65 respectively which are lower than the HPMC gel alone of equivalent concentrations, 1, 2 or 3% HPMC respectively (table 4.5). Gels containing 0.5% w/w total polymer had light transmissions of more than 100% at  $74^{\circ}\text{C}$ . The reason for this finding might be the interaction between the carboxyl groups of NaCMC and hydroxyl groups of HPMC which provided a competition for the distribution of water in the gels (Walker and Wells, 1982).



Figure 4.7: The effect of temperature and polymer concentration (% w/w) on the light transmission of gels containing 1:1 HPMC : NaCMC (Blanose).



## 4.4 THE DISTRIBUTION OF WATER IN GELS CONTAINING HYDROXYPROPYLMETHYLCELLULOSE, SODIUM CARBOXYMETHYLCELLULOSE OR THEIR MIXTURES

### **4.4.1 Theoretical background**

The state of water in hydrogels is a subject of some controversy. When a hydrophilic polymer is placed in water, a gel is formed and water is absorbed and becomes bound to the polymer. In a tablet the gel consists of both free and bound water. There are many reports in the literature about the condition of water in a hydrogel; their discussion usually centres on the distribution of free and bound water in the gels. However, the states of water are often described in terms of their observable freezing and/or melting behaviour because each state has a different physical property (Korsmeyer, 1983).

There are many methods which have been used to investigate the different states of water in gels such as differential scanning calorimetry (DSC) (Yasuda et al, 1972; Ohno et al, 1983; Fielden et al, 1988; Mitchell et al, 1989; 1993a; Ford and Mitchell, 1995), nuclear magnetic resonance (Yasuda et al, 1972; Sung, 1986), thermal gravimetric analysis (TGA) (Yasuda et al, 1972; Fielden et al, 1988), cryogenic scanning electron microscopy (Melia et al, 1990) and dilatometry (Lee et al, 1975). Since DSC has various advantages over other methods, i.e. the ability to evaluate the water content of a small sample rapidly and quantitatively, it was chosen to measure bound and free

water in gels.

The uses of thermal analysis in analyzing polymers have been reviewed by Gedde (1990) and more extensively by Ford and Timmins (1989). Aizawa and Suzuki (1971), Aizawa et al (1972) and Lee et al (1975) described models of gel structures which displayed three different states of water. These were bound water, free water and a weakly bound, interfacial water. Also Taniguchi and Horigome (1975) suggested four different states of water contained in cellulose acetate membranes, which are: completely free water, free water weakly interacting with polymer, bound water which can contain salts and bound water which rejects salts. Bound water can be defined as water that is incapable of freezing at 0°C, because of interaction with the polymer. Korsmeyer (1983) suggested that water tightly bound to the polymer will not be able to contribute much to solvation of another diffusing species whereas free water in the gel provides a good environment for solute transport.

Yasuda et al (1972), utilizing DSC, nuclear magnetic resonance (NMR) and permeability measurements of water on poly(glycerol methacrylate), showed that there were only two kinds of water based on DSC measurements (bound and free water) whereas, their permeability measurements suggested the existence of an intermediate state of water in the gel (loosely bound water). Also, Sung et al (1986) described that the amount of bound water within a gel was constant and once all the binding sites from polymer were occupied, any



added water would be either lightly bound or free. Similarly Haldankar and Spencer (1989) studied poly(acrylic acid) by DSC and explained their results in terms of a three-state model, where the water in the hydrated polymer was identified as "nonfreezing", "freezing with a constant melting temperature" and "freezing with a melting temperature dependent on water content". They claimed that the melting point of the last type of water increased from  $-10^{\circ}\text{C}$ , gradually approaching  $0^{\circ}\text{C}$  at high hydration. However, all the authors are agreed that free water makes up a significant amount of the water content in gels.

#### **4.4.2 Methodology**

Previously Mitchell et al (1989; 1993a) demonstrated that the scans of HPMC gels depended on the gel conditions prior to their testing by Differential Scanning Calorimetry (DSC) or Differential Thermal Analysis (DTA). Two endotherms were displayed by HPMC gels which had been previously cooled rapidly. One was consistent with the melting of unbound water at  $0^{\circ}\text{C}$  and the other showed a peak temperature in the range  $5\text{-}25^{\circ}\text{C}$ . Mitchell et al (1989) reported that only an endotherm at  $0^{\circ}\text{C}$  was seen in samples that were cooled at  $-5^{\circ}\text{Cmin}^{-1}$ . Since the slow cooling of the gels prevents the formation of the secondary peak (Mitchell et al, 1989), all gels were cooled at  $-5^{\circ}\text{Cmin}^{-1}$  and then heated at  $10^{\circ}\text{Cmin}^{-1}$ .

### **4.4.3 Experimental**

#### **4.4.3.1 Gel preparation**

The gels used in this study were prepared using HPMC K4M, NaCMC (Blanose) or their 1:1 mixture, as described in section 2.2.1.1.

#### **4.4.3.2 Method of determination**

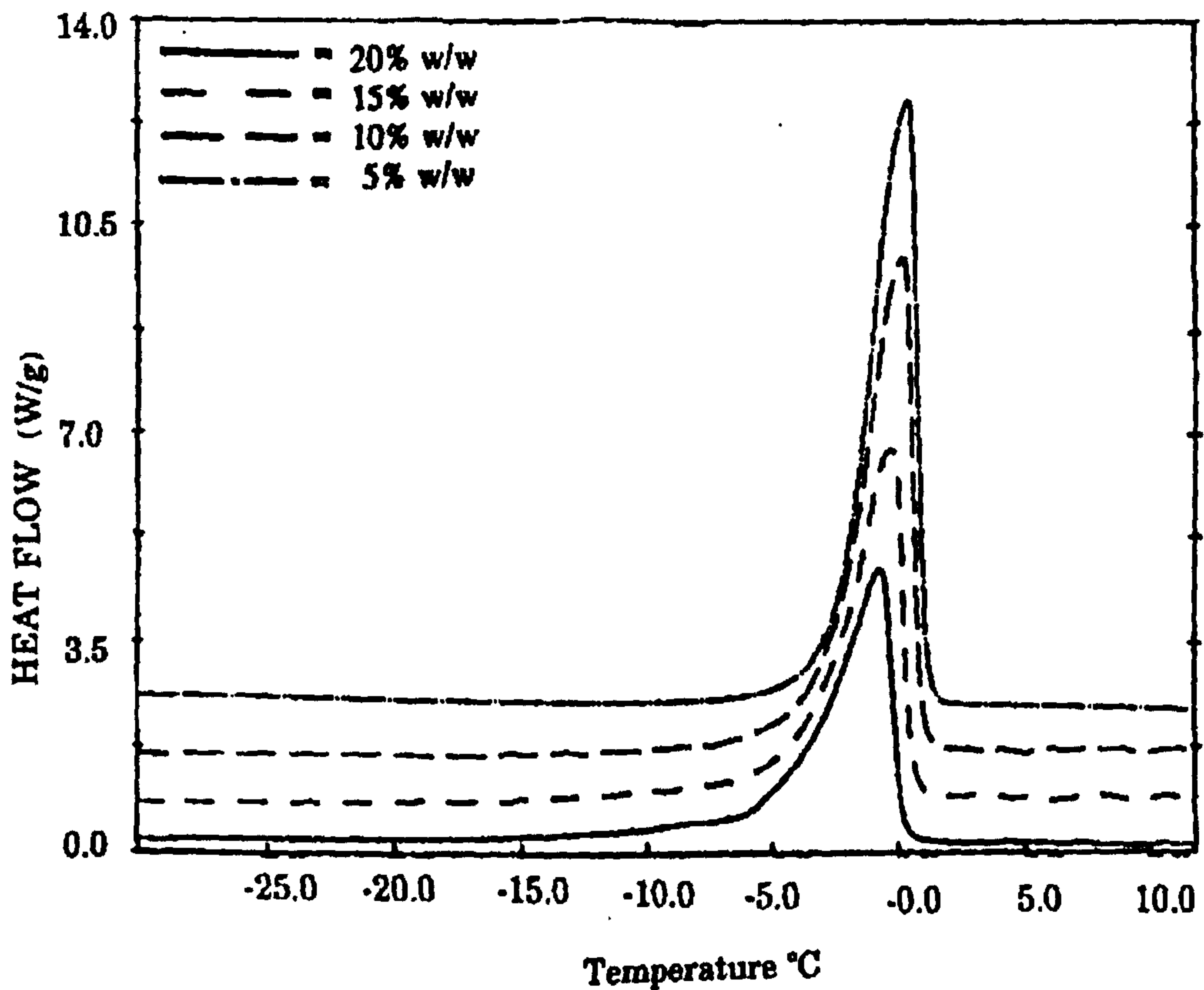
The enthalpy of melting at approximately 0°C of the free water was determined as described in section 2.2.2.3.

### **4.4.4 Results and Discussion**

Figure 4.8 shows typical DSC scans of gels containing 5-20% w/w of HPMC K4M. Similarly figures 4.9 and 4.10 show typical DSC scans of gels containing 5-20% w/w NaCMC (Blanose) and 1:1 mixture of HPMC:NaCMC respectively. Their enthalpies are presented in table 4.6. The enthalpies from all gels decreased as the concentration of the polymers in the gels increased. The onset temperatures for the melting of water in the gels decreased from approximately -5°C to approximately -15°C, as the concentration of gels increased from 5% w/w to 20% w/w, indicating a probable degree of interaction (binding) of water to the cellulose ether.

As previously described, there are at least two thermodynamically different types of water in gels, bound and free. Bound water within a gel is constant (Sung et al, 1986) but free water within a gel depends on the concentration

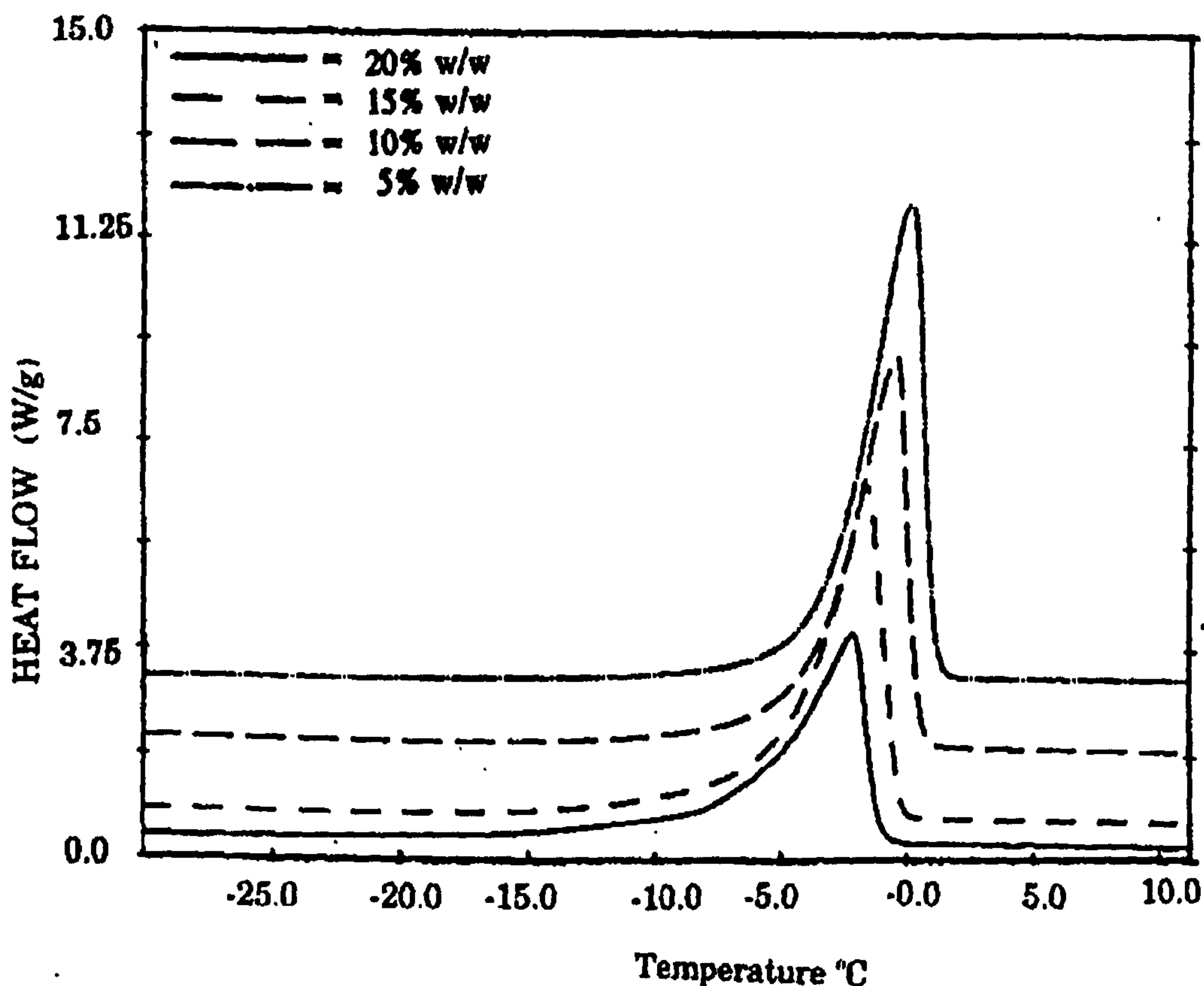
Figure 4.8: The DSC scans of gels containing 5, 10, 15 or 20% w/w HPMC K4M obtained at 10°C/min following cooling at -5°C/min.



of polymer. Once all binding sites are occupied any excess water is either loosely bound or free. The decrease in the onset temperatures might be due to a weak interaction of the water with the polymer chain, which with increasing the temperature, was reduced. Careful examination of figures 4.8, 4.9 and 4.10 reveals that as the concentration of gels increased, the sharpness of the peak decreased again indicating interaction between water and the polymer.

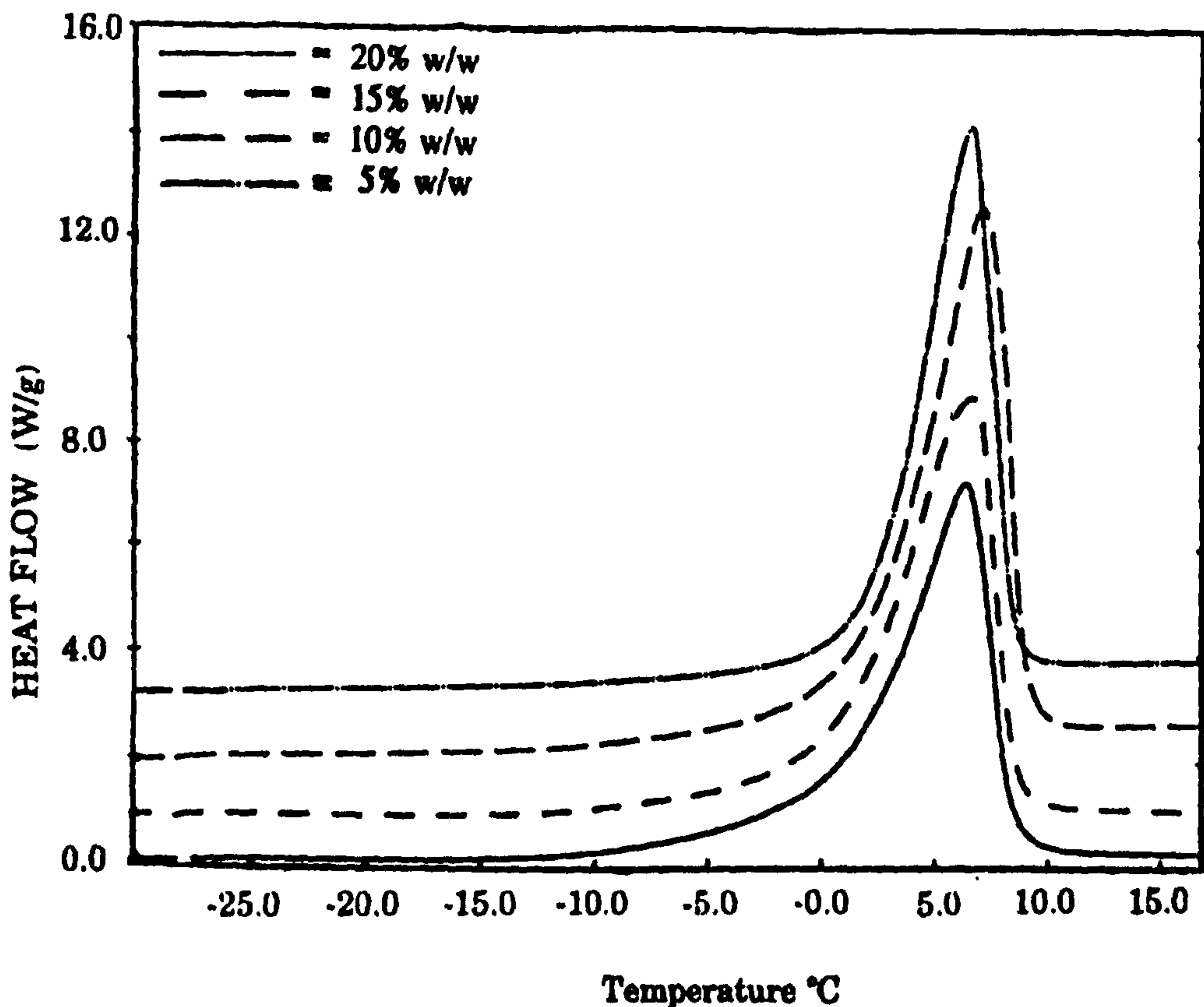


Figure 4.9: The DSC scans of gels containing 5, 10, 15 or 20% w/w NaCMC (Blanose) obtained at 10°C/min following cooling at -5°C/min.



As the concentration of polymer increased, the quantity of free water decreased as shown by the decrease in melting enthalpy of free water (table 4.6). In the case of HPMC K4M gels, extrapolation to zero enthalpy gave the intercept value as  $46.6 \pm 1.3\%$  HPMC K4M and  $53.4\%$  water, that is equal to  $114.8 \pm 5.0$  g water per 100 g HPMC K4M. By considering the molecular

Figure 4.10: The DSC scans of gels containing 5, 10, 15 or 20% w/w mixture of 1:1 HPMC : NaCMC (Blanose) obtained at 10°C/min following cooling at -5°C/min.



weight of water to be 18.02, it was calculated that the number of moles of non-freezing water was  $6.4 \pm 0.3$  moles of water per 100 g of HPMC K4M. This point represents the minimum ratio of water to HPMC that is required for water to occupy the binding sites of HPMC K4M. Previously, Mitchell et al (1991b) gave values of 58.5% : 41.5 and 61.8% : 38.2 HPMC K15M:

Table 4.6: The effect of polymer and polymer concentration on the melting enthalpies of gels containing HPMC K4M, NaCMC (Blanose) or their 1:1 mixture

Polymer	Melting enthalpies				
	water	5% w/w	10% w/w	15% w/w	20% w/w
HPMC K4M	321.2 ± 2.8	283.6 ± 8.1	257.2 ± 11.5	214.1 ± 5.7	188.1 ± 3.4
NaCMC (Blanose)	321.2 ± 2.8	286.4 ± 7.7	240.6 ± 5.1	219.6 ± 5.1	205.1 ± 0.7
1:1 HPMC : NaCMC	321.2 ± 2.8	279.9 ± 7.1	246.8 ± 3.8	230.1 ± 9.8	191.8 ± 9.7

Tukey's test: only differences at 10 and 20% (w/w) between HPMC and NaCMC ( $p > 0.05$ ); at 15% between HPMC and 1:1 mixture ( $p > 0.05$ ). There were no other significant differences.



water for two hour and 24 hour old gels respectively. Joshi and Wilson (1992) studied HPMC E5 by DSC and explained their results in terms of a three-state model, where the water in the hydrated polymer was identified as type I (free water melting at 0°C), type II (water loosely bound to hydrophilic groups on the polymer which melted below 0°C) and type III (tightly bound water which did not freeze). Joshi and Wilson (1993) reported a value of  $6.2 \pm 1.3$  moles bound water per polymer repeating unit of HPMC E5. However, Ford and Mitchell (1995) gave values of 8.5 and 6.6 moles water per polymer repeating unit of HPMC K15M gels stored for 2 hours and 24 hours respectively.

The difference in the results obtained from the present study with those of Mitchell et al (1991b), might be due to different polymer types and the percentage of HPMC in the gels examined. Mitchell et al (1991b) examined gels containing 0-40% w/w HPMC K15M and Joshi and Wilson (1993) used HPMC E5 whereas the polymer used in this study was HPMC K4M a concentrations between 0-20% w/w.

In the case of NaCMC gels, the intercept value for zero enthalpy of gels containing NaCMC and water was obtained as  $48.2 \pm 2.1\%$  NaCMC (Blanose) and 51.8% water. From this value it can be calculated that the amount of water required to fully hydrate 100 g of NaCMC (Blanose) is  $107.9 \pm 7.2$  g water which is equal to  $6.0 \pm 0.4$  mole water. The extrapolated concentration of NaCMC gels which would provide a zero enthalpy compared to the HPMC

gels, indicates that NaCMC might require less amount of water for hydration than HPMC.

The Tukey's statistical test for multiple comparisons was used to assess the significant differences in the data of the melting enthalpies and the concentrations of gels containing HPMC, NaCMC or their 1:1 mixture. For the gels containing HPMC K4M and NaCMC (Blanose) at similar concentrations there were significant differences ( $p < 0.05$ ) in the melting enthalpies of gels containing 10 and 20% w/w polymer whereas there were no significant differences at the other concentrations (5 and 15% w/w).

In the case of the 1:1 mixture of HPMC : NaCMC, the extrapolation to zero enthalpy gave an intercept value of  $49.7 \pm 1.8\%$  polymer and 50.3% water. This amount is equal to  $5.6 \pm 0.3$  mole water per 100 g of 1:1 polymer. The zero-enthalpy for the mixture indicates that the amount of required water for full hydration was probably less than those for the individual polymers. A significant difference (Tukey's test) was observed only between gels containing 15% w/w of HPMC and 15% of 1:1 HPMC : NaCMC. No other statistical differences between the 1:1 mixture and the HPMC or NaCMC gel were observed at equivalent concentration.

The reason for the decrease in the amount of water required for hydration of 1:1 HPMC : NaCMC gels, even though not significant statistically, might be the interaction between the two polymers. Klug (1971) stated that much of

the water absorbed by hydrophilic polymers is held chemically by hydrogen bonding at oxygen atoms in these polymers. Therefore, since the carboxyl groups of NaCMC tended to bind with hydroxyl groups of HPMC, the free hydroxyl groups of the polymers would decrease which subsequently would cause a decrease in the amount of bound water.

The decrease observed in the cloud points of gels containing 1:1 HPMC : NaCMC, is probably due to the higher solubility of NaCMC compared to HPMC (Klug, 1971; Doelker, 1987). This property would probably cause more water to be absorbed by NaCMC and subsequently less water would be left for the HPMC content to absorb, water preferentially binding to the NaCMC.

#### 4.5 WATER UPTAKE OF HYDROXYPROPYLMETHYLCELLULOSE AND SODIUM CARBOXYMETHYLCELLULOSE

##### **4.5.1 Theoretical background**

Mitchell et al (1991a: 1993a) showed that fast hydration of a polymer is critical to good sustained-release action in most hydrophilic matrices. Retardation of drug release is accomplished via the production of a gel layer around the matrix when placed in contact with water. Therefore, the speed at which the polymer absorbs water and forms a gel layer after its initial contact with water is of great importance. Lucisano et al (1989) also reported that two aspects of HPMC govern its performance in a sustained release matrix, polymer hydration rate and viscosity of the polymers. However, Ford



and Mitchell (1995) confirmed the importance of the polymer hydration rate in the successful formulation of a sustained release delivery system. Although, there is some literature on water uptake or swelling of HPMC matrices (Mitchell et al, 1990a; 1993c; Alderman, 1984; Ford and Mitchell, 1995), relatively little has been reported addressing the influence of the rate of NaCMC hydration on the drug release.

Mitchell et al (1993a) showed that the speed of water uptake by a polymer played a significant role in the properties of matrices containing HPMC K15M. Furthermore, from the data described in section 4.4, approximately equal parts of water : polymer were required to give complete hydration of the polymer. Therefore, in order to understand the mechanism of hydration and to determine the speed of water uptake into the polymers, this study was carried out using equal parts of water and the polymers, i.e., HPMC K4M, NaCMC (Blanose) or their 1:1 mixture.

## **4.5.2 Experimental**

### **4.5.2.1 Preparation of wafers**

Wafers were made using approximately 10 mg of unsieved HPMC K4M, NaCMC (Blanose) or their 1:1 mixture as described in section 2.2.2.4.

### **4.5.2.2 Method of determination**

Water uptakes by wafers were determined by the method of Mitchell et al

(1993a) as described in section 2.2.2.4. The same method was used also for determining the water taken up by polymers at 37°C except that the samples were held in the sample compartment of a Perkin Elmer DSC 7 differential scanning calorimeter at 37°C. After storage for 1, 5, 15 or 30 minutes, the pans and their contents were cooled to -30°C at 10°C min<sup>-1</sup>. Each sample was then heated up to 20°C at 5°C min<sup>-1</sup> and the enthalpies of fusion of ice were determined. The quantities of water bound to the polymers were then calculated in the same manner as for the samples held at room temperature.

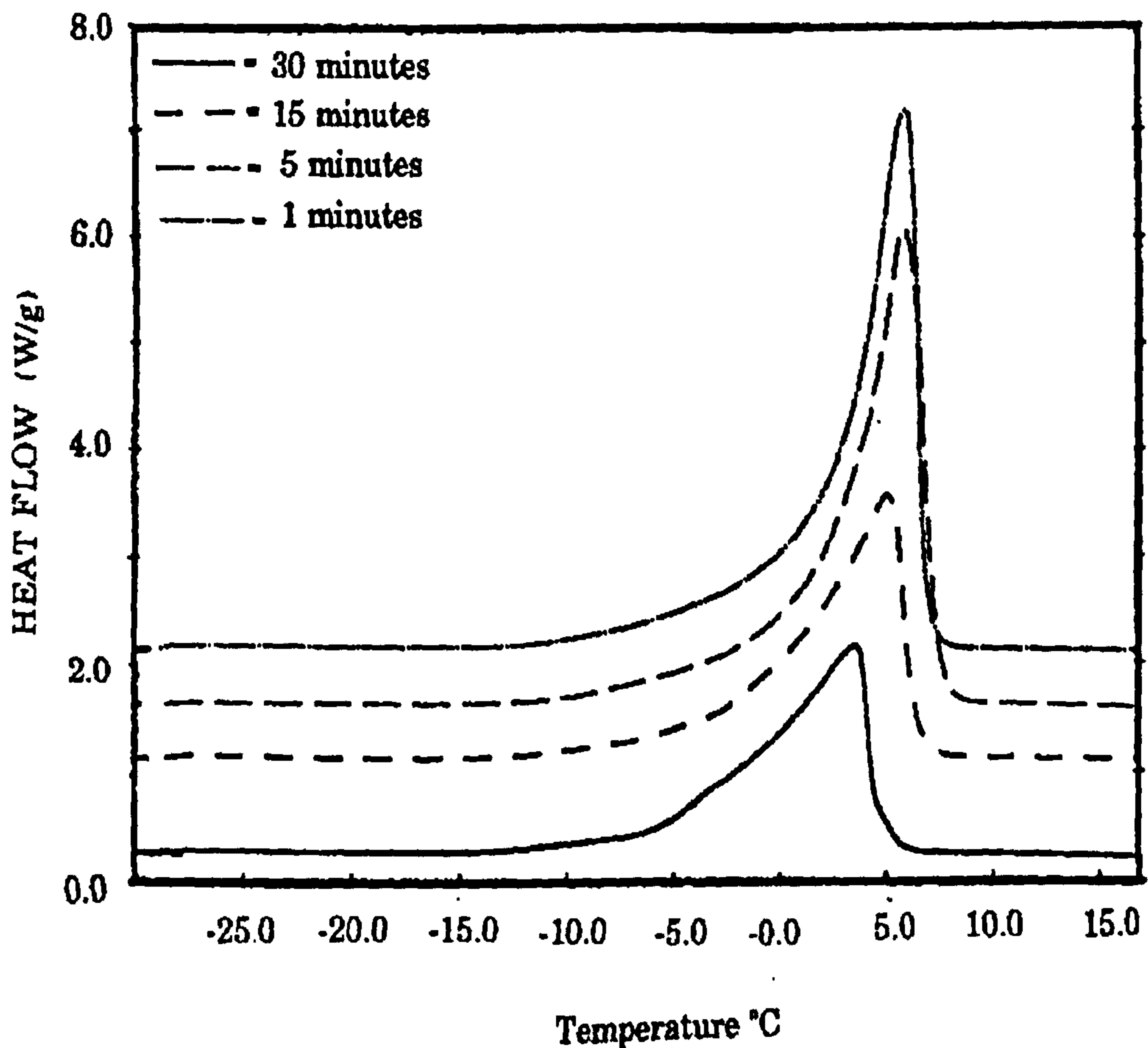
### **4.5.3 Results and discussion**

#### **4.5.3.1 Water uptake by discs at ambient temperature**

Figure 4.11 shows typical DSC scans obtained for the water uptake of discs containing HPMC K4M. The amount of water taken up increased over the 30 minutes period. The data of percentages of water bound are presented in table 4.7. After 5 minutes of contact with water, approximately 32% uptake had occurred. The results confirm the report of Mitchell et al (1993a) that during the initial 5 minutes of contact over 30% of the uptake of water occurred using HPMC K15M. However, the first few minutes of hydration are the most important because this period corresponds to the time when the protective gel layer is formed around the matrix (Ford and Mitchell, 1995).

Typical data obtained for the water uptake of discs containing NaCMC (Blanose) are presented in figure 4.12 and table 4.7. Approximately 39% of

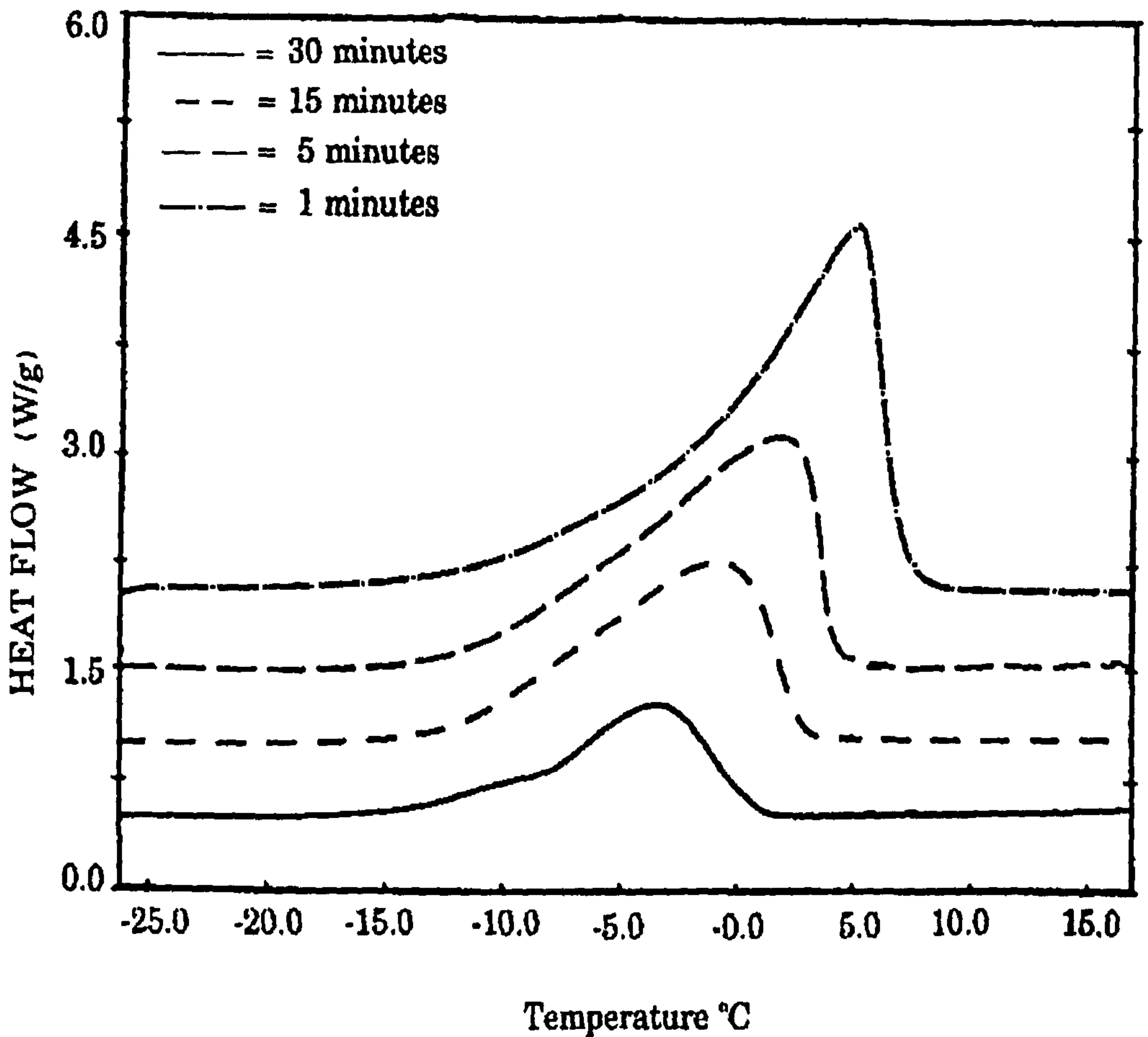
Figure 4.11: The DSC scans showing the melting endotherms of water in contact with HPMC K4M discs following storage at 1, 5, 15 or 30 minutes at ambient temperature.



water taken up occurred after 5 minutes of contact indicating that NaCMC was probably able to absorb water faster than HPMC K4M. The results of Tukey's tests on the data from wafers containing NaCMC (Blanose), in comparison with HPMC wafers, suggest that there were significant



Figure 4.12: The DSC scans showing the melting endotherms of water in contact with NaCMC (Blanose) discs following storage at 1, 5, 15 or 30 minutes at ambient temperature.



differences between the melting enthalpies after 5, 15 and 30 minutes of contact with water ( $p < 0.05$ ). A comparison of figure 4.11 (hydration of HPMC) and figure 4.12 (hydration of NaCMC) indicates that the shapes of the DSC peaks for NaCMC and HPMC were different. This may be due to the

differences in the degree and strength of the interaction between water and these two polymers.

Data for discs containing 1:1 HPMC : NaCMC are presented in figure 4.13 and table 4.7. Discs containing 1:1 HPMC : NaCMC absorbed 34% water during the initial 5 minutes of contact with water which was intermediate to the HPMC and NaCMC discs.

Tukey's tests were performed to compare the significances of the melting enthalpies from wafers containing HPMC K4M, NaCMC (Blanose) and their 1:1 mixture at each of the periods of time. The results of Tukey tests from wafers containing 1:1 HPMC : NaCMC suggest that at  $p < 0.05$ , there were significant differences only at 1 and 30 minutes with HPMC. There were no significant differences between the 1:1 mixture and NaCMC, indicating that they absorbed water in a similar function.

The mean values for the bound water for samples containing HPMC, NaCMC or their 1:1 mixture at ambient are plotted in figure 4.14 as a function of time. The 1:1 mixture had the lowest water uptake at the first minute of contact with water. After that, the water uptake increased and finally hydration of 1:1 HPMC : NaCMC occurred in a manner intermediate to the pure HPMC and NaCMC.

Table 4.7: Effect of time on the percent of bound water by 10 mg discs containing HPMC K4M, NaCMC (Blanose) or 1:1

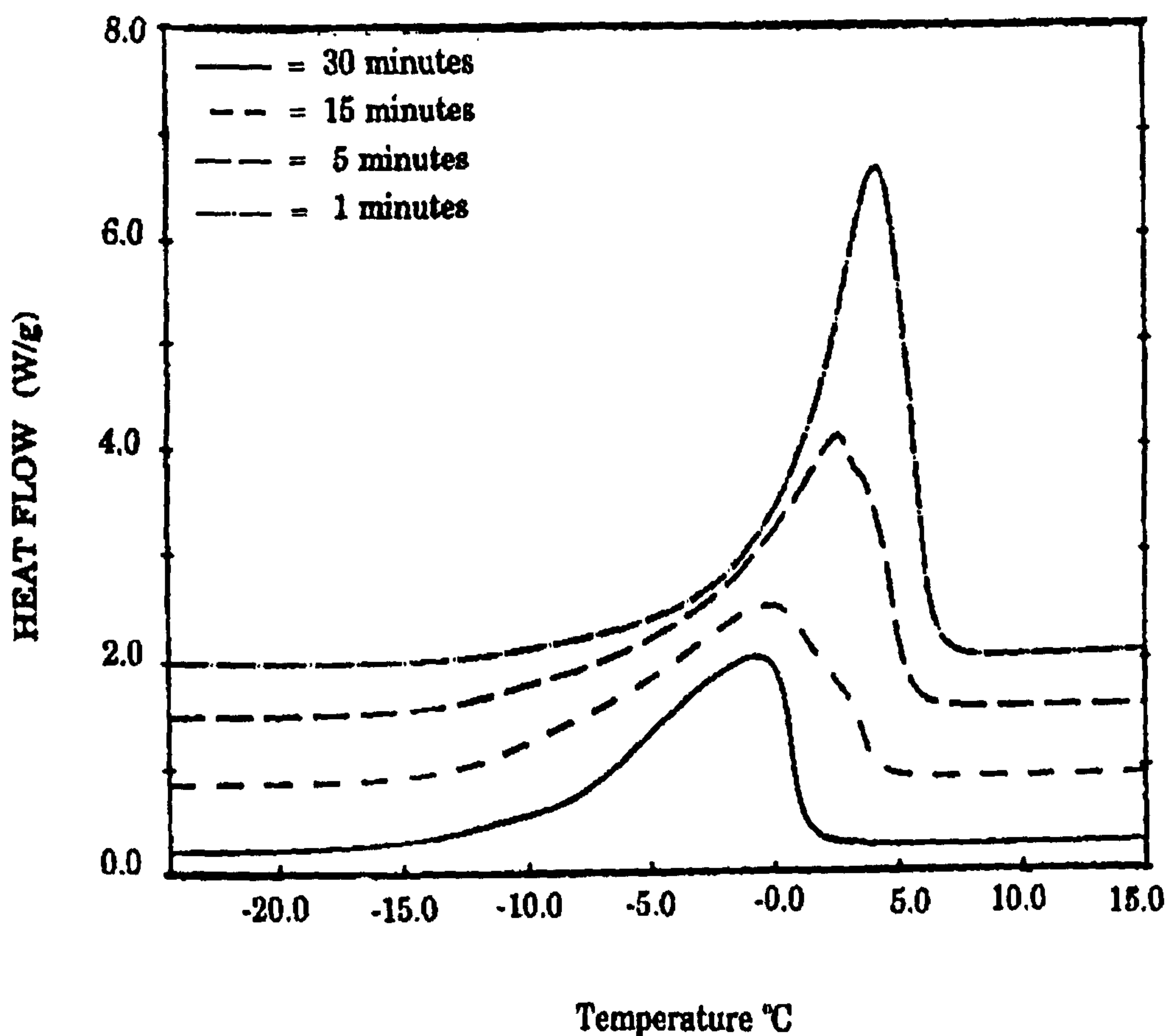
HPMC K4M : NaCMC (Blanose) at ambient and 37°C (results are the means  $\pm$  SD of three determinations)

Time min	HPMC K4M		NaCMC (Blanose)		1:1 HPMC:NaCMC	
	Ambient	37°C	Ambient	37°C	Ambient	37°C
1	27.5 $\pm$ 2.3	37.9 $\pm$ 8.6	22.0 $\pm$ 4.4	33.7 $\pm$ 5.8	15.7 $\pm$ 0.7	31.6 $\pm$ 3.3
5	32.2 $\pm$ 1.2	53.1 $\pm$ 3.3	39.1 $\pm$ 2.6	52.5 $\pm$ 5.1	34.6 $\pm$ 4.1	47.6 $\pm$ 1.3
15	56.6 $\pm$ 0.4	69.0 $\pm$ 3.0	46.6 $\pm$ 2.3	61.3 $\pm$ 6.0	51.4 $\pm$ 2.7	66.3 $\pm$ 2.5
30	63.6 $\pm$ 1.4	81.9 $\pm$ 7.8	48.6 $\pm$ 2.0	78.9 $\pm$ 1.5	53.7 $\pm$ 1.9	86.2 $\pm$ 1.3

Statistical comparison: at ambient significant differences between HPMC and NaCMC at 5, 15 and 30 minutes and also between HPMC and 1:1 mixture at 1 and 30 minutes ( $p < 0.05$ ) were found; at 37°C significant differences between HPMC and NaCMC at 15 minutes and also between NaCMC and 1:1 mixture at 30 minutes ( $p < 0.05$ ) were found.



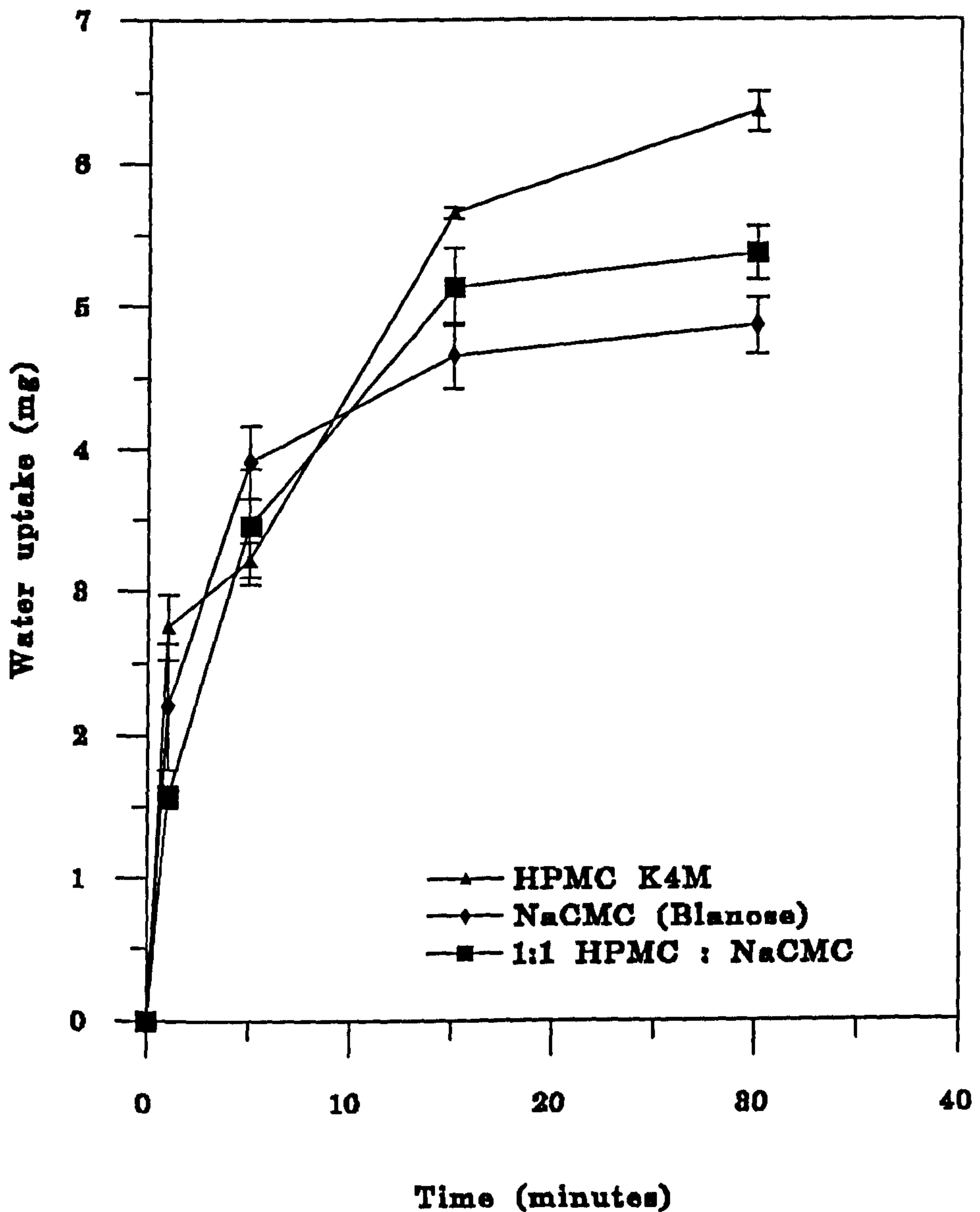
Figure 4.13: The DSC scans showing the melting endotherms of water in contact with discs containing 1:1 HPMC K4M : NaCMC (Blanose) following storage at 1, 5, 15 or 30 minutes at ambient temperature.



#### 4.5.3.2 Water uptake by discs at 37°C

Table 4.7 shows data for discs containing HPMC K4M, NaCMC (Blanose) or 1:1 HPMC : NaCMC obtained also at 37°C. Increasing the temperature

Figure 4.14: The effect of time on the amount of water bound by 10 mg discs containing HPMC K4M ( $\blacktriangle$ ), NaCMC Blanose ( $\blacklozenge$ ) and 1:1 HPMC : NaCMC ( $\blacksquare$ ) from an unbound 10 mg quantity of distilled water at ambient (results are the means  $\pm$  SD of three determinations)



caused an increase in the water taken up by the polymers. Discs containing HPMC K4M, after 30 minutes contact with water at 37°C, absorbed 29% more water compared with similar discs at ambient. Similarly the discs containing NaCMC and the 1:1 mixture absorbed 62% and 60% more water respectively than similar discs at ambient. The water uptakes at 37°C by discs containing the mixture of the two polymers were similar to NaCMC whereas, at ambient it was probably intermediate of the two polymers.

The results of Tukey's tests between the melting enthalpies of discs containing HPMC K4M, NaCMC (Blanose) and their 1:1 mixture at ambient and 37°C, suggest that at  $p < 0.05$  there were no significant differences between the polymers at 1, 5, 15 or 30 minutes of contact with water.

#### 4.6 CONCLUDING REMARKS

The characterization of hydroxypropylmethylcellulose (HPMC) K4M and three viscosity grades of sodium carboxymethylcellulose (NaCMC) was investigated. The NaCMC gels had higher viscosities compared to that of HPMC K4M gels of similar concentration. In mixtures containing HPMC K4M and NaCMC (Blanose), the viscosities in the polymer range of 0.0-0.05% w/w were intermediate to those of the individual polymers whereas in the range of 0.1-0.5% w/w the viscosities of 1:1 mixture were higher than predicted from those of the polymers alone. The viscosity increased with increase in the proportion of NaCMC. The viscosities indicate that the admixture of gels containing



HPMC and NaCMC could provide a synergistic increase in viscosity at higher concentrations.

As the concentration of HPMC gels increased from 0.5 to 5% (w/w), the cloud points decreased by more than 8°C. In spite of gels containing NaCMC not showing a cloud point, gels containing the 1:1 ratio of HPMC and NaCMC showed a decrease in cloud point compared with HPMC gels of equivalent concentration. The reason might be due to the ability of NaCMC to retain its associated water at higher temperatures.

A simple relationship existed between the melting enthalpies of free water and the concentration of polymer in the gels of HPMC, NaCMC or their 1:1 mixture. As the concentration of the polymer in the gels increased the melting enthalpies decreased. Extrapolation to zero-enthalpy indicated that the compositions of the fully hydrated gels were  $6.4 \pm 0.3$ ,  $6.0 \pm 0.4$  or  $5.6 \pm 0.3$  mole water per 100 g of HPMC, NaCMC or their 1:1 mixture respectively. This suggest that 1:1 HPMC : NaCMC may have required less water for hydration than HPMC or NaCMC.

The results of water uptake determination from discs containing HPMC, NaCMC or their 1:1 mixture at ambient and at 37°C (table 4.7) showed that discs containing HPMC, after 30 minutes of contact with water at 37°C, absorbed 29% more water compared with similar discs at ambient. Discs containing NaCMC or their 1:1 mixture at the similar condition absorbed 62%

or 60% more water respectively. Since the shapes of the DSC scans, as well as the effects of increasing the temperature from ambient to 37°C for the mixture was similar to NaCMC alone, it seems reasonable to suggest that when mixed with HPMC, in terms of absorption of water, NaCMC is the dominant component.

# **CHAPTER 5 INTERACTIONS BETWEEN PROPRANOLOL HYDROCHLORIDE AND HYDROXYPROPYLMETHYLCELLULOSE OR SODIUM CARBOXYMETHYLCELLULOSE**

## **5.1 INTRODUCTION**

The characteristics of HPMC, NaCMC and their mixtures were discussed in the previous chapter. Gels containing the 1:1 mixture of HPMC : NaCMC had higher viscosities than gels containing the individual polymers. When the concentration of HPMC in gels increased their cloud points decreased whereas NaCMC gels did not display cloud points. Gels containing 1:1 HPMC : NaCMC had lower cloud points than the corresponding HPMC gels.

It is well known that the presence of a drug in a hydrophilic matrix could change the characteristics of the polymer which subsequently could change the drug release. Factors such as erosion of the matrix (Bonferoni et al, 1994), interaction between the drug and polymer (Tucker, 1988; Lin and Perng, 1993) and water uptake also govern the release of drugs from matrices containing HPMC and NaCMC. The effects of propranolol hydrochloride on HPMC K15M gels have been investigated by Mitchell et al (1991b) but the effects of propranolol hydrochloride on HPMC K4M, NaCMC or their combinations have not been thoroughly investigated. Such information is vital to the understanding of drug release from matrices containing HPMC K4M, NaCMC or their mixtures.



### **5.1.1 Aims and objectives**

Since drugs alter the hydration of HPMC K15M (Ford and Mitchell, 1995), the aims of the studies presented in this chapter were to investigate the effects of propranolol hydrochloride (as a model drug) on the cloud point and water distribution of gels containing HPMC K4M, NaCMC (Blanose) or their mixtures. This was to gain further insight into the mechanisms of drug release from their matrices by investigating their erosion rates and the release of sodium ions.

## **5.2 INTERACTION BETWEEN PROPRANOLOL HYDROCHLORIDE AND HYDROXYPROPYLMETHYLCELLULOSE K4M**

In section 4.4, it was shown that there was a balance between free and bound water in gels containing HPMC K4M. By adding drugs or any other substance, this balance might be changed. It was therefore necessary to determine the effect of propranolol hydrochloride on the characteristics of HPMC K4M gels.

### **5.2.1 The effect of propranolol hydrochloride on the cloud points of hydroxypropylmethylcellulose K4M gels**

Touitou and Donbrow (1982) reported that drugs and uncharged molecules affected the cloud points of cellulose ethers and generally made HPMC more soluble. Mitchell et al (1991b) also showed that the addition of propranolol hydrochloride increased the amount of bulk water within HPMC K15M gels.

### 5.2.1.1 Experimental

#### 5.2.1.1.1 Materials

Propranolol hydrochloride and HPMC K4M were used as described in sections 2.1.5 and 2.1.1.1.

#### 5.2.1.1.2 Gel preparation

Gels (20 g) were prepared to contain 1, 2 or 3% w/w of HPMC K4M and 1 to 5% w/w propranolol hydrochloride according to the methods described in section 2.2.1.1, except that after dispersing the required amount of HPMC K4M in approximately one third of the total volume distilled water (at 80°C) and before adding distilled water, an aqueous solution containing the required amount of propranolol hydrochloride was added. The gels were mixed in a mortar with a pestle, before cold distilled water was added to make up to the required weight.

#### 5.2.1.1.3 Cloud point determination

The cloud point of gels were determined as described in section 2.2.1.3.

### 5.2.1.2 Results and discussion

Figure 5.1 demonstrates the effects of propranolol hydrochloride (1-5% w/w) on the cloud points of gels containing 1, 2 or 3% w/w HPMC K4M. When propranolol hydrochloride was added to the HPMC gels, their cloud points increased and for higher propranolol concentrations (> 3% w/w) cloud points

were not observed below 75°C. The highest values for light transmission were observed for the gels containing 3% w/w HPMC K4M and 5% w/w of propranolol hydrochloride where the light transmission was in excess of 100% at 75°C. This fact suggests that the solubility of HPMC was increased and/or less water was required for hydration of the polymer. Similar results were observed by Mitchell et al (1991b) who showed that the cloud points of HPMC K15M gels were increased by the addition of propranolol hydrochloride. Mitchell et al (1991b) concluded that at high concentrations, propranolol hydrochloride enabled the HPMC K15M to hydrate to a greater extent than at lower concentrations. Hence, propranolol hydrochloride effectively salted-in the HPMC.

### **5.2.2 The effect of propranolol hydrochloride on the distribution of water in gels containing hydroxypropylmethylcellulose K4M**

Since the cloud points of HPMC K4M gels were affected by the addition of propranolol hydrochloride, DSC was performed to find if the water distribution in HPMC gels was modified by propranolol hydrochloride.

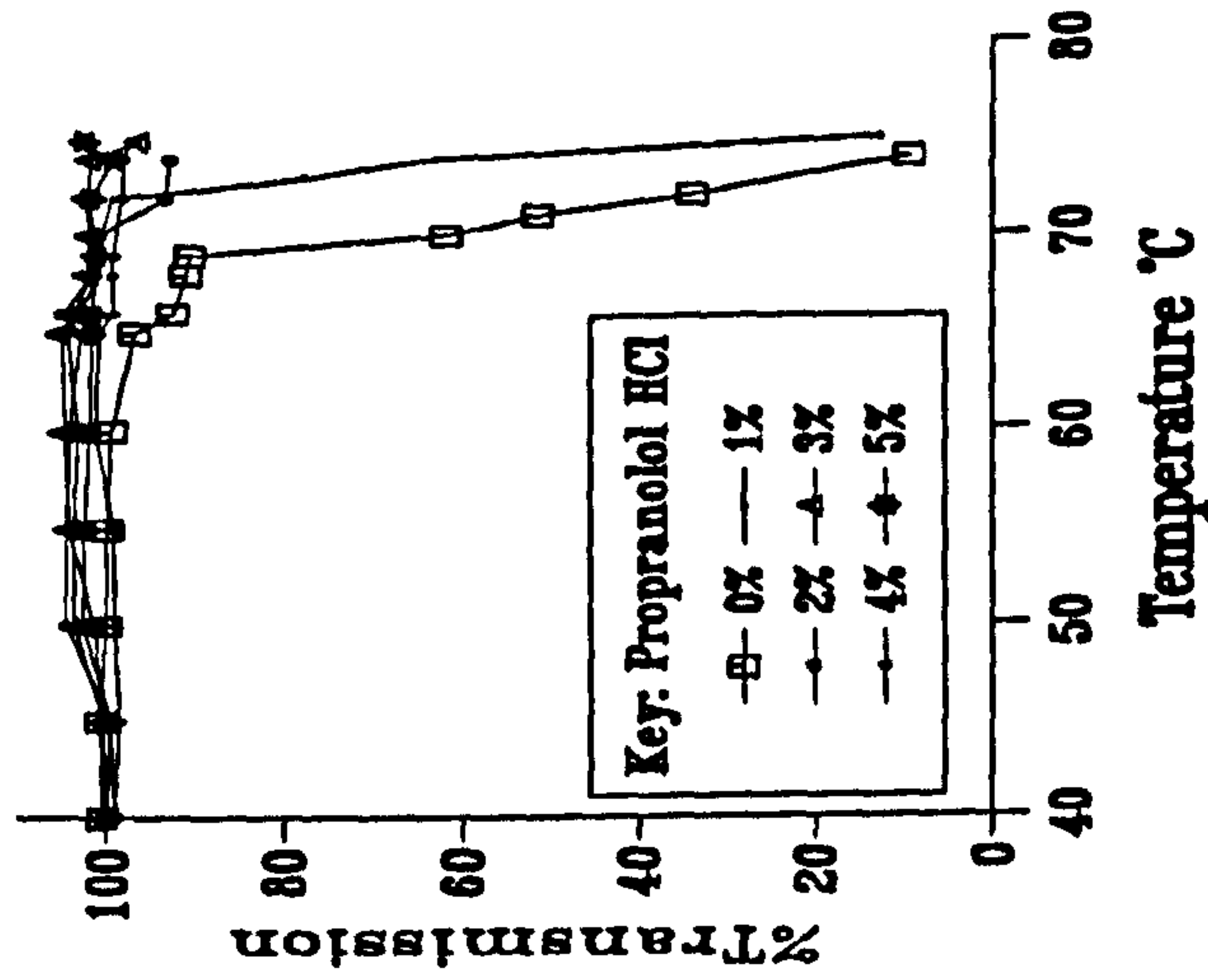
#### **5.2.2.1 Experimental**

##### **5.2.2.1.1 Materials**

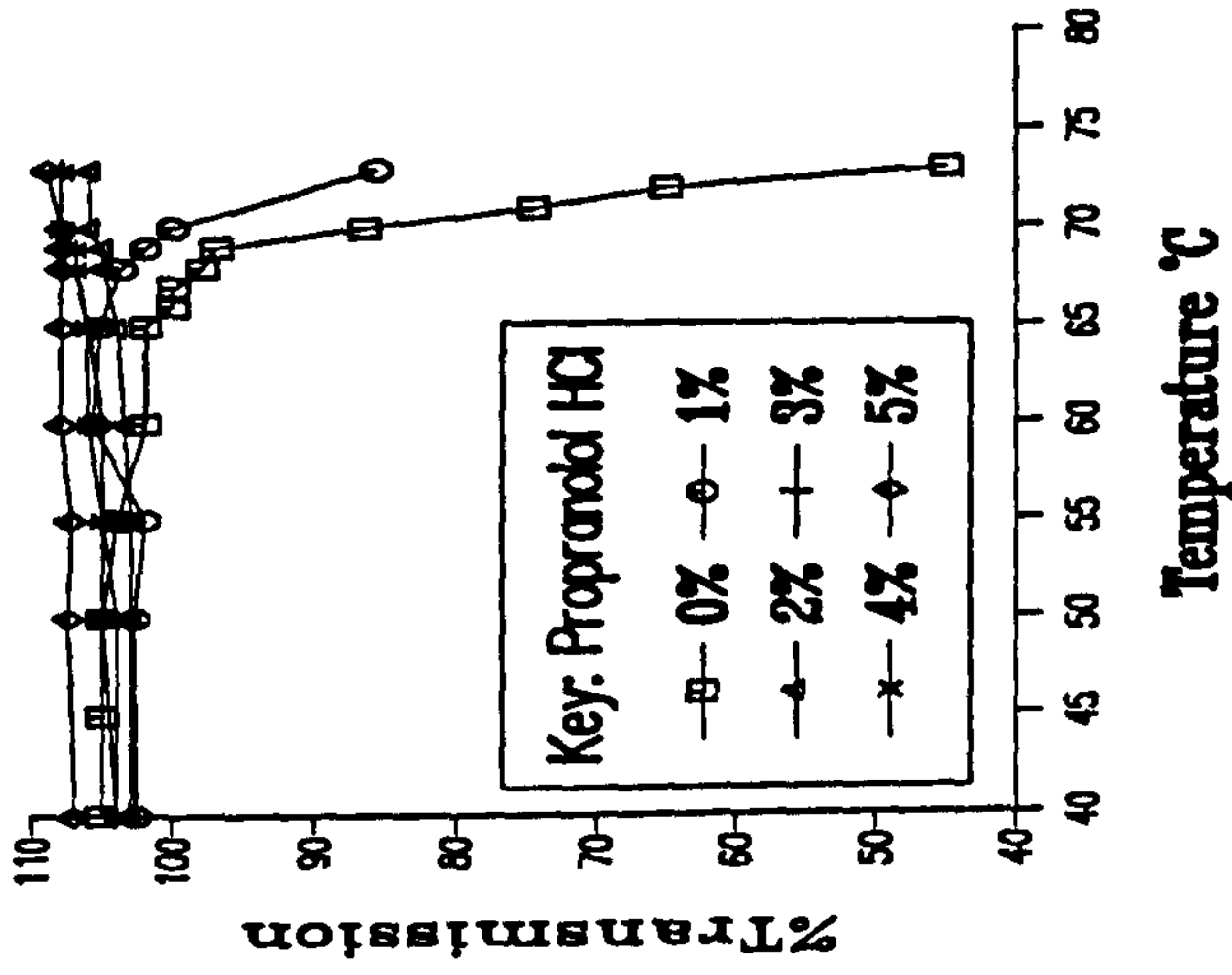
Propranolol hydrochloride and HPMC K4M were used as described in sections 2.1.5 and 2.1.1.1.



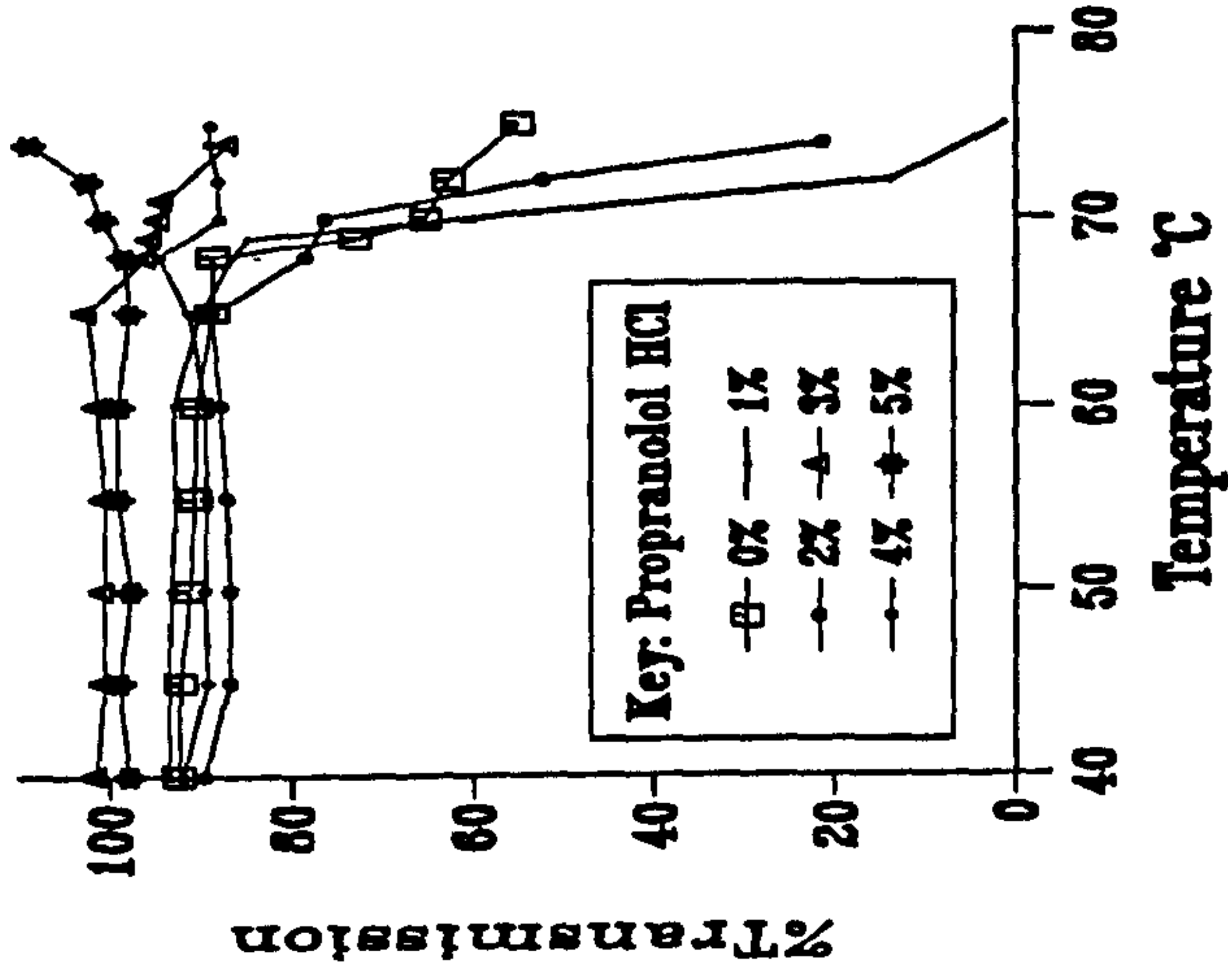
Figure 5.1: The effect of temperature on the % transmission of gels containing (A) 1%, (B) 2% or (C) 3% w/w of HPMC K4M and different concentrations (1, 2 or 3% w/w) of propranolol hydrochloride (results are obtained from at least 3 tests).



(A)



(B)



(C)

#### 5.2.2.1.2 Gel preparation

Gels containing propranolol hydrochloride and HPMC K4M were made as described in section 5.2.1.1.2 to contain 5, 10 or 15% w/w of propranolol hydrochloride and 5, 10, 15 or 20% w/w HPMC K4M. For comparison, aqueous solutions of 5, 10, 15 or 20% w/w propranolol hydrochloride were also prepared. To ensure homogeneity of propranolol hydrochloride solutions, the samples were first heated to dissolve the propranolol hydrochloride and then samples were transferred to sample pans before recrystallisation of the supersaturated solution occurred.

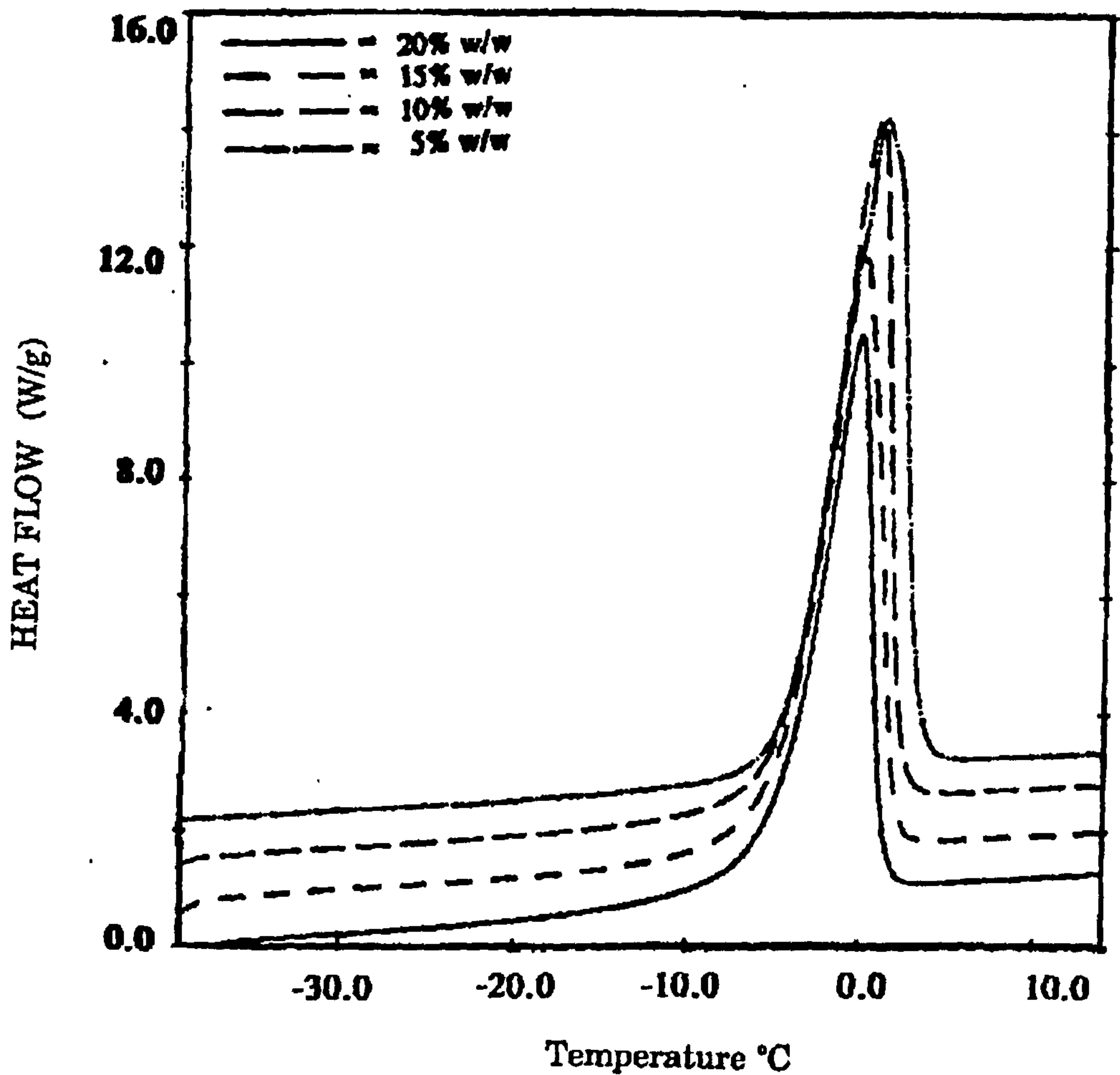
#### 5.2.2.1.3 Methodology

The enthalpies of gels were determined as described in section 2.2.2.3.

#### 5.2.2.2 Results and discussion

Typical DSC scans of aqueous solutions containing propranolol hydrochloride are shown in figure 5.2 and the resultant enthalpies are presented in table 5.1. The values of the melting enthalpy decreased as the concentration of propranolol hydrochloride in the solutions increased. The data were used as basis for comparison of the melting enthalpies of the aqueous propranolol hydrochloride solutions with those of HPMC K4M gels containing similar concentrations of drug. Extrapolation of the data from plot in figure 5.2 to zero enthalpy by linear regression, indicates that the composition of the eutectic of water and propranolol hydrochloride was  $57.8 \pm 3.1\%$  propranolol hydrochloride : 42.2% water. Mitchell et al (1991b) reported a similar value

Figure 5.2 Differential scanning calorimetry scans of solutions containing 5, 10, 15 or 20% w/w propranolol hydrochloride



equal to 61.9% : 38.1% w/w propranolol : water.

Figures 5.3, 5.4 and 5.5 show the DSC scans of gels containing propranolol hydrochloride (5, 10 or 15% w/w) and different concentrations (5, 10, 15 or



20% w/w) of HPMC K4M. Table 5.1 gives the melting enthalpies determined.

Figure 5.6 was obtained by plotting these enthalpies (table 5.1) against the HPMC K4M content of the gels. Acceptable linear relationships ( $r > 0.997$ ) were observed between the free water detected and the concentration of HPMC K4M at each concentration of propranolol hydrochloride (figure 5.6). Data obtained from the extrapolation of the linear portion of the gels containing HPMC K4M and varying concentrations of propranolol hydrochloride (5, 10 or 15% w/w), to zero enthalpy in figure 5.6, are presented in table 5.2 which indicates the minimum water content required to form fully hydrated gels.

These data clearly show that with 10% propranolol hydrochloride and various concentrations of HPMC K4M, the zero enthalpy observed was higher than at gels containing 5% or 15% propranolol hydrochloride, or in other words less water was required to produce the gels. Similar results have been reported by Mitchell et al (1991b) using 10-40% propranolol hydrochloride and varying concentrations of HPMC K15M. They showed that the intercept to zero enthalpy for gels containing 10% propranolol hydrochloride and varying concentrations of HPMC K15M was 55.4% solid (10: 90 propranolol : HPMC K15M) : 44.6% water. Mitchell et al (1989) claimed that with 10% propranolol hydrochloride, less water was required to produce a fully hydrated gel. Mitchell et al (1991b) suggested that the decrease in zero enthalpy following the inclusion of propranolol hydrochloride might be due

Table 5.1: The melting enthalpies of gels containing 0, 5, 10 or 15% w/w of propranolol hydrochloride (PH) and 0, 5, 10, 15 or 20% w/w of HPMC K4M, 24 hours after preparation. Results are obtained from at least two determinations.

HPMC K4M gel Concentration (% w/w)	Melting enthalpies (J g <sup>-1</sup> )			
	0% PH*	5% PH	10% PH	15% PH
0 %	321.2 ± 2.8	318.1 ± 5.7	280.1 ± 4.8	248.2 ± 2.9
5 %	283.6 ± 8.1	286.9 ± 7.3	254.8 ± 7.1	202.7 ± 2.0
10 %	257.2 ± 11.5	240.6 ± 11.4	233.9 ± 7.6	172.0 ± 0.2
15 %	214.1 ± 5.7	214.7 ± 12.2	201.2 ± 3.3	142.9 ± 2.2
20 %	188.1 ± 3.4	175.5 ± 12.3	171.2 ± 10.7	119.3 ± 2.1

\* Equivalent to the melting enthalpies of HPMC K4M gels alone.

Figure 5.3: Differential scanning calorimetry of gels containing 5-20% (w/w) HPMC K4M and 5% w/w of propranolol hydrochloride.

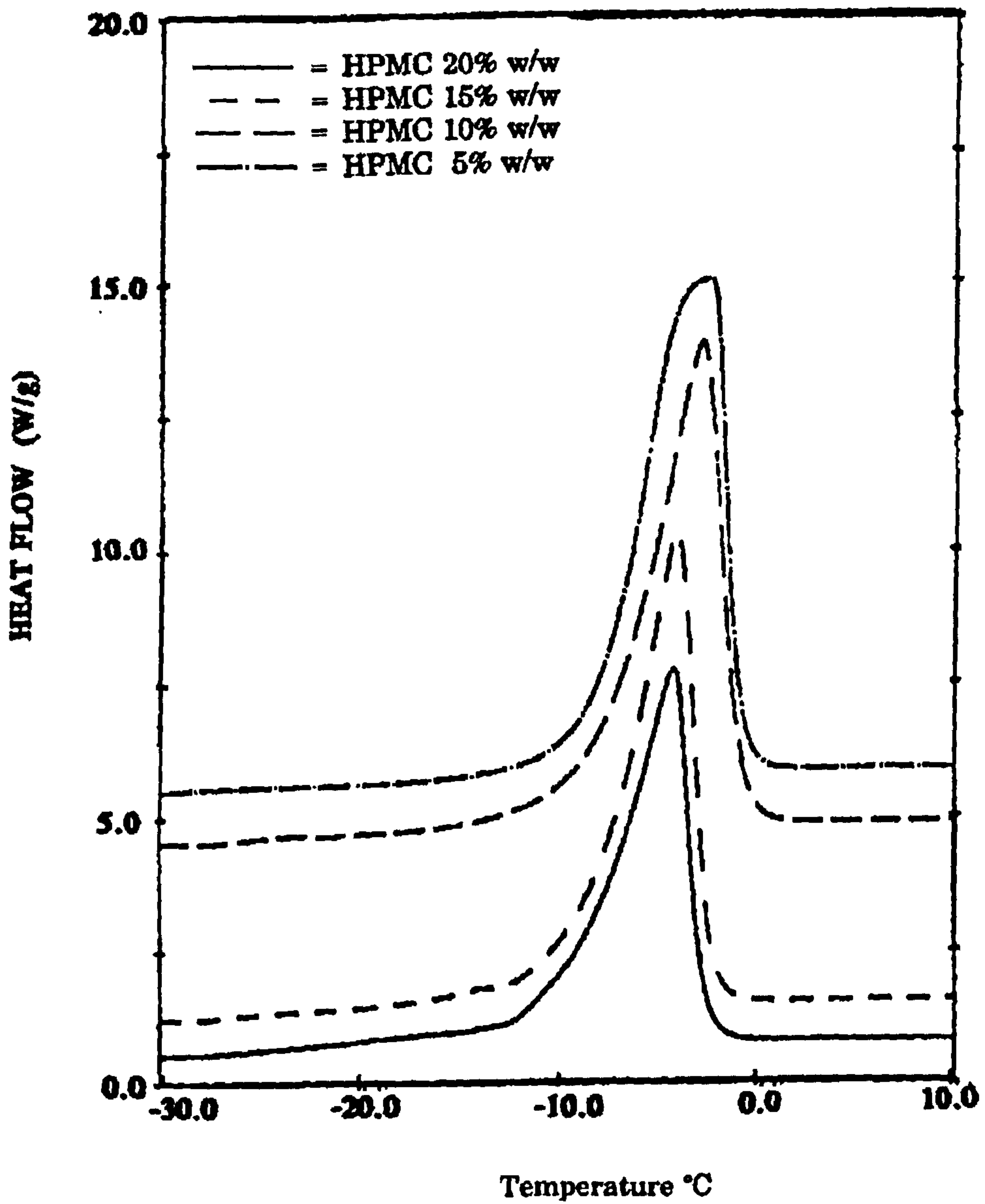




Figure 5.4: Differential scanning calorimetry of gels containing 5-20% (w/w) HPMC K4M and 10% w/w of propranolol hydrochloride.

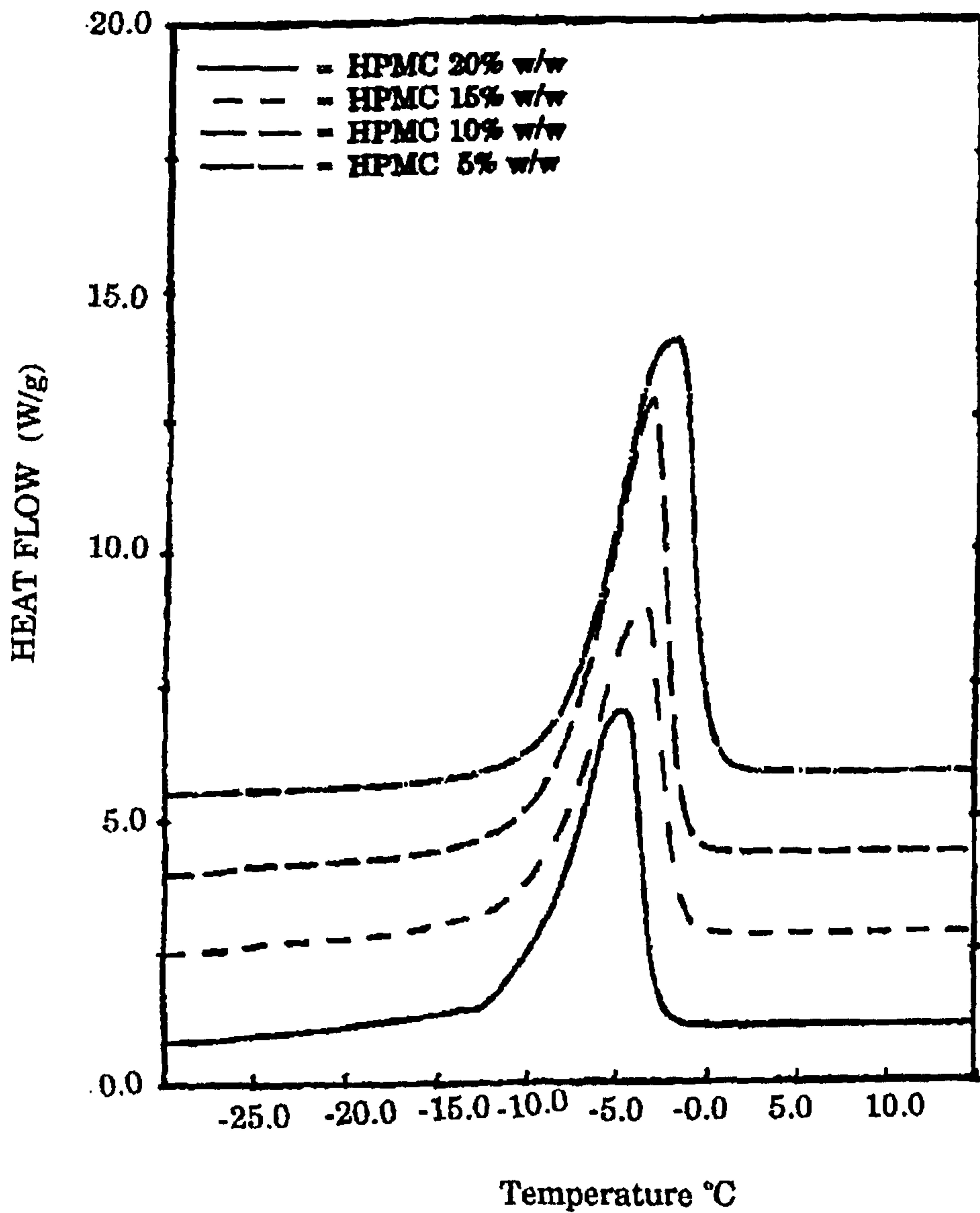


Figure 5.5: Differential scanning calorimetry of gels containing 5-20% (w/w) HPMC K4M and 15% w/w of propranolol hydrochloride.

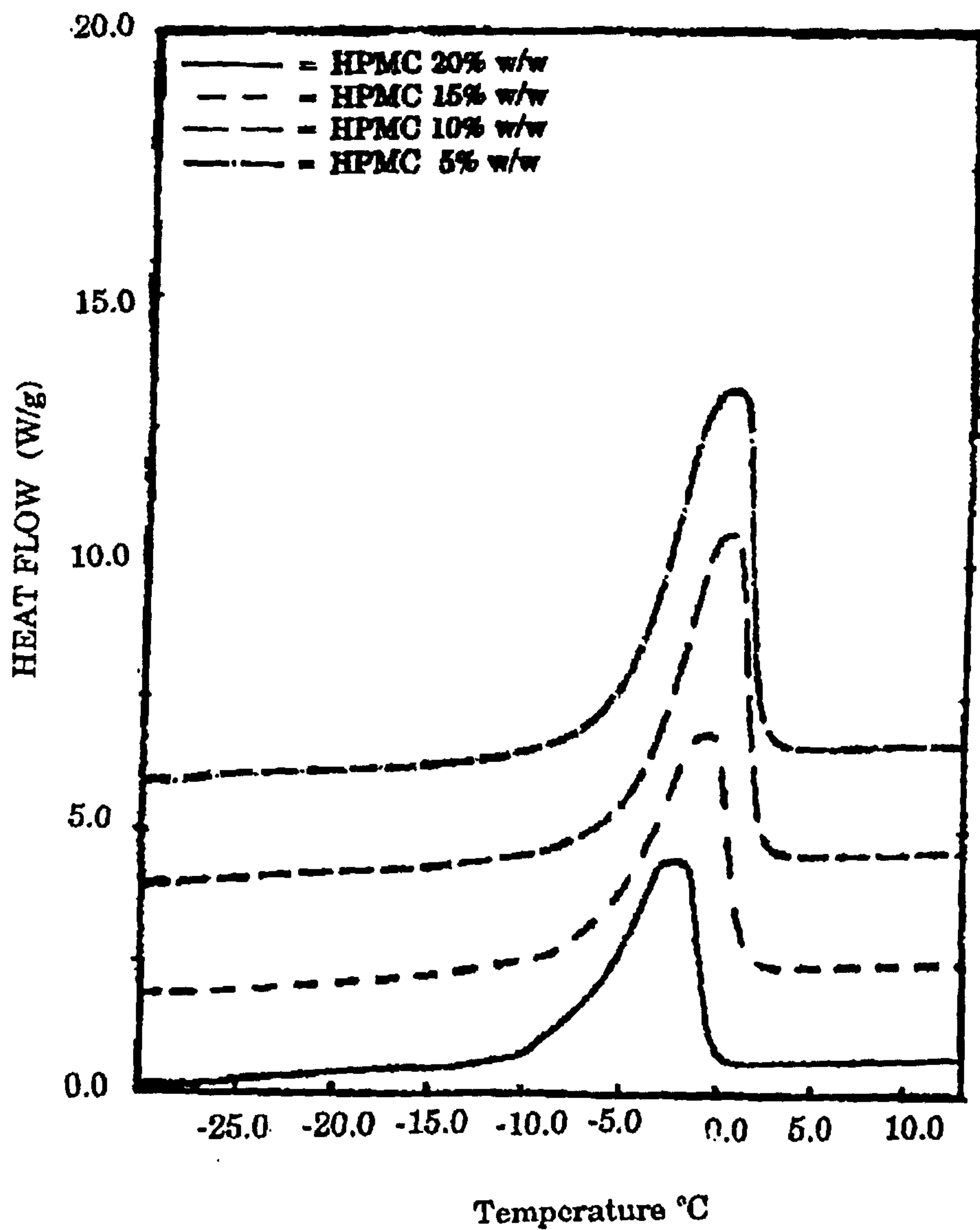


Figure 5.6: The effect of propranolol hydrochloride (0, 5, 10 or 15% w/w) on the melting enthalpies of free water produced from gels containing 0, 5, 10, 15 or 20% w/w HPMC K4M.

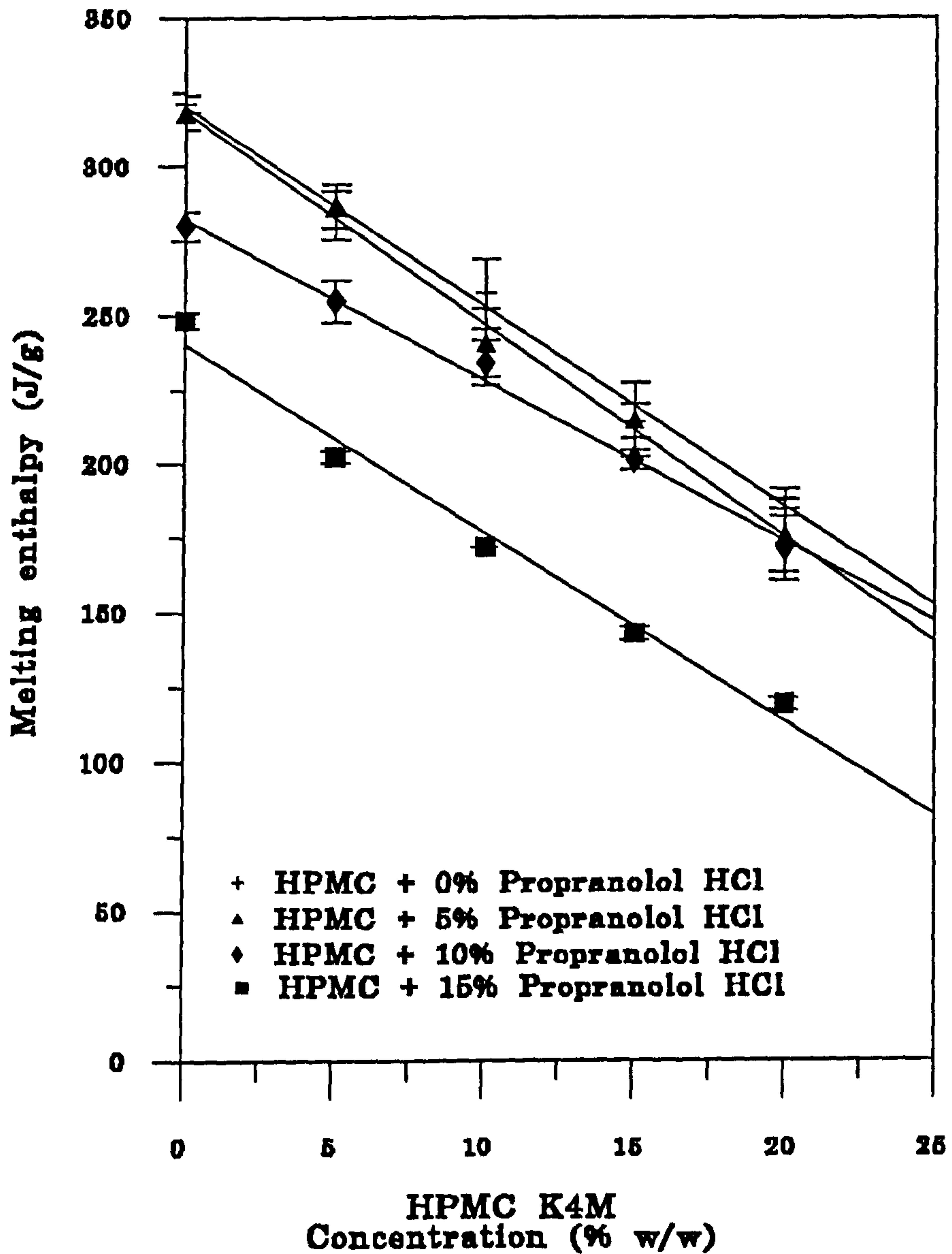




Table 5.2: The effects of propranolol hydrochloride concentrations (% w/w) on the water required to fully hydrate HPMC K4M in gels containing propranolol hydrochloride and HPMC K4M. The ratio of water : HPMC at equilibrium hydration of the gels is also given. Results are the means  $\pm$  SD of three determinations.

Propranolol hydrochloride (% w/w)	HPMC K4M content (% w/w)	Water required (% w/w)	Ratio of g water/100 g HPMC K4M
0	46.6 $\pm$ 1.3	53.4	114.6 $\pm$ 1.5
5	48.1 $\pm$ 7.5	51.9	107.9 $\pm$ 8.1
10	54.4 $\pm$ 6.7	45.6	83.8 $\pm$ 5.6
15	47.5 $\pm$ 7.2	52.5	110.5 $\pm$ 7.9

to the precipitation of propranolol hydrochloride crystals. The mechanism of the effect of propranolol hydrochloride on HPMC matrices is unknown, however the implications of these studies are that drugs play an active role in controlling the structure of HPMC matrices during their hydration.

### 5.3 INTERACTION BETWEEN PROPRANOLOL HYDROCHLORIDE AND SODIUM CARBOXYMETHYLCELLULOSE

Although polymers are usually considered to be chemically inert, many of them interact with drug molecules resulting in physical or chemical

incompatibilities (Lin and Perng, 1993). Interactions between drug and excipient may influence the technological and biopharmaceutical properties of solid dosage forms (Lin and Perng, 1993).

During the study it was found that there was an interaction between propranolol hydrochloride and NaCMC. Addition of aqueous solutions of propranolol hydrochloride to NaCMC gels, immediately produced a precipitate, suggesting an interaction. The interaction between NaCMC and various tranquilizers and hypotensive agents has previously been reported by Graham et al (1963). Graham et al (1963) reported that highly insoluble complexes were formed between NaCMC and promazine hydrochloride or chlorpromazine hydrochloride.

In order to explain the release of propranolol hydrochloride from matrices containing NaCMC, it was necessary to characterize this interaction. Therefore, differential scanning calorimetry (DSC) and equilibrium dialysis were used to evaluate the nature of the interaction.

### **5.3.1 Cloud points of propranolol hydrochloride and NaCMC**

Gels containing NaCMC did not display cloud points (section 4.3). Initially, the aim of this part of the study was to investigate the effect of propranolol hydrochloride on the gels containing NaCMC and 1:1 mixtures of HPMC : NaCMC, but after addition of propranolol hydrochloride to NaCMC gels a precipitate was produced, which made it impossible to determine the cloud

point and water distribution of gels containing NaCMC or admixture of HPMC and NaCMC with propranolol hydrochloride.

### **5.3.2 Differential scanning calorimetric (DSC) analysis**

To study the interaction between propranolol hydrochloride and NaCMC, physical mixtures of propranolol hydrochloride and NaCMC were made and tested.

#### **5.3.2.1 Experimental**

##### **5.3.2.1.1 Materials**

Propranolol hydrochloride, sodium carboxymethylcellulose (Blanose) and glass-distilled water were used as described in section 2.1.

##### **5.3.2.1.2 Preparation of physical mixtures of propranolol hydrochloride and NaCMC**

Physical mixtures of propranolol hydrochloride (<125  $\mu\text{m}$ ) and NaCMC (Blanose) were prepared by mixing the required amounts of propranolol hydrochloride and NaCMC (total amount, 5 g) in a 30 mL jar and blending for 15 minutes using an electric mixer. Mixtures were prepared to contain 1:0, 3:1, 1:1 or 1:3 propranolol hydrochloride : NaCMC (Blanose). Accurately weighed samples in the range of 4-6 mg were placed in aluminum DSC sample pans (6.35 mm diameter).



#### 5.3.2.1.3 Preparation of precipitate of propranolol hydrochloride and NaCMC

The methods of Ranga Rao et al (1988b) were initially used to prepare the precipitate formed between propranolol hydrochloride and NaCMC. These methods were mixing aqueous solutions of drug (pindolol hydrochloride, alperenolol hydrochloride or salicylic acid) with the aqueous dispersions of NaCMC or HPMC K4M at different ratios and drying at room temperature. However, when the precipitate dried, it was very hard and inhomogeneous. Therefore, the methods were slightly changed. Samples containing 4-6 mg of physical mixtures of propranolol hydrochloride : NaCMC were accurately weighed into empty sample pans (Perkin-Elmer, 6.35 mm diameter) and approximately 30 mg distilled water (using a micro syringe) was added into the pans. The samples were placed in an oven at 50°C for about one hour to allow the water to evaporate and to achieve their previous weight. In comparison samples containing only propranolol hydrochloride were similarly examined.

#### 5.3.2.1.4 DSC methodology

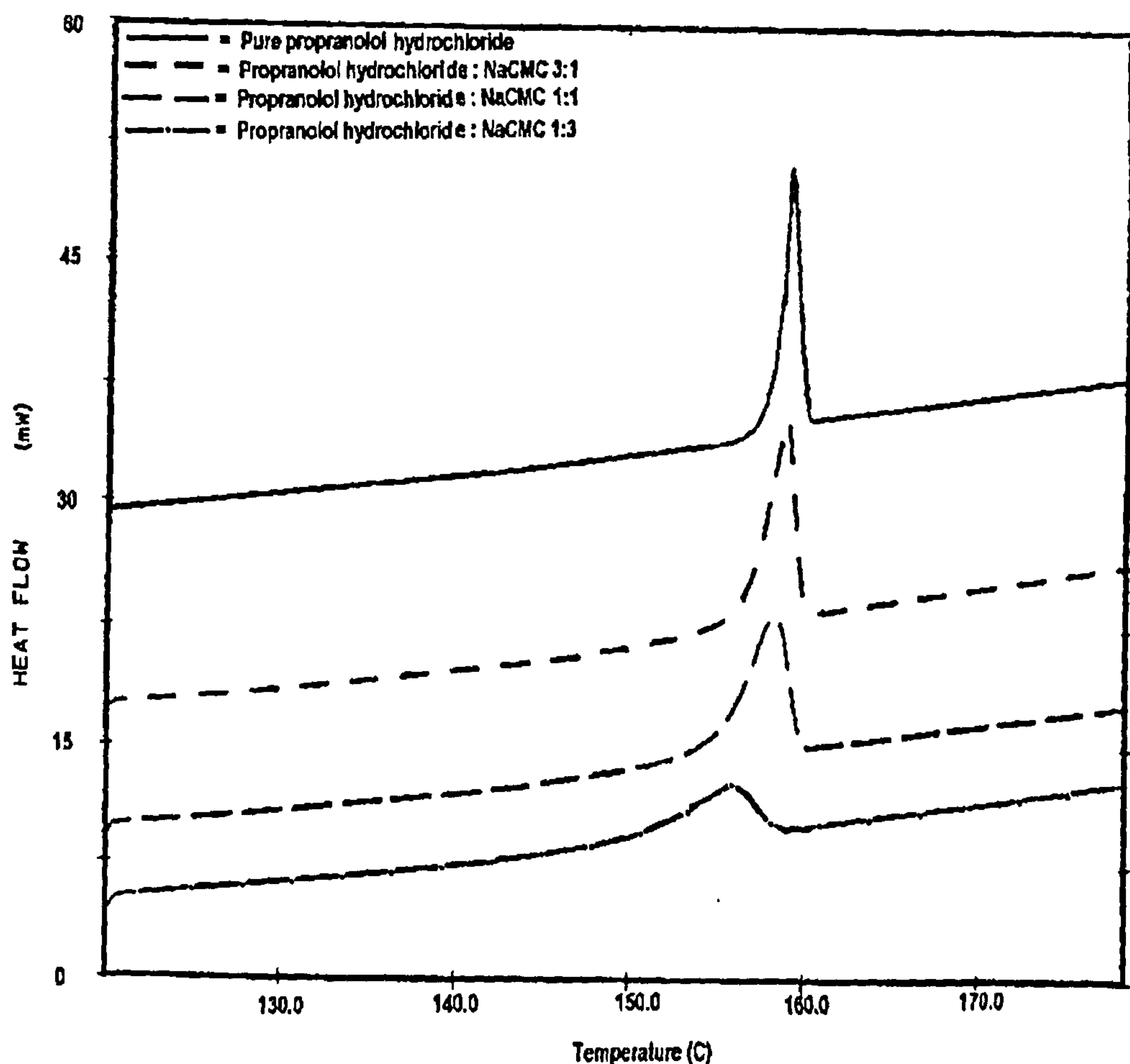
An aluminum lid was placed on top of each sample discussed in sections 5.3.2.1.2 or 5.3.2.1.3. The samples were kept unsealed. The samples were scanned from 120°C to 180°C at 3°C min<sup>-1</sup> and the fusion enthalpies were determined. The enthalpies were determined in at least triplicate.

#### 5.3.2.2 Result and discussion

Figure 5.7 shows typical DSC scans of physical mixtures containing 1:0, 3:1,

1:1 or 1:3 propranolol hydrochloride : NaCMC (Blanose). The enthalpies of fusion associated with the propranolol hydrochloride in the mixtures are presented in table 5.3.

Figure 5.7: DSC scans of samples containing physical mixtures of 1:0, 3:1, 1:1 or 1:3 propranolol hydrochloride : NaCMC



The enthalpy of fusion of propranolol hydrochloride was  $123.8 \pm 1.2 \text{ J g}^{-1}$  (table 5.3). Similar data were reported by Sanghavi and Shiravadekiar (1994)

who showed that propranolol hydrochloride had a melting enthalpy of 122.6 J g<sup>-1</sup>. Neau et al (1993) reported a value 35.1 KJ/mol which was made up of 118.66 J g<sup>-1</sup> for the (-) enantiomer of propranolol hydrochloride and 124.75 J g<sup>-1</sup> for the (+) propranolol hydrochloride.

Table 5.3: The melting enthalpies of propranolol hydrochloride obtained from physical mixtures and dried physical mixtures which had been exposed to water previously, at the ratios 1:0, 3:1, 1:1 or 1:3 propranolol hydrochloride : NaCMC (Blanose) (results are the means  $\pm$  SD of four determinations)

Ratio PH* : NaCMC	Melting enthalpies (J/g propranolol HCl)	
	Physical mixture	Dried samples
1 : 0	123.8 $\pm$ 1.2	117.2 $\pm$ 1.1
3 : 1	112.3 $\pm$ 6.4	22.0 $\pm$ 4.0
1 : 1	108.6 $\pm$ 3.0	8.3 $\pm$ 1.2
1 : 3	77.9 $\pm$ 2.7	2.8 $\pm$ 1.2

\* PH is Propranolol hydrochloride

The DSC data, given in table 5.3, reveal that the scans of propranolol hydrochloride when mixed with NaCMC in dry form, decreased indicating a weak interaction between the two ingredients. In contrast, the values of



enthalpy from samples which had been treated with water and dried, decreased compared to the equivalent physical mixture. These decreases suggest that an interaction occurred between propranolol hydrochloride and NaCMC.

In thermal analysis, a sharp symmetric peak can indicate relative purity whereas broad curves suggest impurities or interaction. This fact is seen in figure 5.7 in which propranolol hydrochloride showed a sharp endothermic peak at about 159°C. As the concentration of NaCMC in the samples increased, the sharpness of the curves decreased and the melting peak slightly decreased (e.g., from 159°C for pure propranolol hydrochloride to 155.9°C for the ratio 1:3 propranolol hydrochloride : NaCMC mixture). The peaks for propranolol hydrochloride powder and recrystallised propranolol hydrochloride and were similar. However, the peaks of propranolol hydrochloride in the presence of NaCMC were examined, following the addition of water, which were considerably reduced. These results indicate that the produced mass is different in its physicochemical properties from the physical mixture of propranolol hydrochloride and the polymer.

Similar results were observed by Ranga Rao et al (1988b) using mixtures of pindolol hydrochloride with NaCMC or HPMC K4M. They reported that admixture of solutions of pindolol hydrochloride and NaCMC or HPMC and analysis of the resultant precipitate, significantly reduced the fusion enthalpy of pindolol hydrochloride whereas, there were small differences between pure

pindolol and its 1:1 physical mixture with NaCMC.

From table 5.3 it is seen that the melting enthalpy decreased as the proportion of NaCMC in the samples increased. Following the addition of water, the interaction between propranolol hydrochloride and NaCMC significantly increased, a possible reason being the formation of a complex between propranolol and CMC. To further investigate this interaction a dialysis method was used.

### **5.3.3 Assessment of interaction between propranolol hydrochloride and NaCMC by equilibrium dialysis**

Dialysis tubing is capable of retaining polymer molecules with large molecular weight with allowing diffusion of smaller molecules such as drugs. If any interaction between drug and polymer occurs, a big molecule will be formed which can not pass through dialysis bag. This method was used to determine the degree of binding between propranolol hydrochloride and NaCMC to evaluate the propranolol-CMC complex formation.

#### **5.3.3.1 Experimental**

##### **5.3.3.1.1 Materials**

Propranolol hydrochloride and NaCMC (Blanose) were used as described in section 2.1.

#### 5.3.3.1.2 Dialysis tubing

Dialysis visking tubing size 5-24/32 (Medicell International, U.K.) was used. Prior to use, the dialysis tubes (15 cm in length) were soaked overnight in deionized water and then rinsed under running deionized water.

#### 5.3.3.1.3 Methodology

The methods of Tucker et al (1988) for determination of binding between propranolol hydrochloride and NaCMC were used with slight modification. Tucker et al (1988) prepared samples (10 mL) by mixing stock solutions of propranolol hydrochloride and NaCMC to contain 10 to 50 mg propranolol hydrochloride and 20 to 50 mg NaCMC at different ratios. They placed the samples in an Amicon Reusable Micropartition System MPS-1 with YMT membrane, then after centrifuging the samples, determined the free propranolol hydrochloride. However, due to the high viscosity produced using NaCMC, transferring the samples to dialysis bags was difficult and the results poorly reproducible. Therefore the methods of Tucker et al (1988) were modified.

After treatment of the dialysis tubes, one end of the tubes was tied by a knot and 0, 25, 50, 100, 200, 300, 400, 500 or 600 mg of NaCMC powder was placed in the bottom of the bags. Five millilitre of an aqueous solution containing 2% (w/v) of propranolol hydrochloride (100 mg) was then placed in each dialysis bag. The bags were then tightly closed by knotting the open end, leaving enough space to allow increase in volume and placed in a



ground-glass stoppered Erlenmyer flask (125 mL). 95 mL distilled water was added to each Erlenmyer flask. The Erlenmyer flasks were then stoppered tightly and agitated in a thermostated shaking water bath at 37°C for 24 hours. Thereafter, 1 mL samples were removed from the Erlenmyer flasks and diluted to 25 mL with distilled water and the amounts of free propranolol hydrochloride released through the dialysis bags were determined spectrophotometrically at 288 nm. The amount of propranolol hydrochloride bound to the NaCMC was then calculated by subtracting the equilibrium content of the free propranolol hydrochloride from the total concentration of propranolol (100 mg) used in the samples. The free propranolol hydrochloride was calculated by equation 5.1 which was produced from equation 2.1, discussed in section 2.2.3.1.

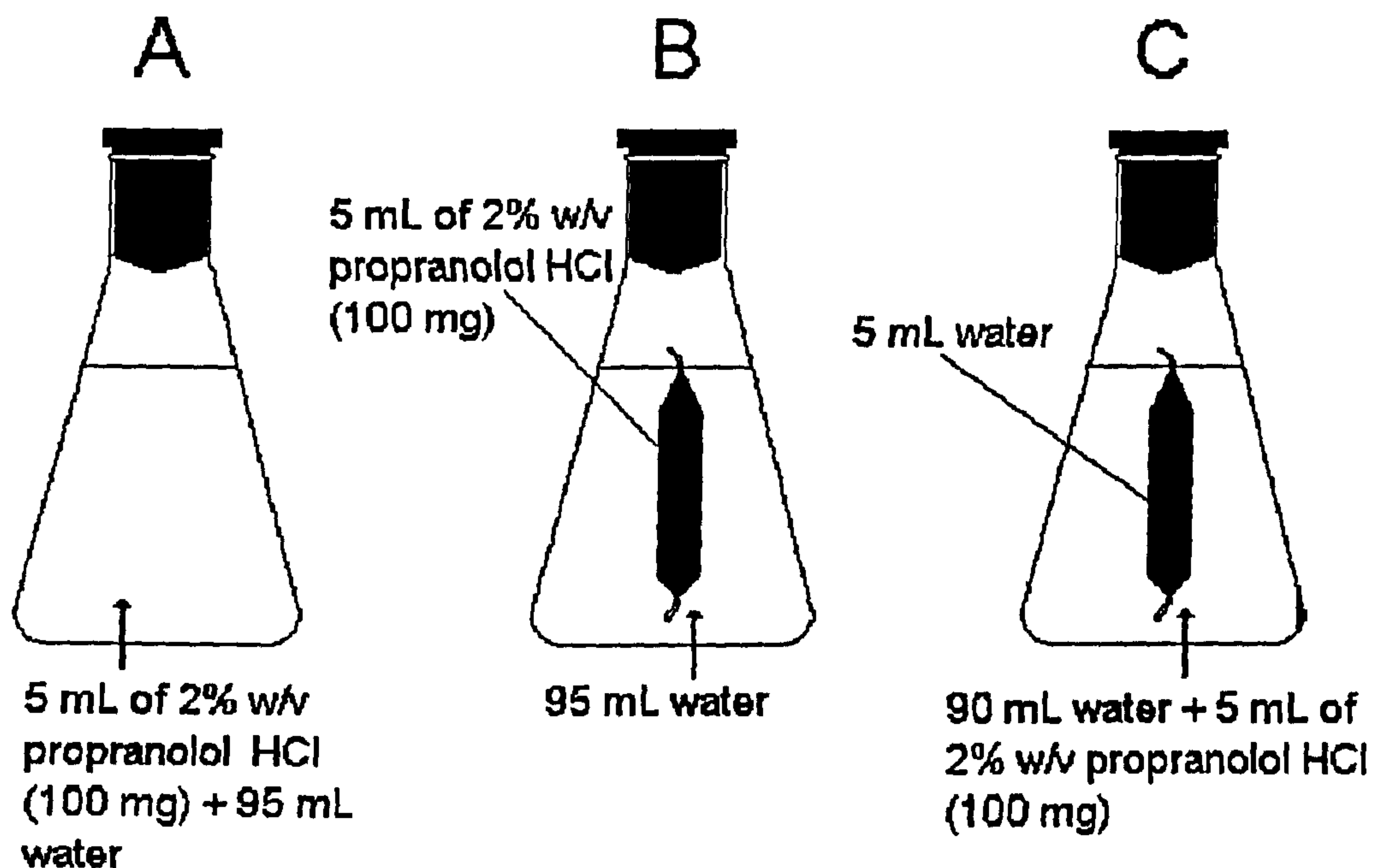
$$C = (Y - 0.054) / 18.11 \qquad \text{Equation 5.1}$$

where: Y = absorbance of propranolol hydrochloride at 288 nm and C = concentration of propranolol (mg) in 1 mL of the sample.

#### 5.3.3.1.4 Validation

Before conducting the experiments, the suitability of the dialysis bag for diffusion of propranolol hydrochloride was investigated by determining the free propranolol hydrochloride in the fluids on either side of the dialysis membrane. For this purpose, the following validation experiments were performed as shown in figure 5.8.

Figure 5.8: Diagram of dialysis tests in Erlenmyer flask at 37°C



Aliquots, 5 mL, of an aqueous solution containing 2% (w/v) of propranolol hydrochloride (=100 mg) were used in each test of A, B and C. The samples of propranolol hydrochloride were placed in a ground-glass stoppered Erlenmyer flask (125 mL) and then kept at 37°C in a shaking water bath. After 1 hour, 1 mL samples from the aqueous solution in the Erlenmyer flasks and from the inside of the dialysis bags were removed and diluted to 25 mL with distilled water. Then the amount of propranolol hydrochloride was measured spectrophotometrically at 288 nm.

Tests A and B were carried out to see if propranolol hydrochloride could be

absorbed by dialysis bag. Tests B and C were performed to understand if propranolol hydrochloride could pass through dialysis bag. However, it was observed that the concentrations of propranolol hydrochloride in all samples (i.e. in the fluids on either side of dialysis bag) were equal. Therefore, these tests showed that propranolol could pass freely through the membranes of dialysis bags in both directions and that it would reach an equilibrium within an hour. Also, calculation of the mass balance revealed that no propranolol was bound to the dialysis membrane at equilibrium.

Another validation experiments was performed by placing samples containing 100 mg propranolol hydrochloride (5 mL of 2% aqueous solution) and 100 mg NaCMC (Blanose) powder as described in section 5.3.3.1.3 in the dialysis bag. Determination of free propranolol at different periods of time (5, 10, 15 or 24 hours) showed an initial decrease in free propranolol but no differences were observed between 15 and 24 hours, indicating that the binding of propranolol to the polymer had reached an equilibrium. Therefore, sampling for equilibrium dialysis studies was made at 24 hours. The data obtained are presented in table 5.4. The validation clearly showed that propranolol hydrochloride could pass through the dialysis bag in both directions.

#### **5.3.4 Results and discussion**

Figure 5.9 shows the effect of increasing NaCMC content on the binding with propranolol hydrochloride. As the NaCMC content in the dialysis bag increased, the free propranolol hydrochloride in the fluid outside the dialysis



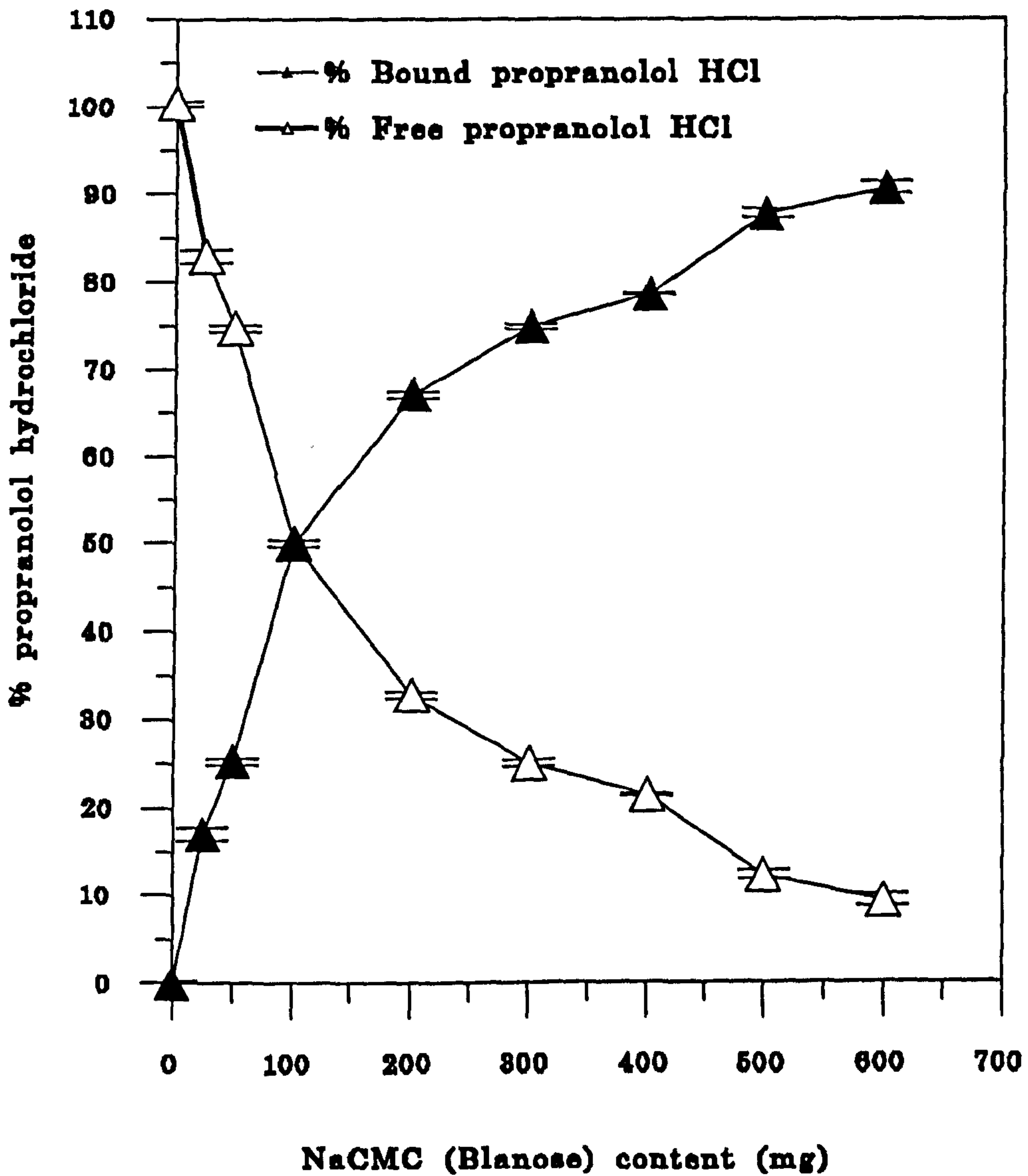
Table 5.4: The effect of time on the binding of propranolol hydrochloride to NaCMC (Blanose) in dialysis bag (results are the means  $\pm$  SD of three tests).

Time (hour)	% Propranolol hydrochloride	
	Free	Bound
5	66.1 $\pm$ 1.7	33.9
10	55.4 $\pm$ 0.7	44.6
15	50.0 $\pm$ 0.4	50.0
24	50.0 $\pm$ 0.4	50.0

bag decreased and subsequently the percentage of propranolol hydrochloride bound to NaCMC increased. Tucker et al (1988) using propranolol hydrochloride and NaCMC, reported that one propranolol cation would be bound to each carboxy anion of the sodium carboxymethylcellulose. Lee et al (1991) reported an interaction by using propranolol hydrochloride and methacrylic acid. They claimed that since the cationic propranolol hydrochloride reacts with the anionic polymer to form a sparingly soluble complex, the product could be used as matrix tablet for prolonged release of propranolol hydrochloride.

However, by considering the approximate value of the polymer repeating unit

Figure 5.9: The effect of NaCMC (Blanose) concentration on its binding to propranolol hydrochloride (100 mg). Results are the means  $\pm$  SD of three determinations.



(PRU) of NaCMC which is 326.2 and the molecular weight of propranolol hydrochloride which is 295.8, it is possible to evaluate the interaction between propranolol hydrochloride and the average PRU of NaCMC.

The structural formula of cellulose ethers is shown in figure 1.8 (section 1.5.1) and the PRU of NaCMC is shown in figure 5.10.

Figure 5.10 : Typical polymer repeating unit of NaCMC.

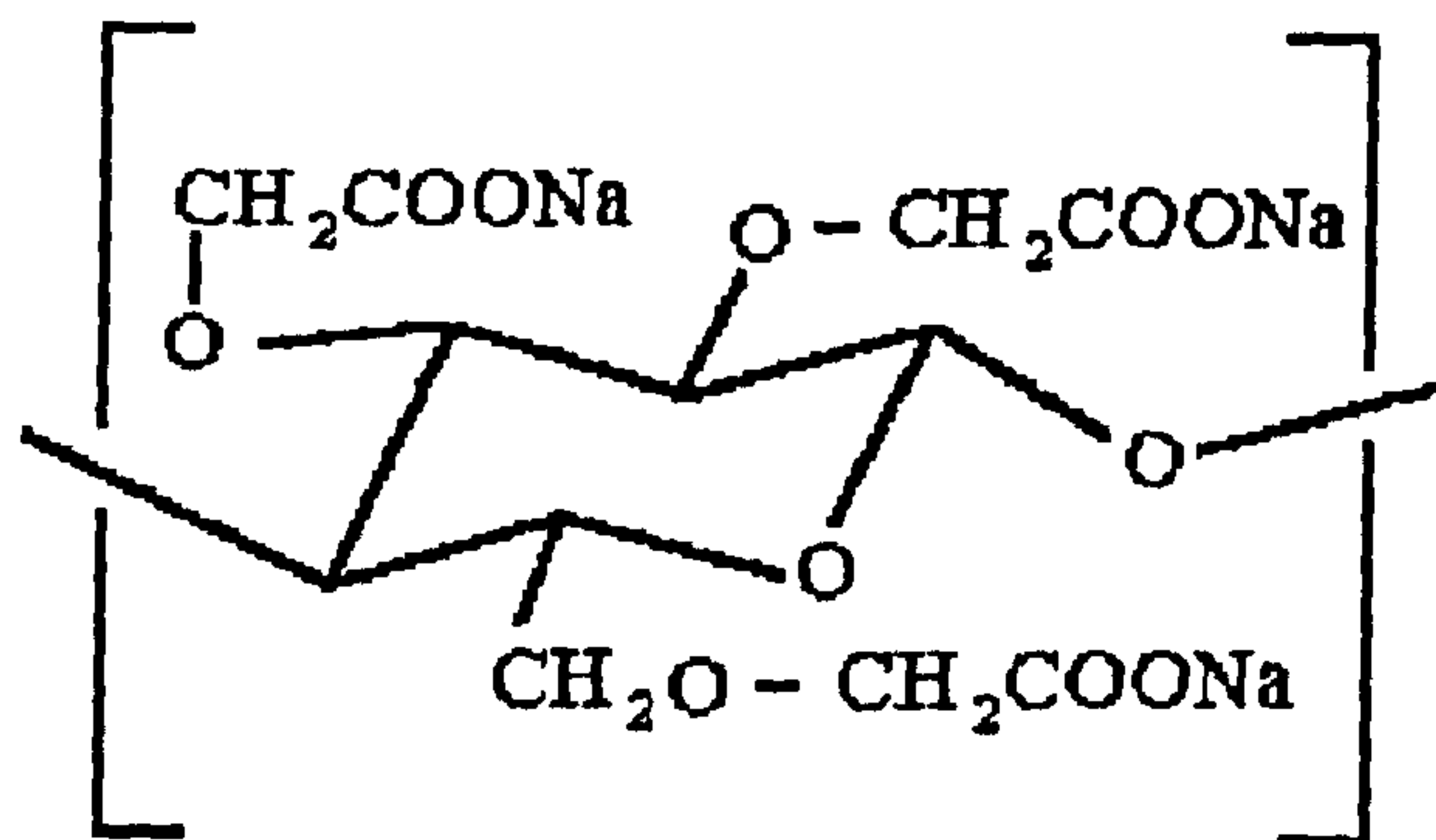


Figure 5.10 shows three sodium ions in each repeating unit of the polymer. However with a DS of 0.7, only 70% of these positions would be taken up. When propranolol hydrochloride is present in aqueous solution with NaCMC, each sodium in NaCMC can potentially be replaced by a propranolol moiety. Therefore each propranolol base can potentially occupy each of the sites and subsequently produce precipitates of an insoluble CMC : propranolol complex. This reaction can be expressed in the following equation:





where PCI is propranolol hydrochloride.

It is obvious that the number of sites occupied depends on the amount of NaCMC and propranolol hydrochloride in the reaction and the DS of NaCMC. The molecule of propranolol hydrochloride is small compared to the molecule of NaCMC, but large compared to the sodium atom whose space it could occupy. It is unlikely that all three sites of sodium would be saturated with propranolol. The number of sites that require replacement before precipitation is unknown. It is therefore difficult to create a model to describe precisely the binding interaction between propranolol hydrochloride and NaCMC, but three interpretations were attempted.

1) A dissociation constant for equation 5.2, may be expressed by the following:

$$K = \frac{[NaCl] [PCMC]}{[PCI] [NaCMC]} \quad \text{Equation 5.3}$$

It is possible to use equation 5.3, to calculate the dissociation constant  $K'$  for the tabulated NaCMC concentrations (table 5.5) using the following assumptions:

(a) the molecular weight of NaCl is 58.5.

- (b) the molecular weight of propranolol hydrochloride (PCl) is 295.8
- (c) the PRU of NaCMC is approximately 326.2.
- (d) from the above, the value of PCMC may be calculated as the PRU of NaCMC plus the molecular weight of propranolol hydrochloride (PCl) less the molecular weight of NaCl. Therefore the value obtained is 563.5.
- (e) The values of free propranolol (FP) and bound propranolol (BP) are measured after 24 hours and are shown graphically in figure 5.9.

An example of the calculation for 25 mg of NaCMC is shown below :

$$\left[ \frac{\left[ \frac{MW(NaCl)}{MW(PCl)} \times (BP) \right] \times \left[ \frac{PRU(PCMC)}{MW(PCl)} \times (BP) \right]}{\left[ (FP) \right] \times \left[ NaCMC(mg) - \frac{PRU(NaCMC)}{MW(PCl)} \times (BP) \right]} \right] \quad \text{Equation 5.4}$$

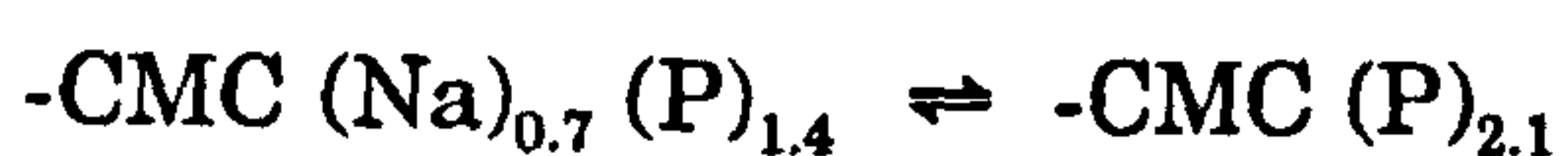
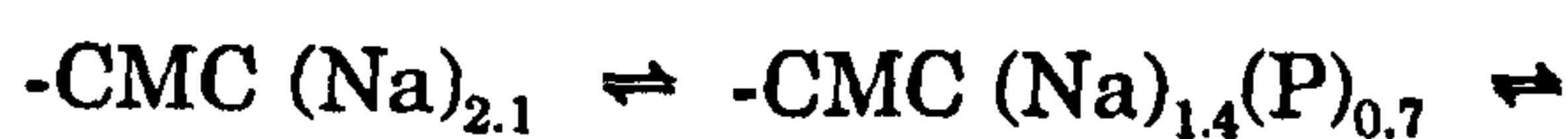
$$\left[ \frac{\left[ \frac{(58.5)}{(295.8)} \times (17) \right] \times \left[ \frac{(563.5)}{(295.8)} \times (17) \right]}{\left[ (83) \right] \times \left[ 25 - \frac{(326.2)}{(295.8)} \times (17) \right]} \right] = 0.21 \quad \text{Equation 5.5}$$

The values of dissolution constant from different amounts of NaCMC which were used in this study are presented in table 5.5. The values show an approximate five-fold range of values showing that the simple model predicted by equation 5.3 is inappropriate.

2) By considering the degree of substitution of NaCMC (0.7) and the three sodium ions in each PRU of NaCMC, the interaction between NaCMC with propranolol hydrochloride should follow equation 5.6.

Table 5.5: The estimated values of dissociation constant from binding interaction between propranolol hydrochloride and NaCMC (Blanose)

NaCMC (mg)	Dissociation constant (K')
25	0.21
50	0.15
100	0.42
200	0.42
300	0.40
400	0.35
500	0.60
600	0.69



Equation 5.6

Therefore it is possible to determine the theoretical values of the weight (mg) of propranolol hydrochloride bound to NaCMC for each of the three propranolol-CMC complexes. The values obtained are presented in table 5.6.

As can be seen from table 5.6, for 25 mg NaCMC, 17 mg propranolol was bound indicating that more than one site previously occupied by sodium was occupied. However, for 50 mg or more NaCMC not even one sodium site



completely is occupied in each PRU of NaCMC. This result is in contrast to the finding of Tucker et al (1988) who reported that one propranolol cation would be bound to each carboxy anion of the NaCMC.

Table 5.6: The theoretical values of mg propranolol hydrochloride bound to NaCMC, assuming different degrees of binding, as well as the assumed in equation 5.6 and actual values.

NaCMC (mg)	mg propranolol hydrochloride bound to NaCMC			
		Degrees of substitution (NaCMC:P)		
	Actual	1:0.7	1:1.4	1:2.1
25	17.0	15.9	31.7	47.6
50	25.4	31.7	63.4	95.2
100	50.0	63.5	127.0	190.4
200	67.4	126.9	253.9	380.9
300	75.2	190.4	380.8	571.3
400	78.8	253.9	507.8	761.7
500	87.9	317.4	634.8	952.1
600	91.0	380.9	761.7	1142.6

3- A Langmuir equation is expressed by equation 5.7,

$$r = \frac{K[PH]}{1 + K[PH]} \quad \text{Equation 5.7}$$

in which  $r$  is number of moles of propranolol bound per mole of total PRU of NaCMC and  $K$  is an association constant. The data obtained are presented in table 5.7. The data are plotted in figure 5.11, following rearrangement of equation 5.7 to give equation 5.8.

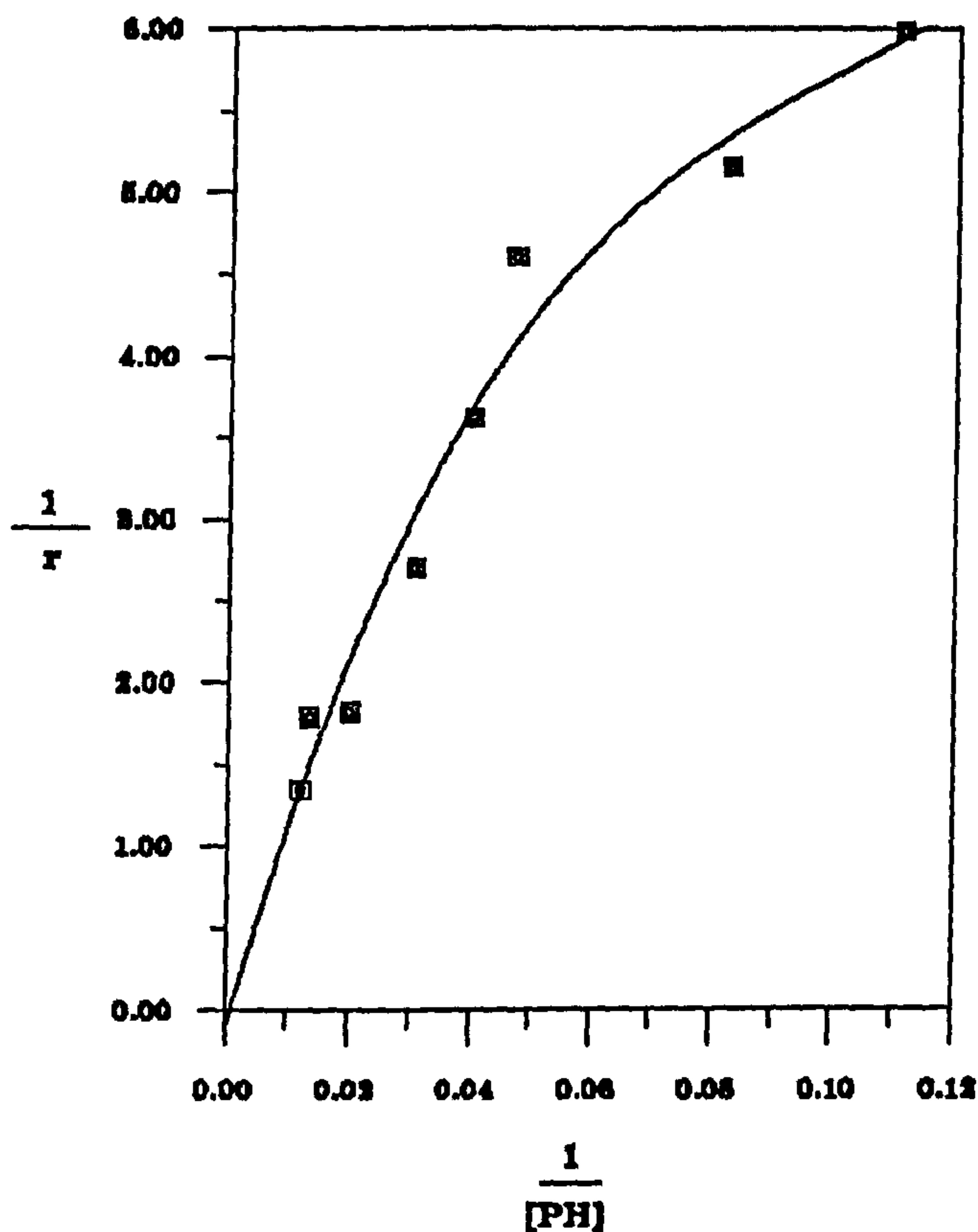
$$\frac{1}{r} = \frac{1}{K[PH]} + 1 \quad \text{Equation 5.8}$$

According to Martin et al (1983) such a plot as shown in figure 5.11 should be a straight line. Clearly, there is considerable curvature and this confirms, along with tables 5.5 and 5.6 that more than one binding site for proprnaolol hydrochloride on NaCMC exist.

Table 5.7: The values of  $r$  (number of moles of drug bound per amount of used NaCMC as PRU of NaCMC) as well as free propranolol hydrochloride

NaCMC (mg)	$r = x/m$	Free PH
25	0.750	83.0
50	0.560	74.6
100	0.550	50.0
200	0.370	32.6
300	0.276	24.8
400	0.217	21.2
500	0.194	12.1
600	0.167	9.0

Figure 5.11: A Langmuir-type plot showing the binding of propranolol hydrochloride to NaCMC



#### 5.4 EROSION OF MATRICES CONTAINING HPMC, NACMC OR THEIR MIXTURES

The erosion of a polymer can be defined as the conversion of an initially water-insoluble material to a water-soluble material and does not necessarily signify a major chemical degradation (Heller, 1987b). Drug release from a hydrophilic matrix is the result of several mass transport phenomena. During the initial contact of the matrix with the dissolution media, the drug present



at or near to the surface will dissolve and surface pores fill with the media; the drug consequently is released by dissolution and diffusion through the pores (Gurny et al, 1982). Eventually, drug release from a swollen hydrophilic matrix occurs by diffusion through the gel layer countercurrently to the incoming dissolution fluid and by erosion of the swollen matrix (Hussain et al, 1994). Ranga Rao et al (1989) showed that the drug release profiles can be modified by optimizing the erosion rate of the matrix and also reported that certain other factors, e.g., interaction between the drug and the polymer(s), might govern the release of the drugs. Bettini et al (1994), using different viscosity grades of HPMC, reported that matrices made with lower viscosity grade of HPMC were more erodible. However, in spite of the large quantity of literature written on the erosion of HPMC matrices, there are relatively few reports on the erosion of matrices containing NaCMC (Bonferoni et al, 1992).

#### **5.4.1 Experimental**

##### **5.4.1.1 Materials**

Propranolol hydrochloride (<125 µm), HPMC K4M, NaCMC (Blanose) and lactose (<105 µm) were used as described in section 2.1.

##### **5.4.1.2 Tablet Preparation**

Flat-faced tablets, 12.7 mm diameter, containing 300 mg HPMC, NaCMC, their 1:1 mixture, 1:1:1 HPMC : NaCMC : propranolol hydrochloride or 1:1:1

HPMC : NaCMC : lactose were directly compressed as described in section 2.2.4 at  $182 \text{ MNm}^{-2}$ .

#### 5.4.1.3 Erosion measurement

The methods of Bonferoni et al (1992), were used to determine the erosion of matrices. The USP XXII (Apparatus 1) was used, rotating at 100 rpm, in 500 mL distilled water at  $37^{\circ}\text{C}$ . Tablets were placed in the baskets of dissolution apparatus and were withdrawn at 0.5, 1, 2, 3, 5, 10 or 15 hours and dried to constant weight in an oven at  $60^{\circ}\text{C}$ . The percent erosion was calculated from the weight loss of the matrices. Results were determined in triplicate.

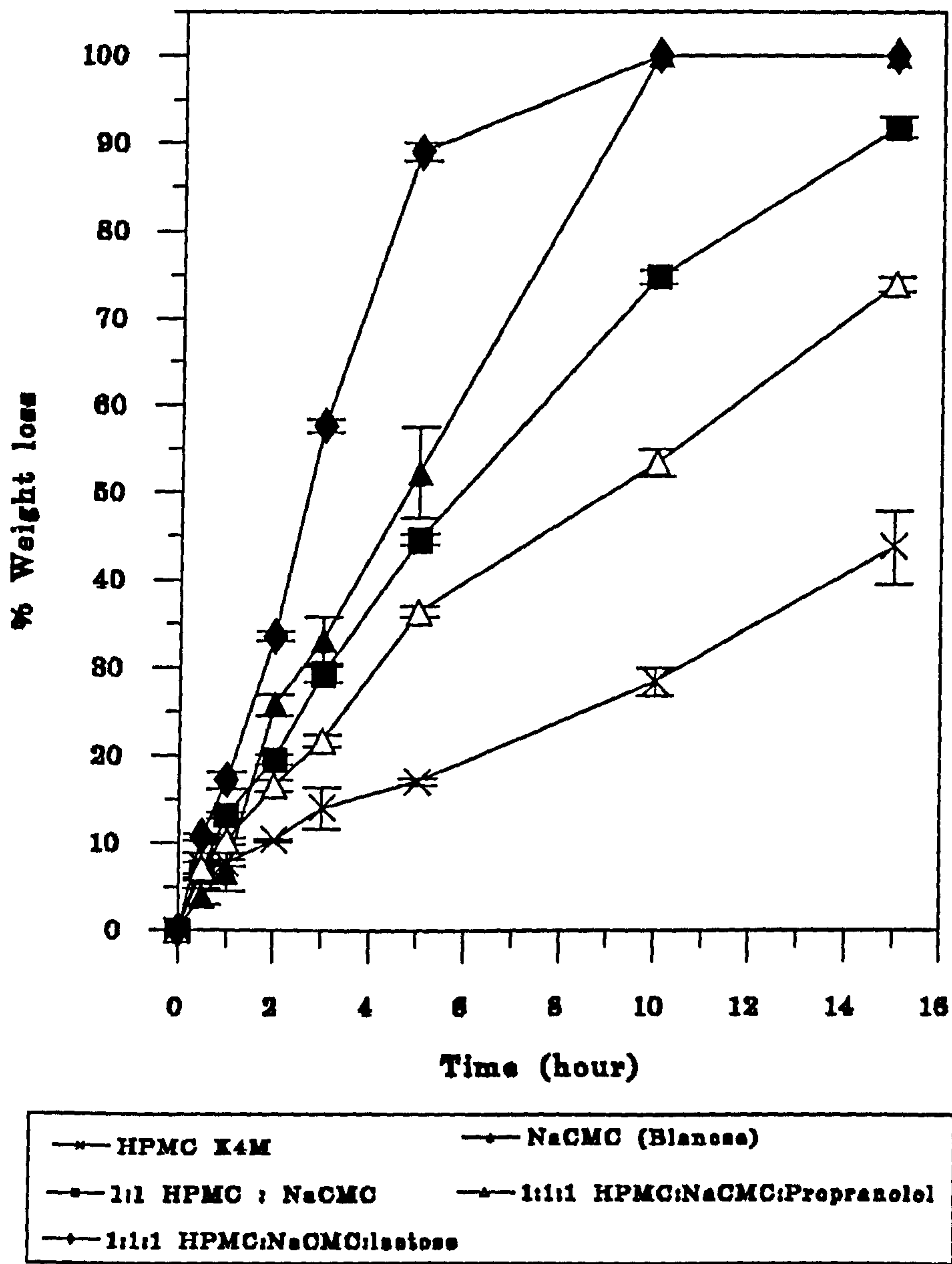
#### 5.4.1.4 Dissolution methodology

Dissolution was measured as described in section 2.2.5 using the means of 6 matrices to calculate drug release.

### **5.4.2 Results and Discussion**

Figure 5.12 shows the polymer erosion, expressed as a function of time. The slopes from erosion of matrices (erosion rates) in figure 5.12, based on time, were obtained to be 2.5, 10.1 and 5.9% per hour for HPMC K4M, NaCMC (Blanose) and their 1:1 mixture respectively. Therefore the synergism in viscosity between HPMC and NaCMC (section 4.2.3.2) did not lead to an increased resistance to erosion. The rapid erosion of NaCMC matrices may be due to the higher solubility of NaCMC compared with HPMC. Hussain et al (1994), using hydroxyethylcellulose (HEC) and NaCMC reported that the

Figure 5.12: Erosion of matrices containing 300 mg HPMC K4M, NaCMC (Blanose), 1:1 HPMC : NaCMC, 1:1:1 HPMC : NaCMC : propranolol hydrochloride and 1:1:1 HPMC : NaCMC : lactose. Results are the means  $\pm$  SD of three determinations.

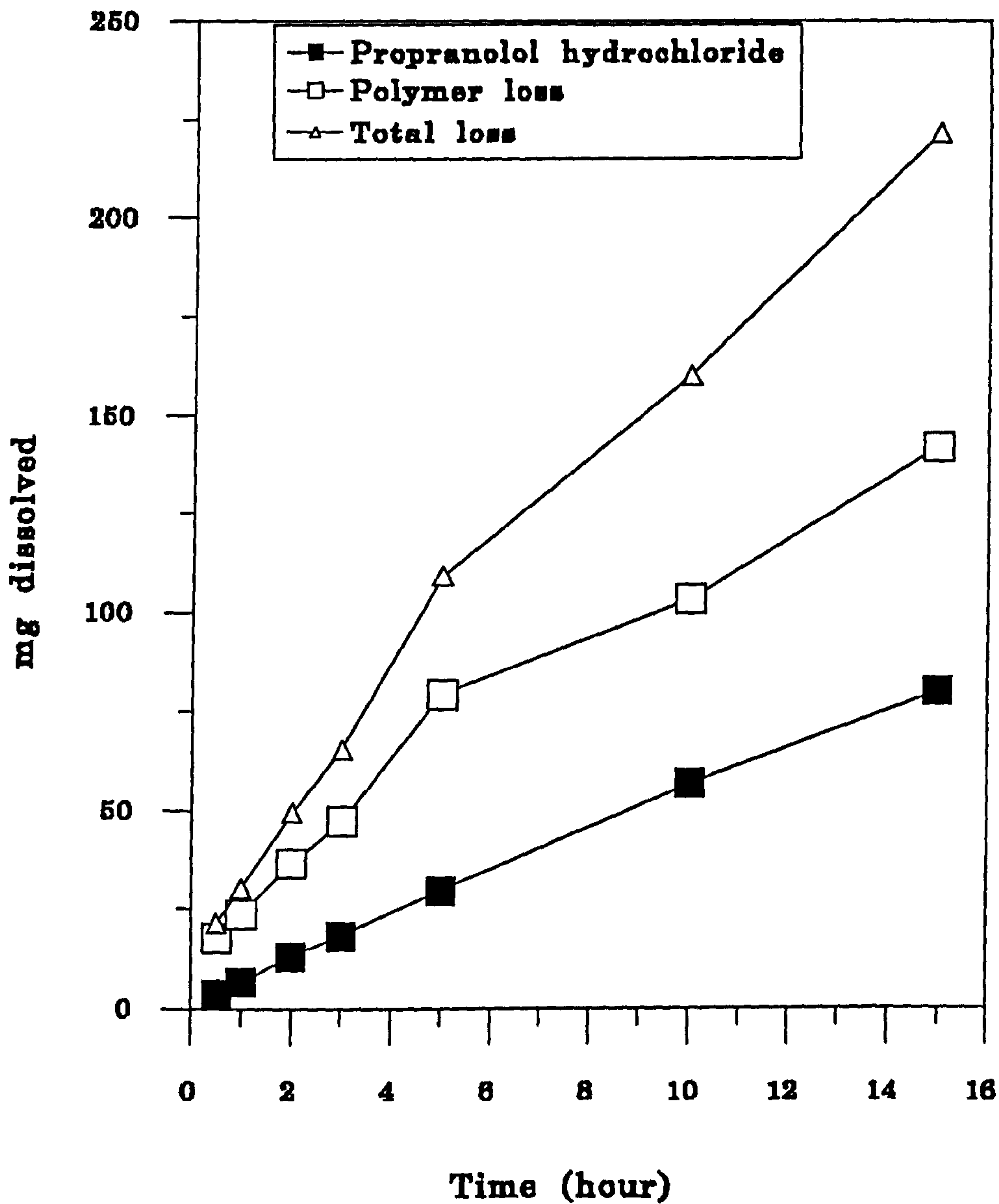




presence of the ionized carboxylic acid groups in NaCMC was responsible for the rapid dissolution of the NaCMC matrices. Addition of propranolol hydrochloride to the matrices, reduced the erosion. This fact might be due to the formation of a complex between propranolol hydrochloride and NaCMC which is less water soluble than pure NaCMC. Propranolol hydrochloride was replaced by the water soluble lactose and did not interact with NaCMC. Replacement of propranolol hydrochloride by lactose, produced more erosion of the matrices (figure 5.12). This clearly proved the importance of the interaction between the drug and NaCMC. The fast erosion of the HPMC : NaCMC : lactose matrices might have been due to the high solubility of lactose which facilitated water penetration into the matrices and subsequently caused disintegration of the matrices (see also section 7.5.2.2.).

Figure 5.13 shows the release of propranolol hydrochloride from matrices containing 1:1:1 HPMC K4M : NaCMC (Blanose) : propranolol hydrochloride versus time. The data for propranolol hydrochloride release and also polymer loss and total weight loss of matrices were fitted to equation 1.2 ( $Q=K_2(t-l)^n$ ), section 1.4.1). The value of release exponent (n) for propranolol hydrochloride release was 0.89, indicating near zero order release of these matrices (Ford et al, 1991). The values of n for polymer loss and total matrix loss which were obtained by subtracting the data for propranolol hydrochloride dissolution were 0.63 and 0.72 respectively. These data indicate that the release mechanisms of each process (release of propranolol hydrochloride, polymer loss and total polymer loss) are different and that admixture of HPMC and

Figure 5.13: Release of propranolol hydrochloride and weight loss (polymer or total loss) from matrices containing 1:1:1 HPMC : NaCMC : propranolol hydrochloride.



NaCMC could lead to higher value of the release exponent.

## 5.5 RELEASE OF SODIUM IONS FROM MATRICES CONTAINING SODIUM CARBOXYMETHYLCELLULOSE

The amount of sodium in NaCMC (Blanose) is considerable (7% w/w according to the manufacturer's information). The aim of the present study was to determine the mechanism of release of sodium ions from NaCMC, HPMC and their 1:1 mixture and the relationship between it (the mechanism of sodium release) and the erosion of its matrices, since sodium ions should be preferentially released if propranolol hydrochloride complexes with sodium carboxymethylcellulose. Additionally the effects of replacement of lactose instead of propranolol hydrochloride on the release of sodium ions was investigated.

### **5.5.1 Experimental**

#### 5.5.1.1 Materials

Sodium carboxymethylcellulose (Blanose), HPMC K4M, propranolol hydrochloride (<125  $\mu\text{m}$ ) and lactose (<105  $\mu\text{m}$ ) were used as described in section 2.1. Sodium standard solution (1000  $\text{mg l}^{-1}$ ) manufactured by BDH (U.K.) (lot No. 7926280P) was used as reference for, the determination of sodium ions by flame photometry.



### 5.5.1.2 Preparation of matrix tablets

Flat-faced tablets, 12.7 mm diameter, were directly compressed at  $182 \text{ MNm}^{-2}$  as described in section 2.2.4. Matrices contained 285 mg NaCMC and 160 mg propranolol hydrochloride or lactose. Matrices containing 285 mg NaCMC or 1:1 HPMC : NaCMC free of drug were also made.

### 5.5.1.3 Calibration of flame photometry

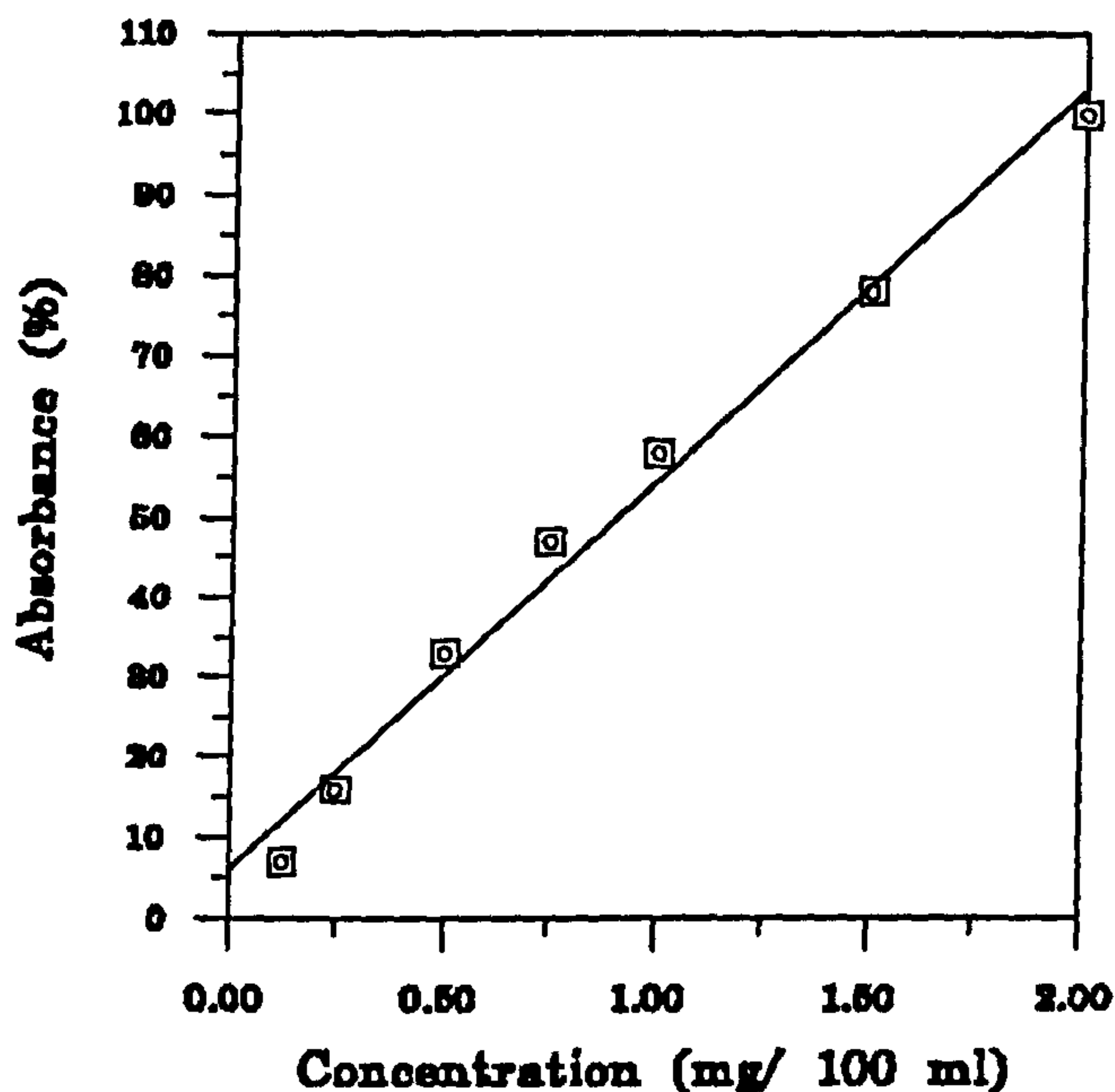
Aqueous solutions containing 0.125, 0.25, 0.5, 0.75, 1, 1.5 and 2 mg sodium ion in 100 mL deionized water were made using the sodium standard solution. The sodium content was determined by Flame photometry (Evans Electro Selenium, England). The flame photometer was initially calibrated using deionized water to give a reading of zero and a solution containing 2 mg sodium ion in 100 mL to give a reading of 100 respectively. Then absorbances of different standard concentrations of sodium ion (0.125 to 1.5 mg/100 mL) were determined. The data obtained are presented in figure 5.14. The best fit equation for the plot of the sodium absorbance versus concentration, is given by equation 5.9,

$$Y = 5.96 C + 48.54$$

Equation 5.9

where, Y is the absorbance and C is the concentration of sodium ion (mg/100 mL). This equation was used for calibration of sodium ion in the samples containing NaCMC or NaCMC : propranolol hydrochloride.

Figure 5.14: Calibration curve absorbance due to sodium ions versus concentration (mg sodium ion /100 mL) in deionized water.



#### 5.5.1.4 Determination of sodium content of NaCMC (Blanose)

To determine the sodium content of NaCMC, 285 mg NaCMC (Blanose) was dissolved and made up to 1000 mL of deionized water and left overnight to completely dispersed. The sodium content of these solutions were determined by flame photometry as described in section 5.5.1.3.

#### 5.5.1.5 Dissolution methodology

Dissolution was measured as described in section 2.2.5. Quantities of 5 mL samples of media at intervals of 1, 2, 3, 5, 7, 10 and 15 hours were withdrawn. Sodium release was determined by placing the samples in the

flame photometer. The values obtained were compared with sodium content from gels containing 285 mg NaCMC (Blanose). The mean of at least three determinations was used for each time for each matrix.

### **5.5.2 Results and discussion**

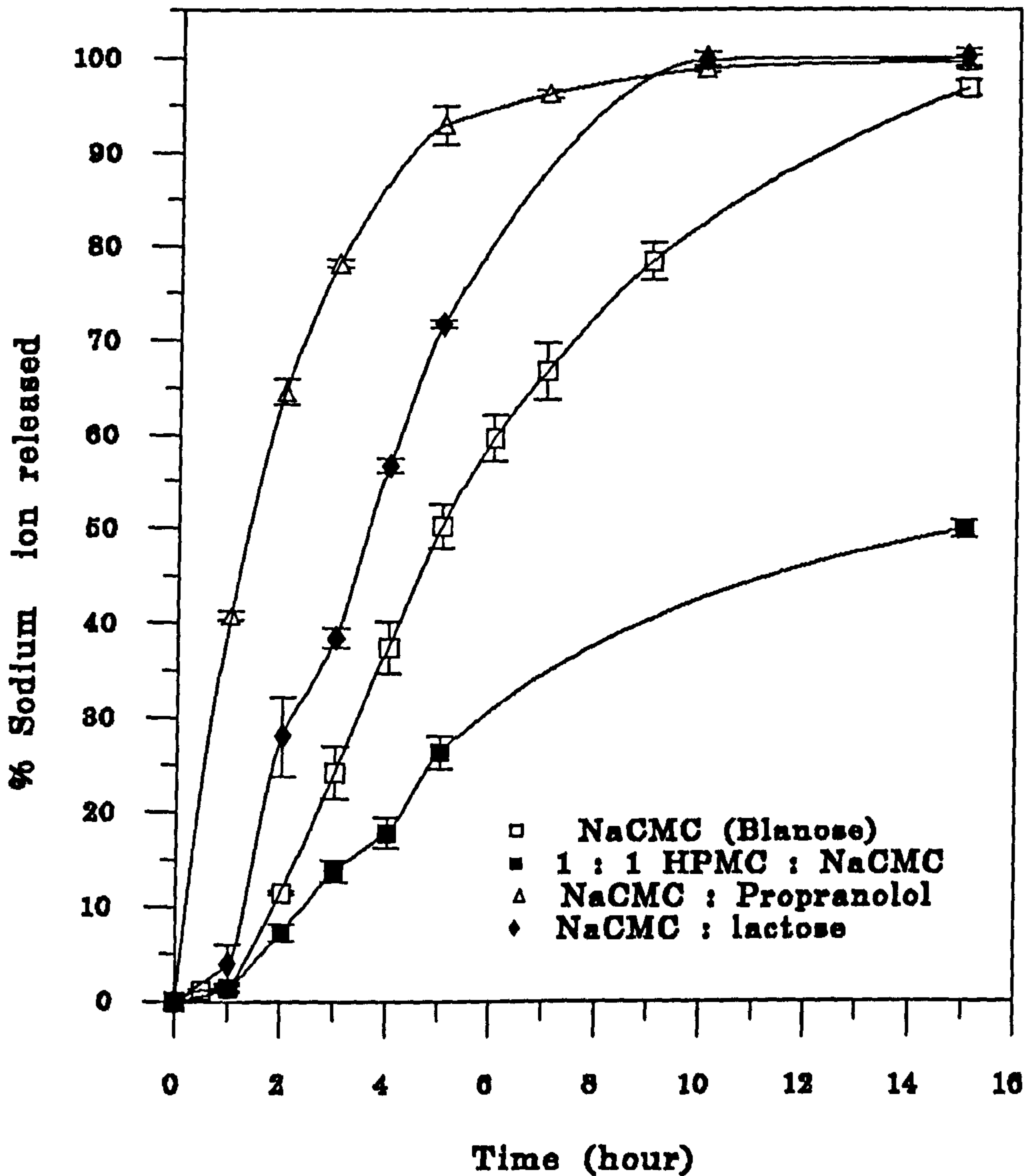
Figure 5.15 shows that the release of sodium ion from various matrices. The sodium content of NaCMC (Blanose) was 5.5% w/w of the dry polymer, compared to the manufacturer's value of 7%. The value of 5.5% was assumed as 100% sodium content for dissolution data, varied according to the NaCMC content of the matrices. The release of sodium ions was accelerated by the presence of both lactose and propranolol hydrochloride. Propranolol hydrochloride would react with NaCMC to form the propranolol-CMC complex with liberation of sodium ions. Therefore, for matrices containing NaCMC, the less soluble form of CMC, at its complex with propranolol hydrochloride, would control release. In order to compare the erosion of matrices containing NaCMC : propranolol hydrochloride and NaCMC : lactose, lactose was chosen because it is a soluble excipient and does not interact with NaCMC. Lactose increased the release of sodium, and hence the dissolution of the polymer could be explained by an increase in porosity caused by dissolution of lactose. HPMC reduced the release of sodium (figure 5.15).

### **5.6 CONCLUDING REMARKS**

Cloud point data indicated that the amount of water required for the



Figure 5.15: Percentage release of sodium ions from matrices containing 285 mg NaCMC (Blanose), 285 mg 1 : 1 HPMC : NaCMC, 285 mg NaCMC : 160 mg propranolol hydrochloride or 285 mg NaCMC : 160 mg lactose. Results are the means  $\pm$  SD of three determinations.



hydration of HPMC K4M gels decreased in the presence of propranolol hydrochloride (section 5.2.1.2). DSC showed that propranolol hydrochloride altered the balance between bound water and propranolol hydrochloride in HPMC gels.

A weak interaction was observed in physical mixtures between NaCMC (Blanose) and propranolol hydrochloride by DSC. Following the prior addition of distilled water to the physical mixtures, the fusion enthalpies of the propranolol hydrochloride content significantly decreased indicating a stronger interaction (section 5.3.2.2). A binding study of this interaction by dialysis showed that as the NaCMC admixture with propranolol hydrochloride increased, the amount of propranolol bound to NaCMC increased.

Matrices consisting solely of NaCMC eroded more quickly than similar HPMC matrices. The addition of propranolol hydrochloride to the matrices containing NaCMC, reduced the erosion rates, due to the insoluble complex formed between NaCMC and propranolol hydrochloride. Since lactose is a soluble excipient and does not interact with NaCMC, it was chosen to compare the erosion of matrices containing NaCMC : propranolol hydrochloride and NaCMC : lactose. Replacement by lactose of the propranolol hydrochloride caused an increase in the rate of erosion. This clearly proved the importance of the interaction between the propranolol hydrochloride and NaCMC, to the stability of matrices.

The results of sodium release showed that matrices containing NaCMC and propranolol hydrochloride or NaCMC and lactose had a rapid release of sodium ions compared to matrices containing NaCMC alone. From the results of interaction between propranolol hydrochloride and NaCMC, it could be suggested that the formation of propranolol - CMC complex, which is insoluble, might be the reason for the rapid release of sodium ion. The reason for fast release of sodium ion from matrices containing NaCMC : lactose could be explained by an increase in porosity caused by dissolution of lactose.



# **CHAPTER 6 THE INFLUENCE OF DISSOLUTION MEDIUM ON THE RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING HYDROXYPROPYLMETHYLCELLULOSE AND SODIUM CARBOXYMETHYLCELLULOSE**

## **6.1 INTRODUCTION**

Oral dosage forms are conveyed to the stomach via the esophagus, then to the duodenum, jejunum, ileum and finally to large intestine (Hui et al, 1987; Skelly 1988). Via their journey, controlled-release dosage forms would encounter a spectrum of pH ranging from 7 in the mouth, 1 to 4 in the stomach and 5 to 7 in the small intestine gradually increasing up to 8 in the distal section of the intestinal tract (Hui et al, 1987; Sutinen et al, 1993). Conceivably, since most of drugs are either weak acids or weak bases, their release from sustained release formulations is pH dependent (Hui et al, 1987). Therefore, pH becomes a major variable that must be considered in both the design and the evaluation process of controlled dosage forms. In addition, since controlled-release dosage forms may be swallowed in the extremes of the presence of food or under fasting conditions, dramatic pH changes as well as the solubilizing influence of both bile and highly buffered pancreatic secretions, should be considered. Obviously these variables will greatly influence the dissolution rate of controlled-release dosage forms and present a much more complex situation than that observed with conventional preparations (Skelly, 1988). However,

it is imperative that a controlled release formulation should have a uniform release pattern at the different sites of the gastrointestinal tract over the period of dosing. This would assure a low variability of release during its transit along the gastrointestinal tract and a low sensitivity to the effects of food.

It is well known that the behaviour of the gel layer that is formed around hydrophilic matrices after water intake is of major importance to the drug release profile (Ford and Mitchell, 1995). It is also known that the behaviour of gel layer is sensitive to interchain interactions and entanglements and to the influence of the medium on swelling or shrinking of the polymer coil (Bonferoni et al, 1995). Therefore, the release of a drug probably would depend on the composition of the surrounding medium.

However, since the biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery requires knowledge of the release and solubility of the drug at different pHs (Ritschall, 1989), the solubility and release of propranolol hydrochloride in different media were investigated. Since in section 3.2.3 it was found that the matrices containing 285 mg 1:1 HPMC : NaCMC (Blanose) gave the lowest release rate ( $1.3 \pm 0.1 \% \text{min}^{-1/2}$ ) of propranolol hydrochloride and a high release exponent value (0.81) (table 3.6), this study focused mainly on the release of drug from matrices containing 1:1 HPMC : NaCMC.

### **6.1.1 Aims and objectives**

The main aim of the studies described in this chapter was to investigate the release of propranolol hydrochloride from matrices containing 1:1 HPMC : NaCMC in different media. To undertake this study, the release of propranolol hydrochloride from matrices containing 285 mg HPMC K4M, NaCMC (Blanose) or 1:1 their mixture was investigated firstly in 0.1 M hydrochloric acid. Then the release of propranolol hydrochloride from matrices containing 1:1 HPMC and different viscosity grades of NaCMC at various media was investigated, in order to find out the effect of viscosity grade of NaCMC on the release of propranolol hydrochloride into various media. Additionally the solubilities of propranolol hydrochloride in the various media were determined.

## **6.2 RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING HYDROXYPROPYLMETHYLCELLULOSE, SODIUM CARBOXYMETHYLCELLULOSE OR THEIR 1:1 MIXTURE IN 0.1 M HYDROCHLORIC ACID**

Since all oral dosage forms first pass from the stomach, it is important to investigate the release of drugs into 0.1 M hydrochloric acid. In the case of HPMC matrices, Alderman (1984) stated that HPMC provided a matrix component which is stable over a pH range of 3 to 11. In the case of NaCMC, due to its ionic characteristics, the pH of the media effects the behaviour of its matrices (Bonferoni et al, 1992). However, the release of



drug from matrices containing 1:1 HPMC : NaCMC has not been thoroughly investigated.

## **6.2.1 Experimental**

### **6.2.1.1 Materials**

Propranolol hydrochloride (<125  $\mu\text{m}$ ), HPMC K4M, NaCMC (Blanose) and magnesium stearate as described in section 2.1, were used in this part of the study.

### **6.2.1.2 Tablet preparation**

Tablets were prepared as described in section 2.2.4, containing 160 mg propranolol hydrochloride (<125  $\mu\text{m}$ ), 0.75% magnesium stearate as lubricant and 285 mg HPMC, NaCMC (Blanose) or their 1:1 mixture at 182  $\text{MNm}^{-2}$ .

### **6.2.1.3 Dissolution methodology**

Dissolution was performed as described in section 2.2.5, except that 0.1 M hydrochloric acid maintained at 37°C were used as media. The UV absorbance for a solution containing 0.1 mg/mL propranolol hydrochloride into 0.1 M hydrochloric acid was determined at 288 nm ( $1.822 \pm 0.01$ ,  $n=3$ ) and its E 1%, 1 cm value was 182.2.

### **6.2.1.4 Analyses of propranolol hydrochloride**

The data corresponding to 5-60% drug release were fitted into equation 1.2

$(Q=K_2(t-l)^n)$  that is described in section 1.4.1. Release rates were calculated from the data in the range of 5-60% drug release.

### **6.2.2 Results and discussion**

Figures 6.1, 6.2 and 6.3 show the drug release profiles from matrices containing 285 mg HPMC K4M, NaCMC (Blanose) or 1:1 HPMC : NaCMC (Blanose) into distilled water and 0.1 M hydrochloric acid respectively. Matrices containing HPMC K4M (figure 6.1) did not show a major difference between the release in the two media, whereas matrices containing NaCMC (figure 6.2) and matrices containing 1:1 HPMC : NaCMC (figure 6.3) showed differences in the two media. Table 6.1 shows the release rates and values of  $K_2$ ,  $n$  and  $l$  based on equation 1.2 in 0.1 M hydrochloric acid.

Data in table 6.1 indicate that the exponent value for HPMC matrices (0.65) is close to those of 1:1 HPMC : NaCMC (0.59) whereas, the exponent value for matrices containing NaCMC was higher (0.82). A comparison between the release rates of propranolol hydrochloride from similar matrices containing HPMC, NaCMC or 1:1 mixture in distilled water (table 3.1) and in 0.1 M hydrochloric acid (table 6.1) showed that the release rates from HPMC matrices were similar in both media, whereas the release rates of matrices containing NaCMC changed. More than 70% of drug released from matrices containing NaCMC (Blanose) during 2 hours and all drug released within 3 hours. The fast release of propranolol hydrochloride into 0.1 M

Figure 6.1: The release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg HPMC K4M into distilled water ( $\blacktriangle$ ) and 0.1 M hydrochloric acid ( $\blacksquare$ ). Results are the means  $\pm$  SD of six determinations.

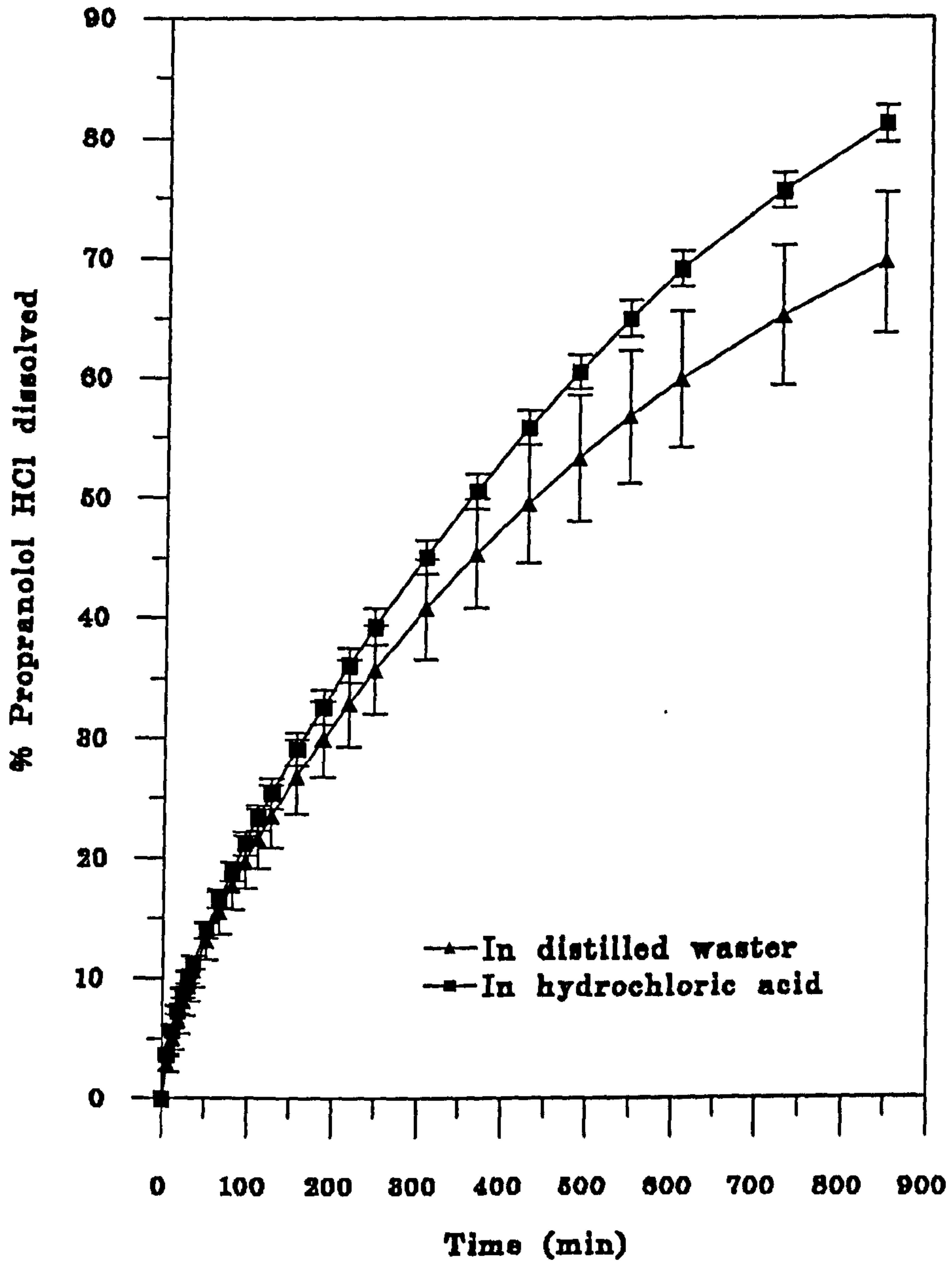




Figure 6.2: The release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg NaCMC (Blanose) into distilled water ( $\blacktriangle$ ) and 0.1 M hydrochloric acid ( $\blacksquare$ ). Results are the means  $\pm$  SD of six determinations.

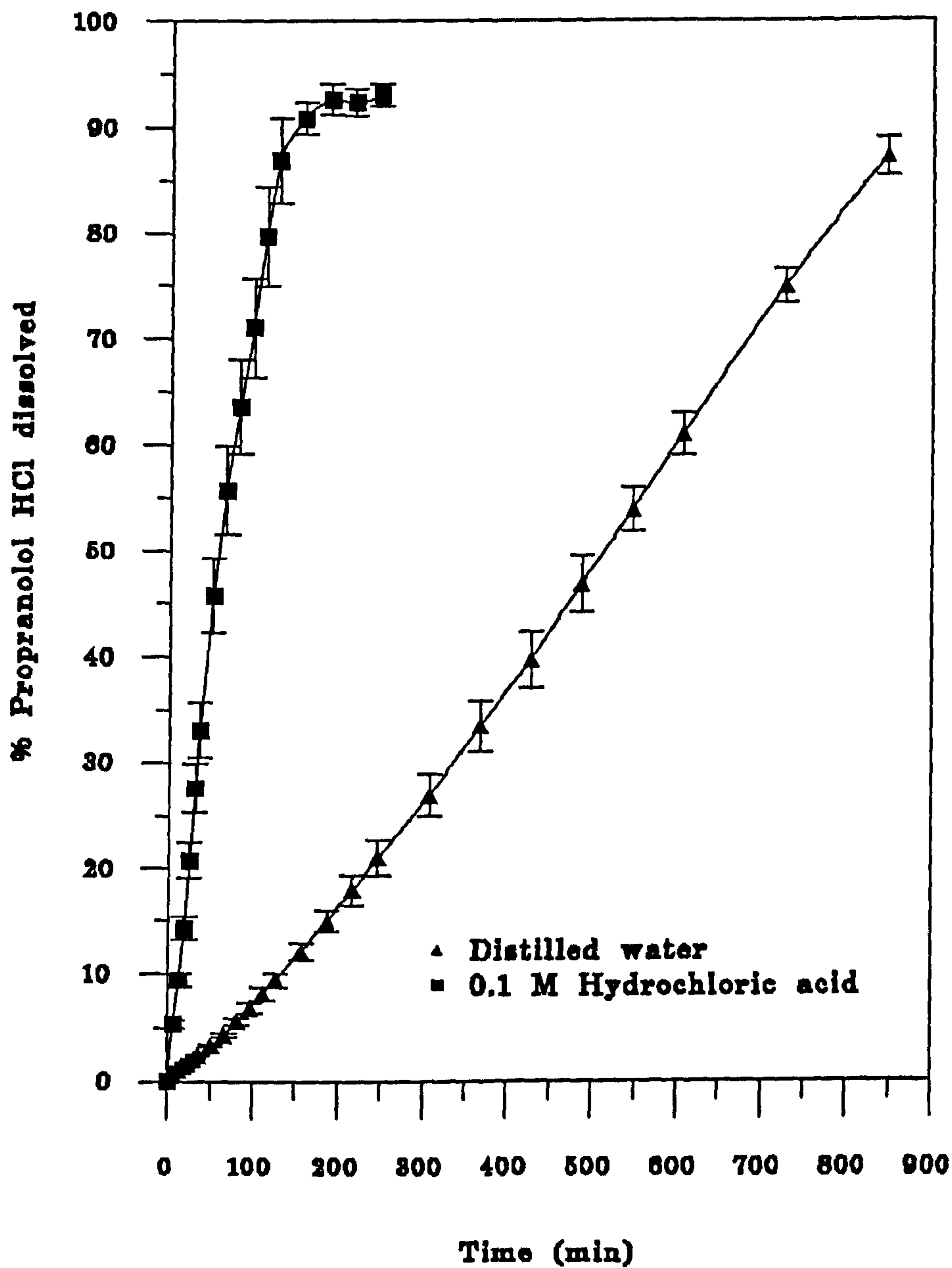


Figure 6.3: The release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg 1:1 HPMC K4M : NaCMC (Blanose) into distilled water ( $\blacktriangle$ ) and 0.1 M hydrochloric acid ( $\blacksquare$ ). Results are the means  $\pm$  SD of six determinations.

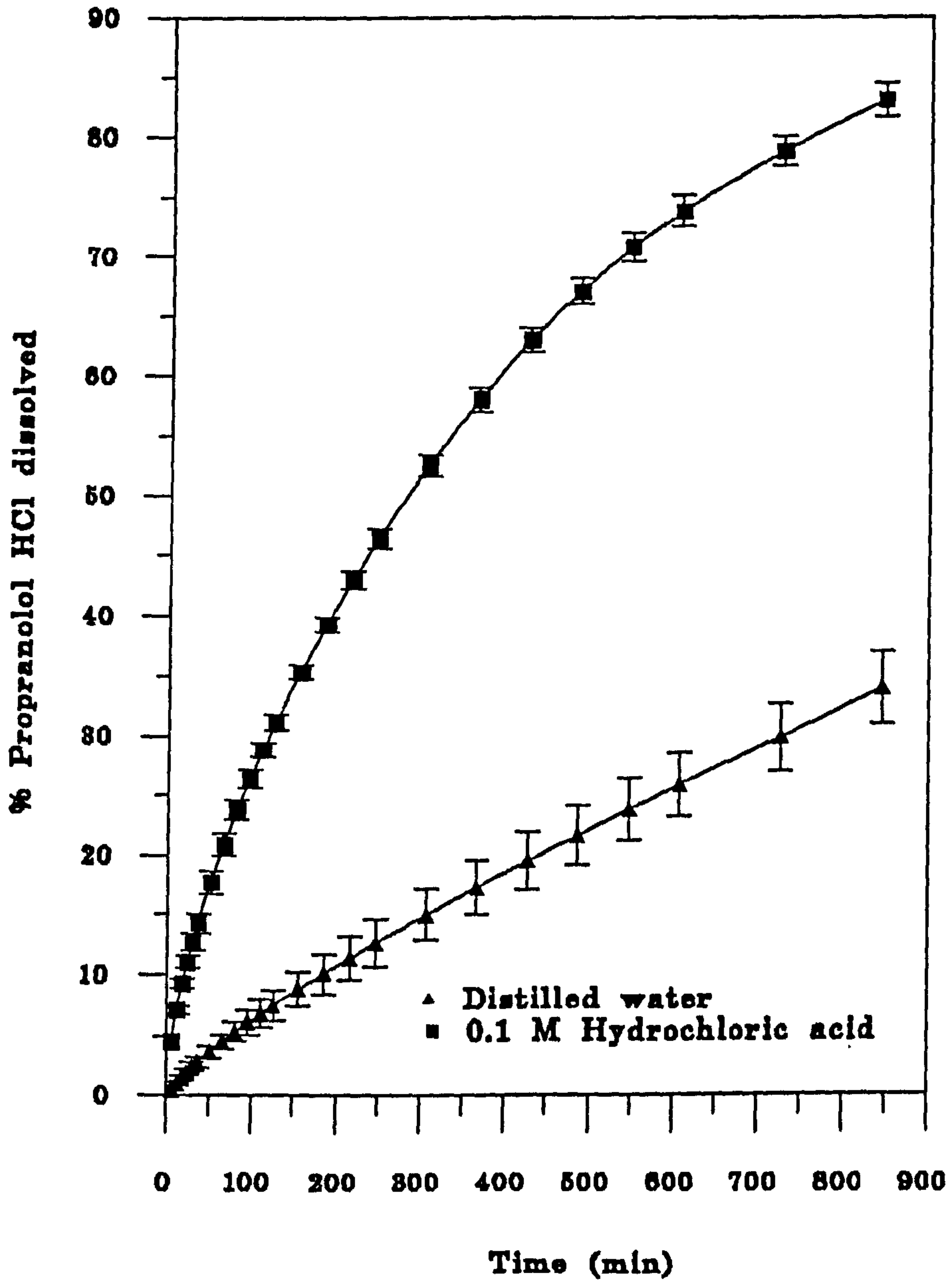


Table 6.1: Release rates ( $\% \text{min}^{-1/2}$ ) and  $K_2$ ,  $n$  and  $l$  based on equation 1.2, calculated in the range of 5 - 60% propranolol hydrochloride release from matrices containing 285 mg HPMC K4M, NaCMC (Blanose) or their 1:1 mixture into 0.1 M hydrochloric acid

Polymers in 0.1 M HCl	Release rate ( $\% \text{min}^{-1/2}$ )	Equation 1.2		
		$K_2$	$n$	$l$
HPMC K4M	$2.9 \pm 0.1$	1.11	0.65	-0.03
NaCMC (Blanose)	$8.8 \pm 0.7$	1.83	0.82	3.6
1:1 HPMC:NaCMC	$3.2 \pm 0.1$	1.85	0.59	2.0

hydrochloric acid from NaCMC matrices is probably due to the insolubility of NaCMC in 0.1 M hydrochloric acid (Bonferoni et al, 1992). Bonferoni et al (1992) used salbutamol sulphate and reported that at pH values below the pKa of NaCMC (which is 4.3), the polymer reverted to its non-ionized form which is less water soluble and less capable of interacting with drug. Therefore, the solubility of the NaCMC is much lower in 0.1 M hydrochloric acid than in distilled water. Subsequently matrices containing NaCMC in hydrochloric acid could not make the protective gel layer that is essential to produce controlled drug release. Another reason for the higher release rate of propranolol hydrochloride in 0.1 M hydrochloric acid might be due



to the interaction between propranolol hydrochloride and NaCMC in distilled water (section 5.3). This interaction could not occur in 0.1 M hydrochloric acid due to the insolubility of NaCMC.

As discussed in section 3.2.3, the lowest release rates were obtained from matrices containing 1:1 HPMC : NaCMC in distilled water. The increase in release rates from matrices containing 1:1 HPMC : NaCMC into 0.1 M hydrochloric acid (table 6.1) compared with distilled water (table 3.1), would be again due to the insolubility of NaCMC.

### 6.3 EFFECT OF WIDER pH RANGE ON THE RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING 1:1 HPMC : NaCMC (BLANOSE)

In spite of the efforts directed at the use of HPMC and NaCMC or their mixtures, little attention has been paid to the performance of these tablets when subjected to changes in pH. As was observed in section 6.2, the drug release was different in water and 0.1 M hydrochloric acid and also several investigators have reported that the pH and ionic strength of a dissolution media may modify the release of drug substances from HPMC matrices (Ford et al, 1985c; Pagay, 1988; Mitchell et al, 1990b). Therefore the release of propranolol hydrochloride from matrices containing 1:1 HPMC : NaCMC was investigated at a wider range of pH.

### **6.3.1 Methodology**

Tablets were prepared as described in section 2.2.4, containing 160 mg propranolol hydrochloride <125 µm, 0.75% magnesium stearate as lubricant and 57, 95 or 285 mg of 1:1 HPMC K4M : NaCMC (Blanose) at 182 MNm<sup>2</sup>.

#### **6.3.1.1 Dissolution methodology**

Dissolution was measured as described in section 2.2.5 using various media maintained at 37°C. The media were 0.1 M hydrochloric acid, phosphate buffer solutions pH 6.8 or pH 7.4 and borate buffer solution pH 9.4. The formulae of the different buffer solutions are given in appendix 1. The UV absorbances for solutions containing 0.1 mg/mL propranolol hydrochloride in phosphate buffer solution pH 6.8, phosphate buffer solution pH 7.4 or borate buffer solution pH 9.4 were determined at 288 nm and were 1.885 ± 0.01, 1.891 ± 0.01 or 1.926 ± 0.01 respectively. The corresponding E 1%, 1 cm values were 188.5, 189.1 or 192.6 respectively.

Dissolution tests were also carried out by changing the pH of the medium. Dissolution was initially performed in 750 mL of 0.1 M hydrochloric acid for two hours and then, by adding 250 mL of 0.2 M trisodium phosphate solution, the pH was adjusted to 6.8. This method is described in (USP 23 / NF 18, 1995) as the delayed-release method. To simplify referring to this method, it is called changed pH and shown by letter (C) in figures 6.4, 6.5 and 6.11 and tables 6.3 and 6.4.

### 6.3.1.2 Determination of propranolol hydrochloride solubility

The solubility of propranolol hydrochloride was determined as described in section 2.2.3 except that it was determined in 0.1 M hydrochloric acid, phosphate buffer solutions pH 6.8 and pH 7.4 and borate buffer solution pH 9.4 (see appendix 1) as described in section 6.3.1.1.

## **6.3.2 Results and discussion**

### 6.3.2.1 Solubility of propranolol hydrochloride

The solubilities of propranolol hydrochloride in different media at 37°C, are shown in table 6.2. Shivanand and Sprockel (1993) reported a value of  $115 \pm 24$  mg/mL for propranolol hydrochloride in distilled water at 37°C. Lee et al (1991) reported that the solubilities of propranolol hydrochloride in 0.1 M hydrochloric acid, distilled water and phosphate buffer solution pH 7.4 at 25°C were 56.53, 155.72 and 140.37 mg/mL respectively. Comparing the reported data by Lee et al (1991) with the obtained data in table 6.2, the solubility of propranolol hydrochloride in distilled water and phosphate buffer pH 7.4 were similar but the solubility in 0.1 M hydrochloric acid was different. The lowest solubility of propranolol hydrochloride was in borate buffer pH 9.4 and was a consequence of the pKa of propranolol hydrochloride (Mitchell et al, 1990b; Sutinen et al, 1993). Sutinen et al (1993) determined the solubility of propranolol hydrochloride at 4 different pHs (1.6, 4.6, 7.3 and 9.4) and 2 different ionic strengths and reported that the solubility of propranolol hydrochloride at pH 9.4 was lower (0.5 mg/mL)



than at the other values of pH.

Table 6.2. Solubilities of propranolol hydrochloride (mg/mL) in distilled water, 0.1 M hydrochloric acid, phosphate buffer pH 6.8 or 7.4 and borate buffer pH 9.4 at 37°C (results are the means  $\pm$  SD of three determinations)

Media	Solubility (mg/mL) $\pm$ SD
0.1 M Hydrochloric acid	134.5 $\pm$ 5.4
Phosphate buffer pH 6.8	143.3 $\pm$ 6.4
Phosphate buffer pH 7.4	137.3 $\pm$ 2.1
Borate buffer pH 9.4	57.4 $\pm$ 1.2
Distilled water	159.8 $\pm$ 1.3

6.3.2.2 Influence of pH on the release of propranolol hydrochloride from matrices containing 1:1 HPMC : NaCMC (Blanose)

Figures 6.4, 6.5 and 6.6 give the release profiles of propranolol hydrochloride from matrices containing 1:1 HPMC : NaCMC (Blanose) and 285, 95 and 57 mg total polymer respectively. Matrices containing 57 mg total polymer were not examined by the pH change method, because all the

drug was released within 2 hours. The dissolution rates and values of  $K_2$ ,  $n$  and  $l$  obtained using equation 1.2, are presented in table 6.3.

In spite of the solubility of propranolol hydrochloride being higher in distilled water than at the other pHs (table 6.2), its release rates from matrices containing 285 mg polymer into distilled water was slower than into the other media except at pH 9.4. The reason might be the interaction between propranolol hydrochloride and NaCMC which was discussed in sections 3.2.3 and 5.3.3. The release rates from matrices containing 285, 95 and 57 mg 1:1 HPMC K4M : NaCMC (Blanose) into 0.1 M hydrochloric acid were fast, which would be attributed to the insolubility of NaCMC in 0.1 M hydrochloric acid (section 6.2).

The effect of the pH change method on the drug release is clearly seen in figure 6.4. After two hours in 0.1 M hydrochloric acid, when the medium was adjusted to pH 6.8, a decrease in release rate was observed. The values of the release exponent based on equation 1.2 from matrices containing 285 mg 1:1 HPMC : NaCMC were 0.65 between 5-30% (first 2 hours) drug release and 0.32 between 30-60% drug release which indicate that two mechanisms were apparent in the two portions of the profile. This fact indicates that mixed diffusion and erosion of matrices containing NaCMC occurred in acidic medium and that diffusion probably predominated at the high pH. The decreased release rate observed in phosphate buffer solution pH 6.8 or phosphate buffer solution pH 7.4 could be attributed to the

Figure 6.4: The effect of pH on the dissolution of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose).

Results are the means  $\pm$  SD of six determinations.

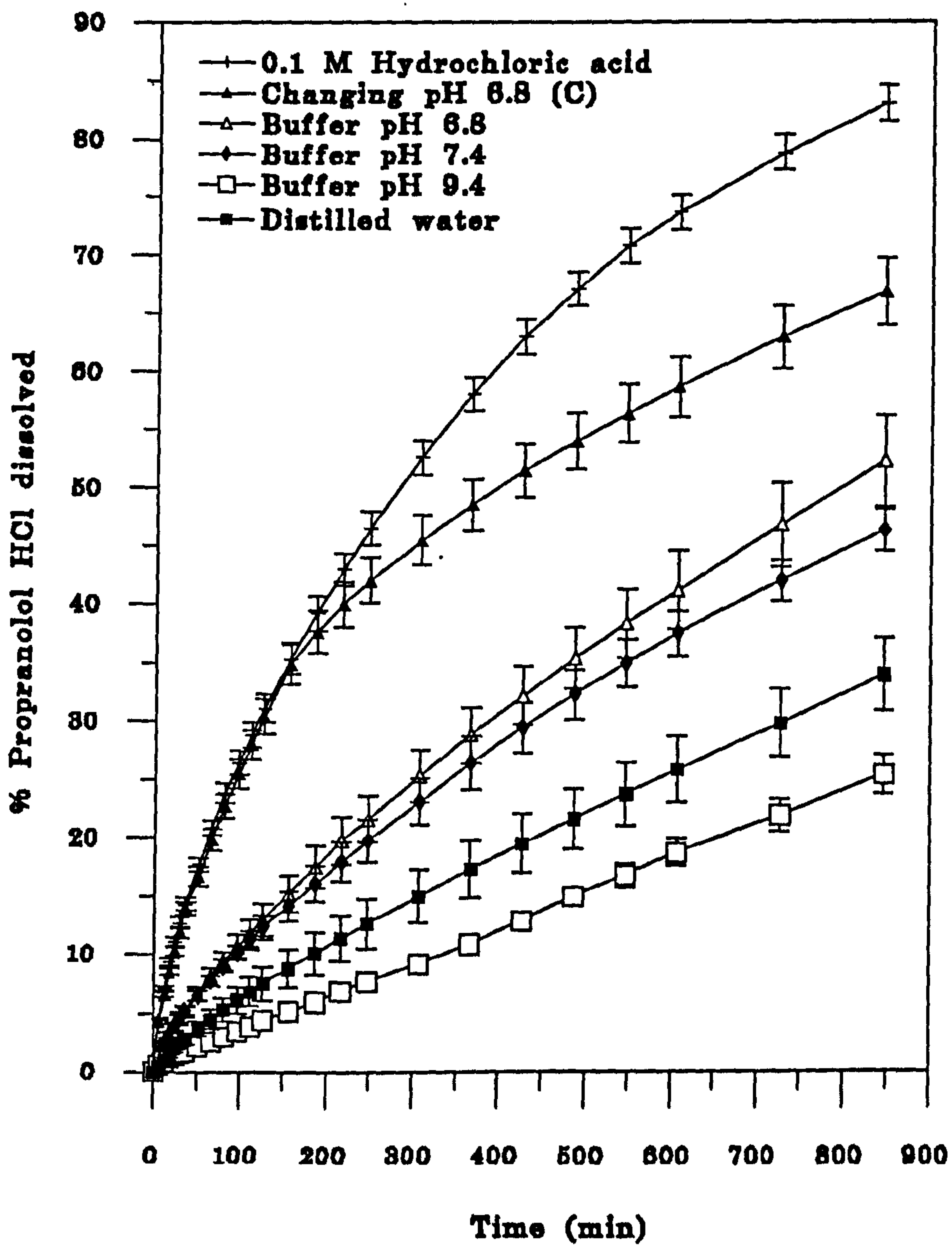




Figure 6.5: The effect of pH on the dissolution of propranolol hydrochloride from matrices containing 95 mg 1:1 HPMC K4M : NaCMC (Blanose). Results are the means  $\pm$  SD of six determinations.

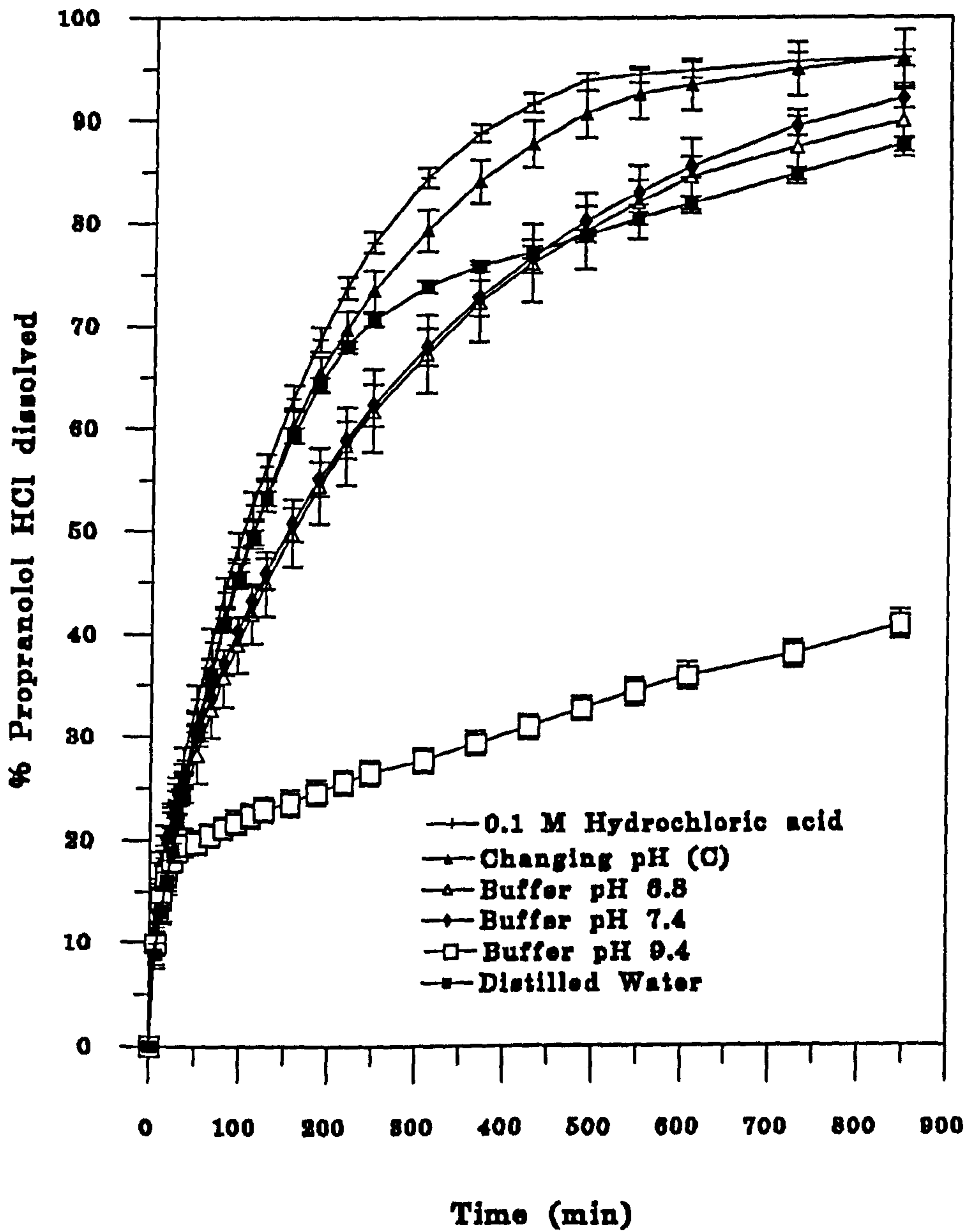


Figure 6.6: The effect of pH on the dissolution of propranolol hydrochloride from matrices containing 57 mg 1:1 HPMC K4M : NaCMC (Blanose). Results are the means  $\pm$  SD of six determinations.

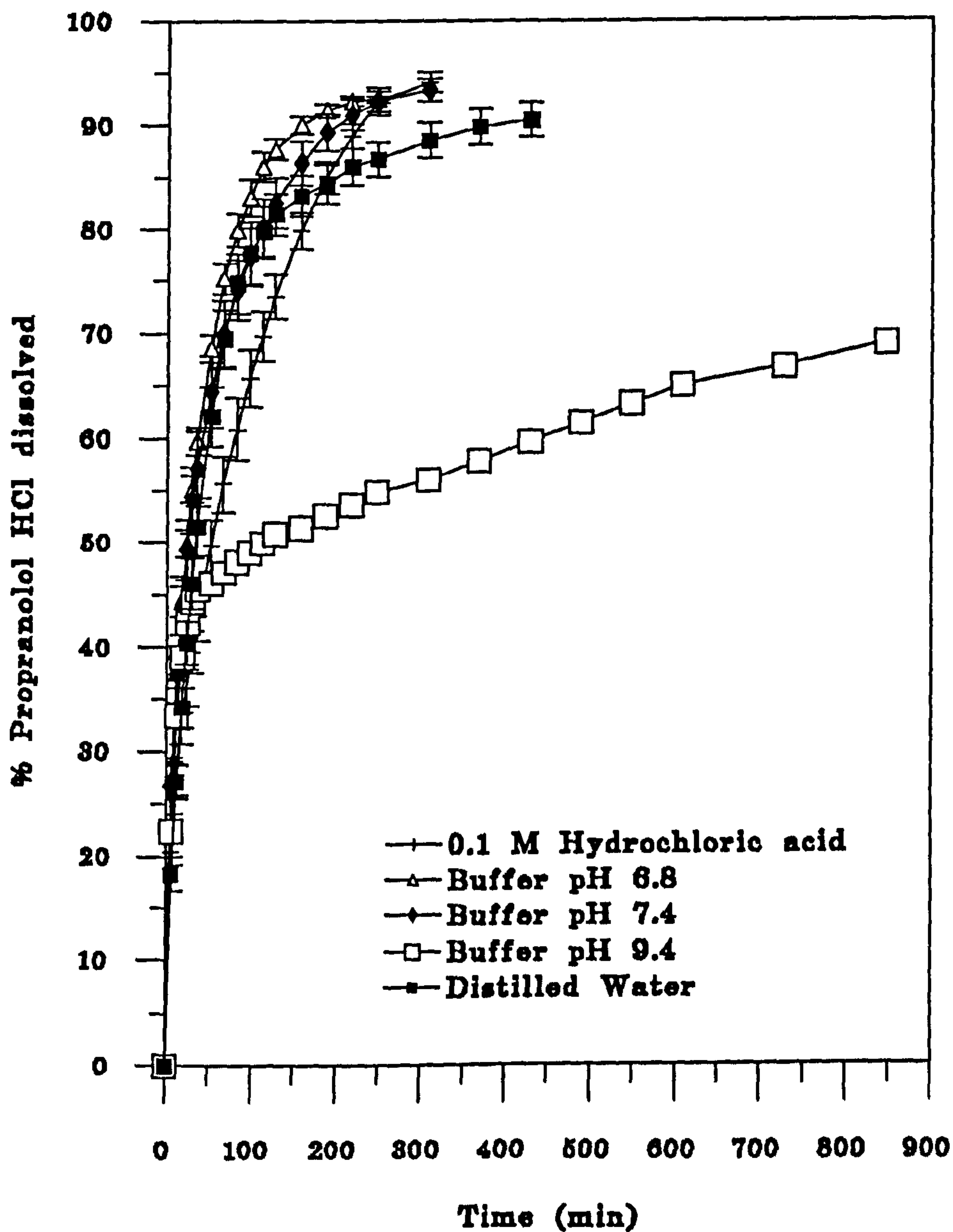


Table 6.3: Estimated values of  $T_{50\%}$  (hour), release rates ( $\% \text{ min}^{-1/2}$ ),  $K_2$ ,  $n$  and  $l$  based on equation 1.2 from matrices containing 1:1 HPMC : NaCMC (Blanose) into different pH.

Matrices containing 285 mg 1:1 HPMC : NaCMC					
Media	$T_{50\%}^*$ (hour)	Release rate ( $\text{min}^{-1/2}$ )	$K_2$	$n$	$l$
Distilled water	$18.1 \pm 1.1$	$1.3 \pm 0.1$	0.14	0.81	-6.4
0.1 M HCl	$4.7 \pm 0.2$	$3.2 \pm 0.1$	1.85	0.59	2.0
pH 6.8(c) <sup>+</sup>	$6.3 \pm 0.5$	$3.0 \pm 0.2^{2h}$	1.29	0.65	-0.2
		$2.1 \pm 0.1^R$	7.68	0.32	49.9
pH 6.8	$12.4 \pm 1.0$	$2.1 \pm 0.1$	0.44	0.71	5.0
pH 7.4	$14.9 \pm 0.8^{40\%}$	$1.7 \pm 0.1$	0.47	0.68	5.7
pH 9.4	$27.6 \pm 0.5^{25\%}$	$1.1 \pm 0.1^{25\%}$	0.03	1.00	-11.5
Matrices containing 95 mg 1:1 HPMC : NaCMC					
Distilled water	$1.9 \pm 0.1$	$5.1 \pm 0.1$	2.75	0.61	-0.4
0.1 M HCl	$1.7 \pm 0.1$	$5.5 \pm 0.1$	3.66	0.56	-0.3
pH 6.8 (c) <sup>+</sup>	$1.7 \pm 0.1$	$5.0 \pm 0.2^{2h}$	2.94	0.60	-1.6
		$5.6 \pm 0.3^R$	-	-	-
pH 6.8	$2.4 \pm 0.4$	$4.3 \pm 0.3$	3.89	0.50	-1.8
pH 7.4	$2.5 \pm 0.2$	$4.1 \pm 0.2$	4.46	0.48	-4.8
pH 9.4	$13.7 \pm 0.9^{35\%}$	$1.4 \pm 0.1$	5.56	0.29	-17.3
Matrices containing 57 mg 1:1 HPMC : NaCMC					
Distilled water	$0.6 \pm 0.1$	$9.7 \pm 0.1$	6.70	0.57	0.2
0.1 M HCl	$0.1 \pm 0.1$	$6.9 \pm 0.2$	8.97	0.43	-0.7
pH 6.8	$0.4 \pm 0.0$	$11.0 \pm 0.3$	13.60	0.41	0.5
pH 7.4	$0.4 \pm 0.1$	$11.0 \pm 0.5$	17.90	0.33	2.7
pH 9.4	$2.1 \pm 0.3$	$3.0 \pm 0.4$	No response		

<sup>+</sup> Changing pH method (see section 6.3.1.1). <sup>2h</sup> data from 5% drug release up to first 2 hours in 0.1 M hydrochloric acid, <sup>R</sup>data for 2 hours up to 60% release. <sup>40%</sup>, <sup>25%</sup> and <sup>35%</sup> indicate maximum release.



reduction in propranolol solubility (Clarke and Cahoon, 1987).

The release rates were slower at pH 9.4 than at the other pHs. Table 6.3 indicates that as the pH of medium increased from 1 to 9.4, the release rate from matrices containing 285 mg polymer decreased from  $3.2 \pm 0.1$  to  $1.1 \pm 0.1$   $\% \text{min}^{-1/2}$ . The decrease in release rates at pH 9.4 could be explained on the basis of the reduced solubility of the drug at this pH. The pKa of propranolol hydrochloride is 9.5 (Clark's Isolation and Identification of Drugs, 1986) and the solubility will decrease near a pH of 9.5. Thus, the drug release would be reduced. When the matrices were removed at the end of the test a white precipitate had been formed on the outer gel layer presumably of propranolol base. The reason for lower total release of drug (about 25% after 14 hours) might be due to formation of this base (i.e., lower solubility of propranolol) and also that it might not allow propranolol hydrochloride to diffuse from the matrix. In similar studies, Ford et al (1985c) showed that the release of promethazine hydrochloride from HPMC matrices was highest at pH 1 but decreased as the pH increased to 9. They attributed this to a reduction in the solubility of the drug. The solubility of propranolol hydrochloride in borate buffer pH 9.4 was  $57.4 \pm 1.2$  mg/mL, compared with  $159.8 \pm 1.3$  mg/mL for distilled water (table 6.2) and this reduction alone could account for the reduction in release.

Figures 6.5 and 6.6 indicate that, as the polymer content decreased, the differences observed between the release profiles in different media

decreased. In matrices containing 95 mg (figure 6.5) or 57 mg (figure 6.6), the amount of polymer was insufficient to protect the matrix. Therefore, the release rates of propranolol hydrochloride would depend on its solubility at the pH of medium. It was discussed in section 5.3.3 that, as the amount of NaCMC in the dialysis bags containing constant amount of propranolol increased, the quantity of bound propranolol to NaCMC increased. Therefore a decrease in the polymer content, leaves more propranolol to be free, or in other words, the interaction between the drug and the polymer would decrease. The release rates from matrices containing 95 mg 1:1 HPMC K4M : NaCMC into pH change method were  $5.0 \pm 0.2 \text{ min}^{-1/2}$  for first 2 hours (5% to 53% drug release) when the media was 0.1 M hydrochloric acid and  $5.6 \pm 0.3 \text{ min}^{-1/2}$  between 53-60% drug release (into phosphate buffer pH 6.8). Due to lack of enough points (only 2 points) between 53% and 60% release, estimating the release exponent from matrices containing 95 mg in pH change method was impossible and therefore the data are missing in table 6.3. The increase in release rates of these matrices may also be due to the same reason, so the value of  $5.6 \pm 0.3 \text{ min}^{-1/2}$  for the rest of release is an estimate. It was observed that as the polymer content decreased from 285 to 57 mg, the release exponent in the same media decreased. The mechanism of release from values of release exponent less than 0.45 is unknown. The values less than 0.45 which were obtained from matrices containing 95 or 57 mg polymer content might be due to the initial burst drug release.



## 6.4 EFFECT OF pH ON THE RELEASE RATE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING 1:1 HPMC AND DIFFERENT VISCOSITY GRADES OF NaCMC

In section 3.2.3.2, the release of propranolol hydrochloride from matrices containing 57, 95, 140 and 285 mg polymer content in the ratio 1:1 of HPMC : NaCMC Blanose, HPMC : NaCMC P 800 and HPMC : NaCMC P 350 in distilled water was determined. The results obtained showed that the viscosity grade of NaCMC affected the drug release (see figure 3.15) whereas the viscosity grade of HPMC was generally considered unimportant (Ford et al, 1985a). In this section, the release of propranolol hydrochloride from matrices containing 57, 95 or 285 mg of 1:1 HPMC : NaCMC (Blanose, NaCMC P 800 or NaCMC P 350) in different media is described.

### **6.4.1 Methodology**

Tablets were prepared as described in section 2.2.4 containing 160 mg propranolol hydrochloride <125 µm, 0.75% magnesium stearate as lubricant and 57, 95 or 285 mg 1:1 HPMC K4M : NaCMC (Blanose, NaCMC P 800 or NaCMC P 350). Dissolution was performed as in section 6.3.1.1.

### **6.4.2 Results and discussion**

Figures 6.7 - 6.11 show the release profiles of propranolol hydrochloride from matrices containing 285 mg total polymer in ratio 1:1 of HPMC : NaCMC (Blanose), HPMC : NaCMC P 800 or HPMC : NaCMC P 350 into



0.1 M hydrochloric acid, phosphate buffer pH 6.8, phosphate buffer pH 7.4, borate buffer solution pH 9.4 and the pH change method respectively. The release rates and exponent values from these matrices are presented in table 6.4. Matrices containing 285 mg 1:1 HPMC : NaCMC (Blanose, P 800 or P 350) at pH 7.4 or 9.4 after 14 hours, had a maximum of 40% or 25% drug release from the total drug in the matrix respectively, therefore data between 5% to the end of dissolution testing were fitted into the equation 1.2.

There were no major differences in the release of propranolol hydrochloride from the matrices at 0.1 M hydrochloric acid (figure 6.7 and table 6.4) whereas, as was shown in figure 3.15 and table 3.6, the release rates were different from these matrices into distilled water and depended on the viscosity grade of NaCMC. The viscosity grades of NaCMC therefore had little effect on the release of propranolol hydrochloride into 0.1 M hydrochloric acid.

As the pH increased the differences between the release rates from matrices increased (table 6.4), indicating that the viscosity grades of NaCMC increasingly influence the release of propranolol hydrochloride. The rank order was observed to be NaCMC (Blanose) < NaCMC P 800 < NaCMC P 350. Figures 6.7 to 6.10 indicate that the total release of propranolol hydrochloride decreased as the pH of media increased.

Figure 6.7: The release of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose), 1:1 HPMC : NaCMC P 350 or 1:1 HPMC : NaCMC P 350 into 0.1 M hydrochloric acid. Results are the means  $\pm$  SD of six determinations.

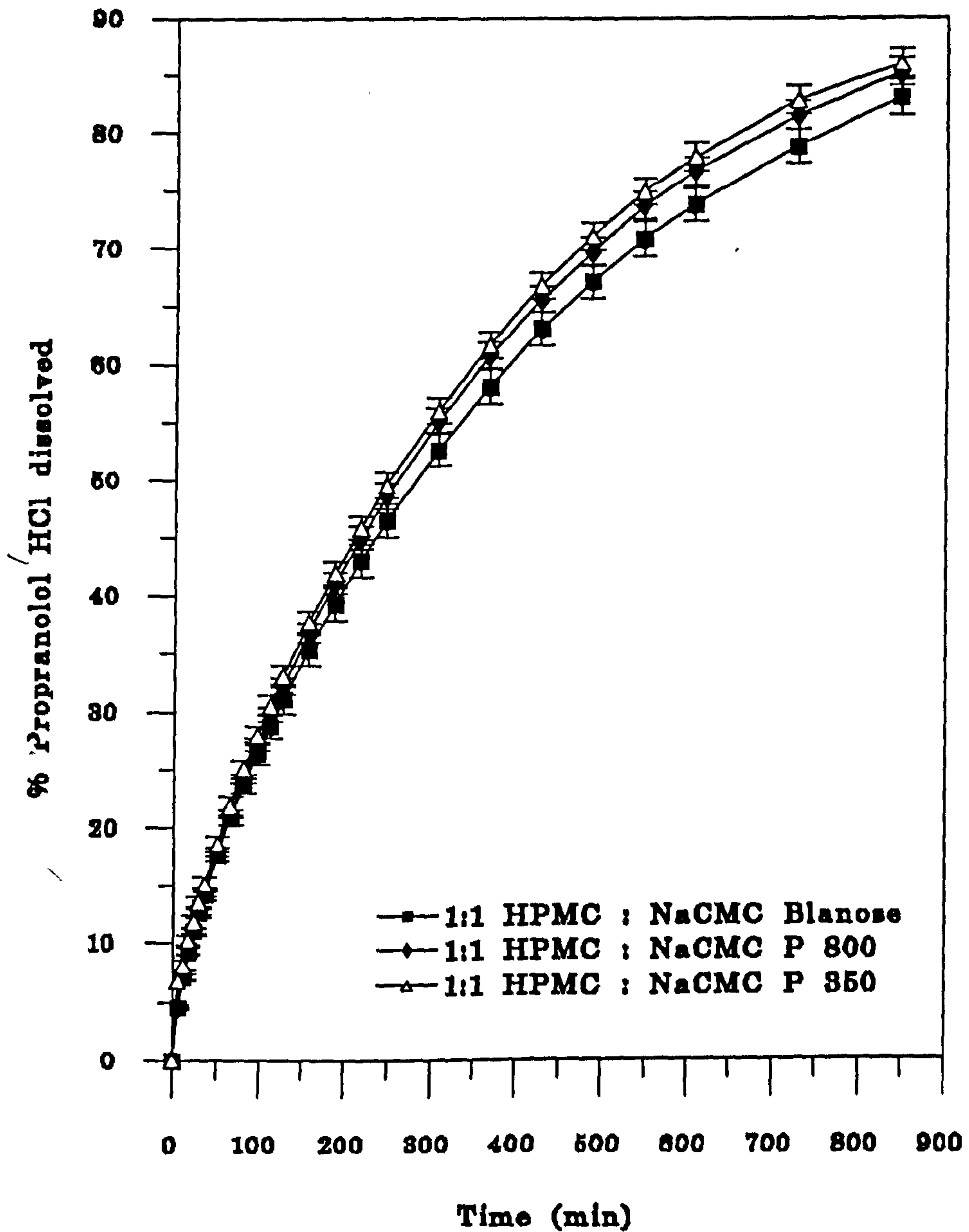


Figure 6.8: The release of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose), 1:1 HPMC : NaCMC P 350 or 1:1 HPMC : NaCMC P 350 into phosphate buffer solution pH 6.8. Results are the means  $\pm$  SD of six determinations.

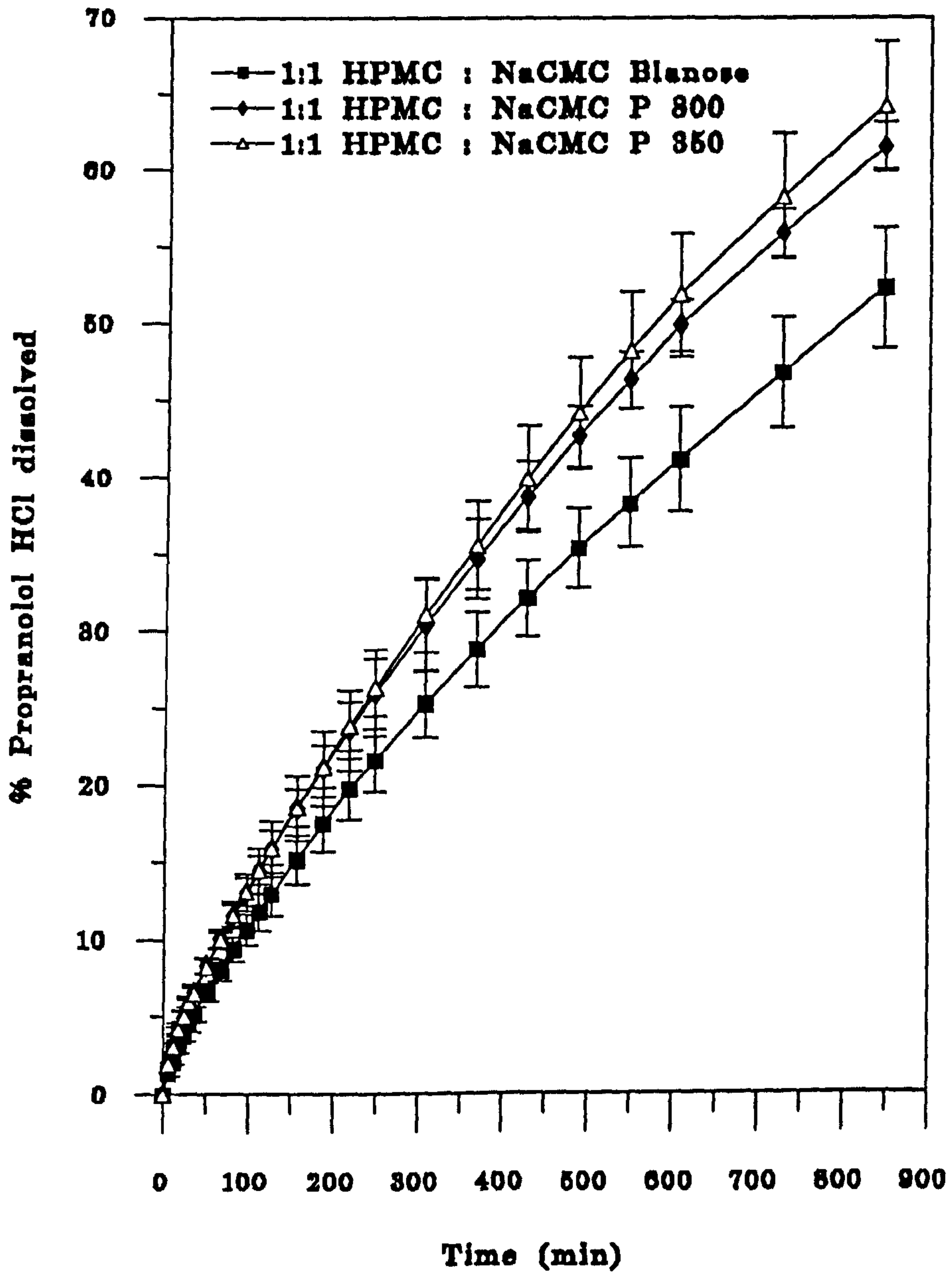




Figure 6.9: The release of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose), 1:1 HPMC : NaCMC P 350 or 1:1 HPMC : NaCMC P 350 into phosphate buffer solution pH 7.4. Results are the means  $\pm$  SD of six determinations.

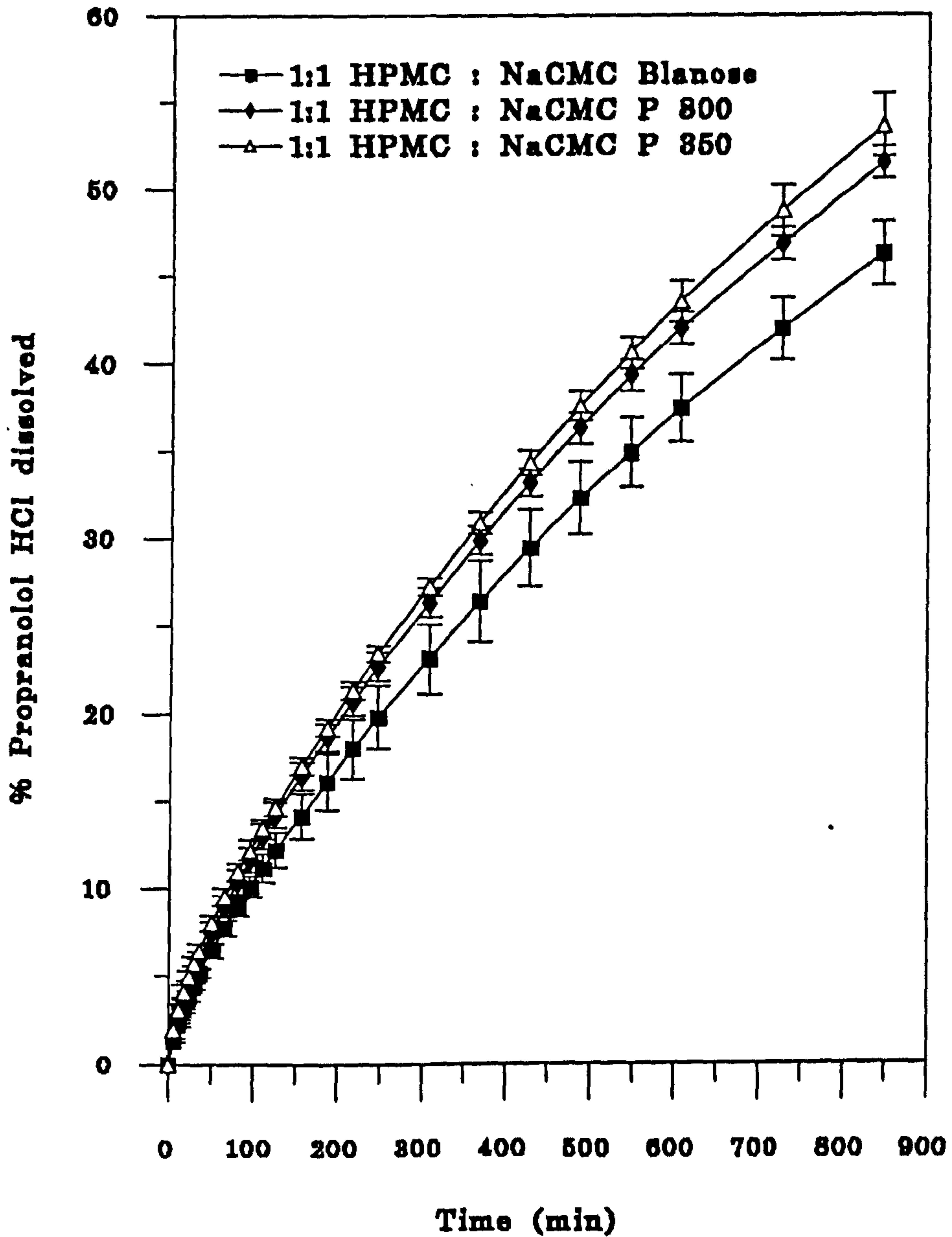


Figure 6.10: The release of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose), 1:1 HPMC : NaCMC P 350 or 1:1 HPMC : NaCMC P 800 into borate buffer solution pH 9.4. Results are the means  $\pm$  SD of six determinations.

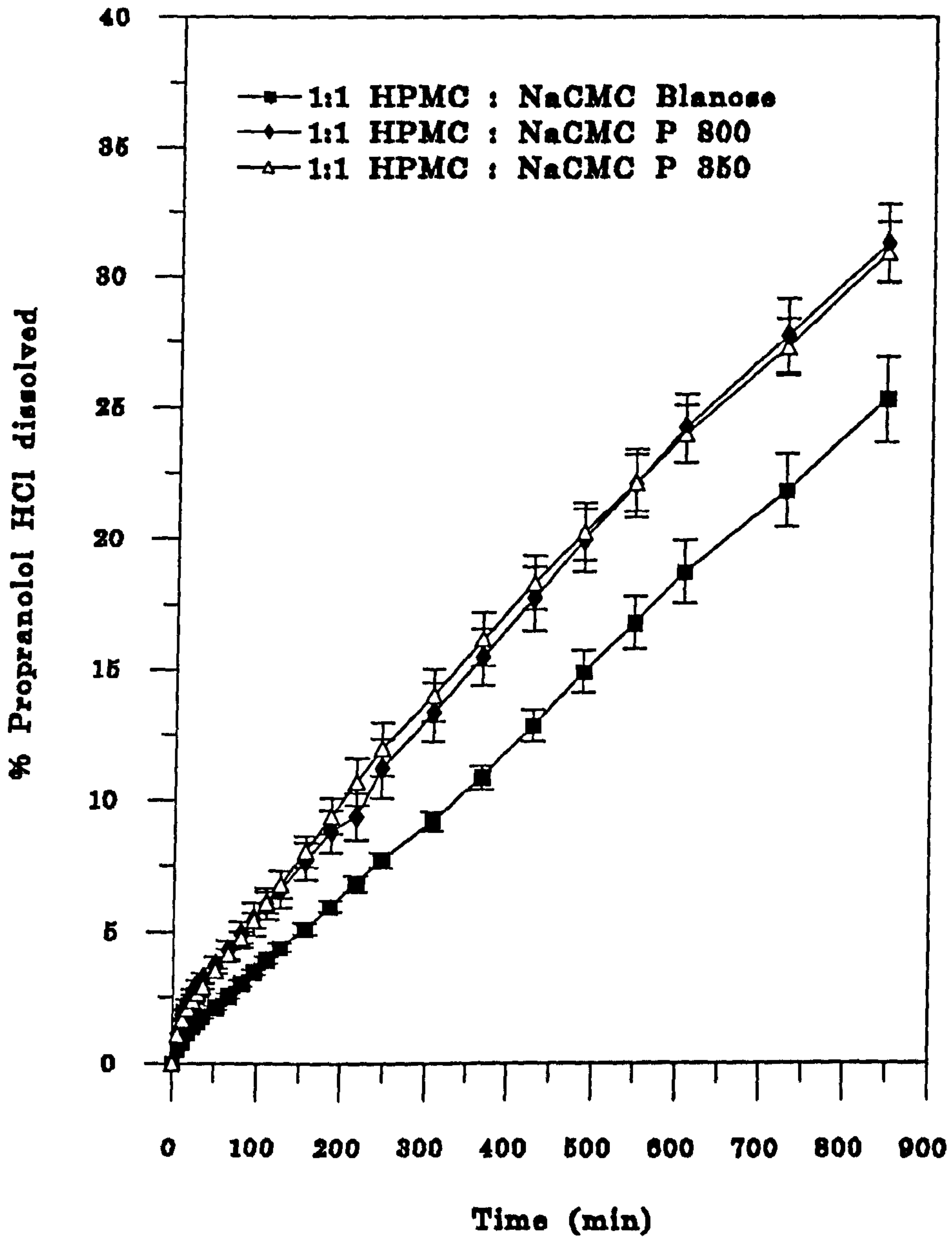


Figure 6.11: The release of propranolol hydrochloride from matrices containing 285 mg 1:1 HPMC K4M : NaCMC (Blanose), 1:1 HPMC : NaCMC P 350 or 1:1 HPMC : NaCMC P 350 into changing pH media (C). Results are the means  $\pm$  SD of six determinations.

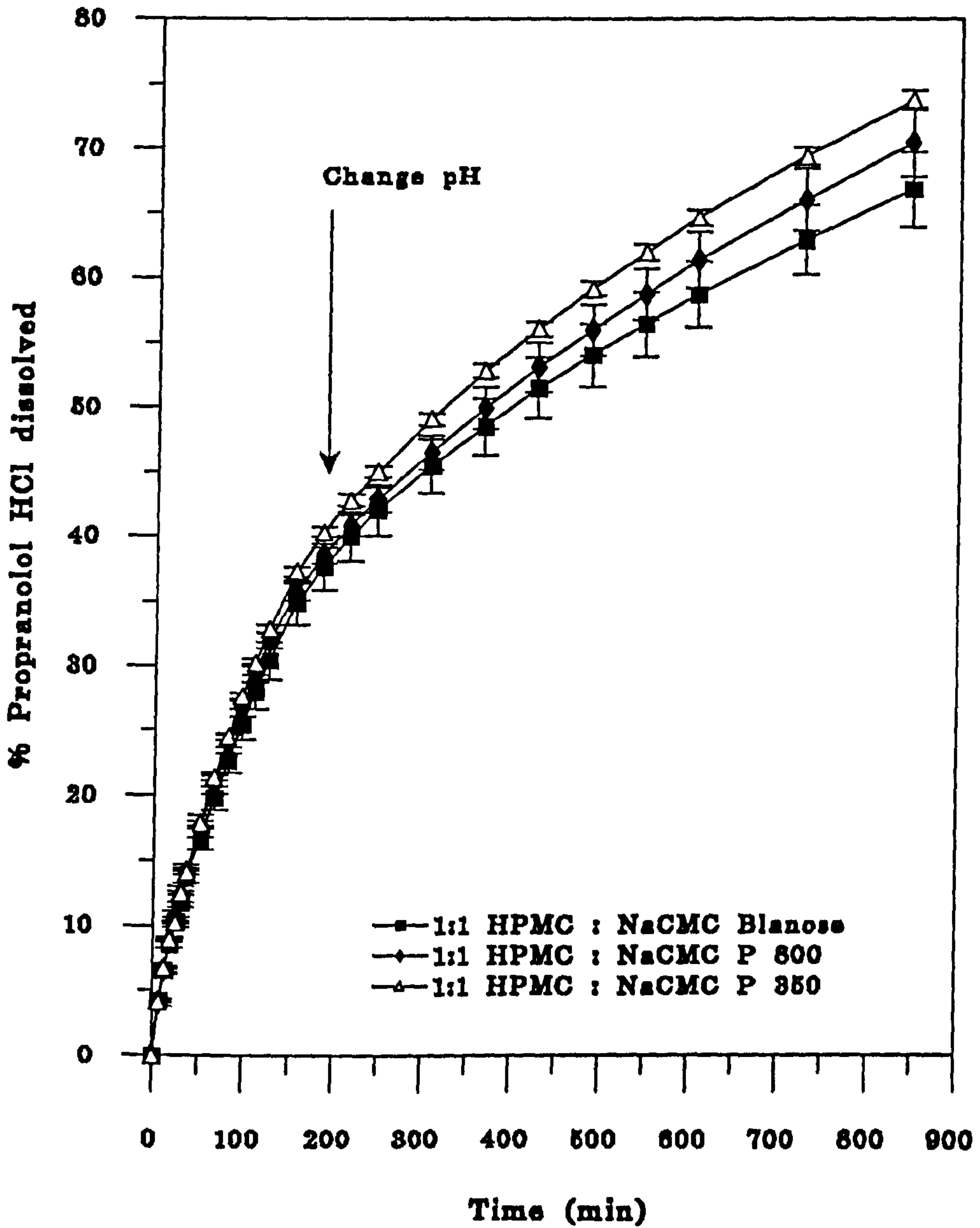




Table 6.4: Estimated values of release rates ( $\% \text{ min}^{-1/2}$ ) and release exponent based on equation 1.2 from matrices containing 285, 95 and 57 mg 1:1 HPMC : NaCMC (Blanose), 1:1 HPMC : NaCMC P 800 or 1:1 HPMC : NaCMC P 350 in different media

Polymer 1:1 HPMC: mg	0.1 M HCl		pH 6.8(c)*		pH 6.8		pH 7.4		pH 9.4	
	RR	n	RR	n	RR	n	RR	n	RR	n
285	3.2±0.1	0.59	3.0±0.2 <sup>2h</sup>	0.65	2.1±0.1	0.71	1.7±0.1	0.68	1.1±0.1	1.00
			2.1±0.1 <sup>R</sup>	0.32						
			3.3±0.1 <sup>2h</sup>	0.65						
P 800	3.4±0.1	0.61	2.2±0.1 <sup>R</sup>	0.37	3.2±0.1	0.75	2.0±0.1	0.66	1.2±0.1	0.86
			3.4±0.1 <sup>2h</sup>	0.67						
P 350	3.4±0.1	0.61	2.4±0.1 <sup>R</sup>	0.34	3.4±0.1	0.75	2.1±0.1	0.68	1.2±0.1	0.75
			5.0±0.2 <sup>2h</sup>	0.60						
95	5.5±0.1	0.56	5.6±0.3 <sup>R</sup>	-	4.3±0.3	0.50	4.1±0.2	0.48	1.4±0.1	0.29
			5.0±0.2 <sup>2h</sup>	0.54						
P 800	6.2±0.1	0.45	5.1±0.2 <sup>R</sup>	-	6.8±1.3	0.41	5.4±0.3	0.40	1.6±0.2	0.40
			6.3±0.2	0.51						
P 350	6.7±0.2	0.59	6.3±0.2	0.51	10.7±1.2	-	7.3±0.6	0.37	2.0±0.2	0.34
57	6.9±0.2	0.43	Not examined		11.0±0.1	0.41	11.0±0.5	0.33	3.0±0.4	-
			11.3±1.2	0.38						
P 350	9.7±0.7	0.38	20.3±1.6	0.48	20.3±1.6	0.48	17.1±0.4	0.37	7.8±0.4	0.33

RR is release rate ( $\% \text{ min}^{-1/2}$ ), \* changing pH method (see section 6.3.1.1), <sup>2h</sup> data from 5% drug release up to first 2 hours in 0.1 M hydrochloric acid, <sup>R</sup> data for 2 hours up to 60% release.

Mitchell et al (1991a) examined the effect of electrolytes on the dissolution of propranolol hydrochloride from matrices containing HPMC K15 and reported that since ions, such as phosphate ions have a great affinity for water, caused reduction in the cloud point of HPMC. However, Mitchell et al (1991a) stated that any reduction in hydration of polymer, such as increasing the concentration of salt in the dissolution media or increasing the temperature of the dissolution media, will start to prevent gelation and therefore may cause failure in sustained release.

Figure 6.11 shows the release profiles from matrices containing 285 mg total polymer by the pH change method. No difference in propranolol hydrochloride, release between the three NaCMCs, in the first two hours when the media was 0.1 M hydrochloric acid, was observed. When the pH was adjusted to 6.8, differences became apparent due to their viscosity grades.

The release from matrices containing 95 mg polymer into different media had release exponents less than 0.60 (table 6.4) and as the pH of media increased from 1 to 9.4, the value of release exponent decreased. Matrices containing 57 mg into all media tested gave a release exponent of less than 0.48. As mentioned before (section 6.3.2.2), the values less than 0.45 might be due to initial burst of drug release.



## 6.5 CONCLUDING REMARKS

The pH of media affected the drug release from NaCMC matrices whereas the release of propranolol hydrochloride from HPMC matrices were relatively insensitive to pH (table 6.1). The release of propranolol hydrochloride in 0.1 M hydrochloric acid was faster than in distilled water but its solubility in 0.1 M hydrochloric acid was lower than distilled water. Replacing NaCMC (Blanose) by two other viscosity grades of NaCMC, namely NaCMC (P 800) and NaCMC (P 350) showed no significant difference in release rate of propranolol hydrochloride into 0.1 M hydrochloric acid. This fact probably indicates that because of insolubility of NaCMC at 0.1 M hydrochloric acid, the interaction between NaCMC and propranolol hydrochloride is very low. The release rates decreased as the pH increased from that of 0.1 M hydrochloric acid to pH 9.4. As the pH increased the difference between release of drug from matrices with different viscosity grades of NaCMC was more obvious. The most significant difference between three viscosity grades of NaCMC admixture with HPMC was observed in distilled water (table 6.4) which might have been due to the maximum interaction between propranolol and NaCMC. The reason for the maximum interaction between propranolol hydrochloride and NaCMC in distilled water, probably is the fact that NaCMC is less soluble at 0.1 M hydrochloric acid and propranolol hydrochloride is less soluble at high pHs, therefore they must have their most ability to interact into distilled water. This interaction is weak at other pHs, due to reduction in the solubility of propranolol hydrochloride (table 6.2) or insolubility of NaCMC (in 0.1 M HCl).



# CHAPTER 7 DRUG RELEASE FROM MATRICES CONTAINING ETHYLCELLULOSE

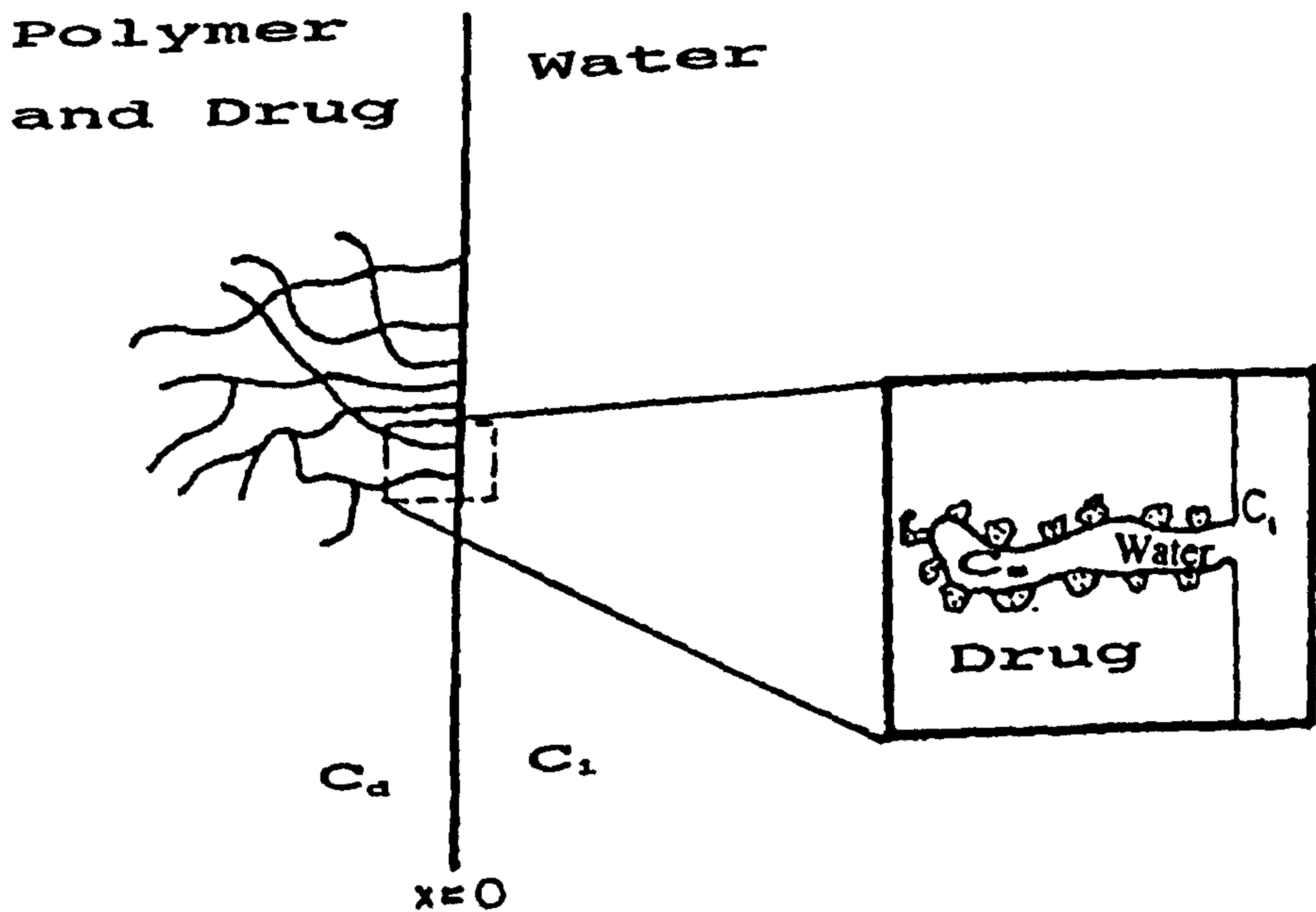
## 7.1 INTRODUCTION

Ethylcellulose (EC) is an inert, hydrophobic polymer and has properties such as lack of toxicity, stability during storage (Dubernet et al, 1990) and good compersibility (Upadrashta et al, 1993) which make it suitable for sustained release matrices. Ethylcellulose is used to control the dissolution rate of drugs from sustained-release products in, for example, matrix tablets (Stamm and Tritsch, 1986; Upadrashta et al, 1993), film-coated tablets (Porter, 1989; Narisawa et al, 1994) and microencapsulated dosage forms (Deasy et al, 1980). It has also been used as a matrix in the preparation of both water-soluble and sparingly water-soluble drugs using the solid dispersion technique (Shaikh et al, 1987a, b).

Gurny et al (1982) reported that when porous hydrophobic polymeric drug-delivery systems are placed in contact with an appropriate dissolution medium (usually water), the release of the drug to the medium must be preceded by drug dissolution in the water-filled pores and by diffusion through the water-filled channels. They reported that the geometry and structure of the pore network were important to this drug release process. Gurny et al (1982) proposed a model for drug diffusion through porous systems. In their model (figure 7.1), they denoted  $C_0$  as the initial drug loading in the sample,  $C_s$  as the drug saturation concentration at the pore

wall-dissolution medium interface where dissolution occurs and  $c_1$  as the surface concentration of the drug at the slab dissolution medium interface. In figure 7.1, it is assumed that the water entering the pores does not interact with the polymer or otherwise make it swell (contrary to hydrophilic polymers). Consequently Gurny et al (1982) claimed that the porosity was the major factor effective on drug release. This fact was in close agreement with the report by Higuchi (1963) that showed, in the matrix type delivery system, that the porosity and degree of tortuosity in the capillaries influenced the drug release rate.

Figure 7.1: Simplified diagram of drug release from porous polymers (after Gurny et al, 1982)



### **7.1.1 Aims and objectives**

The purpose of this study was to investigate the possible application of ethylcellulose, as a potential carrier for the preparation of prolonged release formulations using propranolol hydrochloride again as a model drug. The effects of drug : polymer ratio, viscosity grades and compaction pressure on drug release and also the replacement of ethylcellulose by hydrophilic polymers such as HPMC or NaCMC were investigated. Additionally, the water uptake of ethylcellulose on its own or admixture with HPMC, was investigated in an attempt to quantify the dissolution processes.

## **7.2 EFFECT OF PROPRANOLOL HYDROCHLORIDE : ETHYLCELLULOSE 7 cP RATIO ON DRUG RELEASE**

The effect of polymer concentration within a matrix is a direct consequence of Higuchi's equation (Higuchi, 1963). Several workers (Shaikh et al, 1987a; Doelker, 1989; Van Bommel et al, 1990; Bonny and Leuenberger, 1991) reported that the greater the concentration of the polymer within a matrix, the slower the release of a drug. In this section the effect of ethylcellulose content on the release of propranolol hydrochloride is described.

### **7.2.1 Experimental**

#### **7.2.1.1 Materials**

Propranolol hydrochloride (<125 µm), ethylcellulose 7 cP (<125 µm) and



magnesium stearate were used in this part of the study and are described in section 2.1.

#### 7.2.1.2 Matrix preparation

Tablets containing 160 mg propranolol hydrochloride, 95, 140 or 285 mg ethylcellulose 7 cP (<125  $\mu\text{m}$ ) and 0.75% magnesium stearate and were made as described in section 2.2.4. The compaction pressure used was 181.1  $\text{MNm}^{-2}$ .

#### 7.2.1.3 Dissolution methodology

Dissolution was carried out at 37°C as described in section 2.2.5.

#### 7.2.1.4 Analyses of drug release

The data between 5 to 80% release were fitted to equations 1.2 ( $Q=K_2 (t-l)^n$ ) and 1.3 ( $Q=K_3 t^{1/2} + C$ ) which were discussed in section 1.4.1.

### **7.2.2 Results and discussion**

Figure 7.2 shows the effect of drug : ethylcellulose ratio on the release of propranolol hydrochloride. The release kinetics from matrices composed of the varying amount of ethylcellulose are shown in table 7.1. As the polymer fraction increased, the release rate of the drug decreased (value of  $K_3$  in table 7.1) whereas the release exponents remained almost unchanged. The value of  $n$  below 0.5 indicates that the diffusion release mechanism predominated (Ritger and Peppas, 1987). It is clearly seen that the polymer content,

Figure 7.2: The effect of ethylcellulose 7 cP content on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 95, 140 or 285 mg ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations

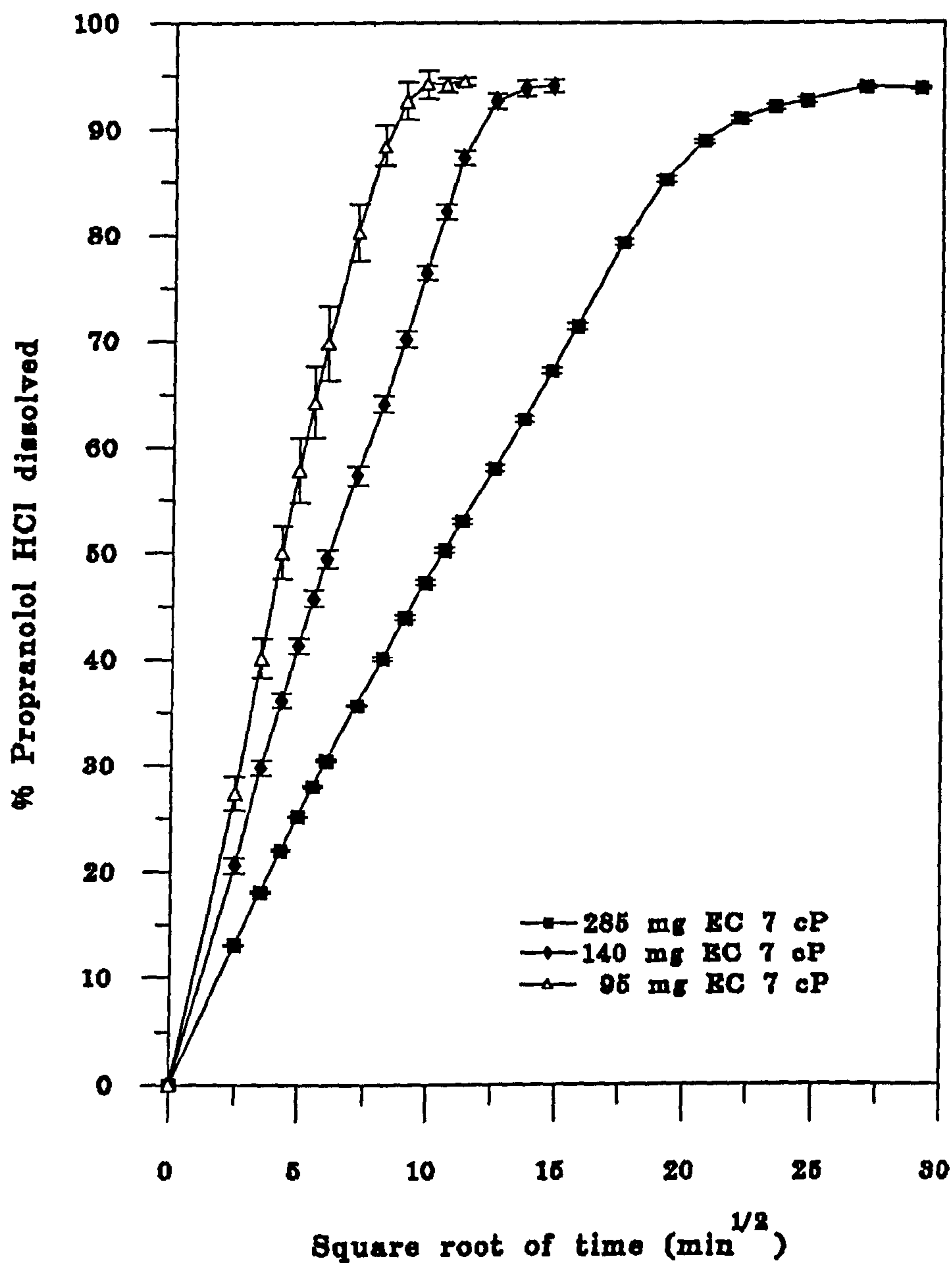


Table 7.1: Effect of ethylcellulose 7 cP content on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and different amount of ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations

EC 7 cP content (mg)	$T_{50\%}$ minutes $\pm$ SD	Equation 1.2			Equation 1.3	
		$K_2$ (%min <sup>-n</sup> )	n	l (min)	$K_3$ (%min <sup>-1/2</sup> )	C (%)
95	18.3 $\pm$ 1.8	11.4	0.49	0.95	12.48 $\pm$ 0.72	-5.46
140	37.1 $\pm$ 1.3	9.7	0.46	1.24	7.98 $\pm$ 0.15	-0.26
285	109.8 $\pm$ 1.1	6.3	0.44	0.82	4.53 $\pm$ 0.03	3.95

$K_2$ , n, l,  $K_3$  and C are parameters described by equations 1.2 or 1.3 (see section 1.4.1)



between 95 and 285 mg did not affect the release mechanism. Negative values of C indicate a burst release of drug and high positive values imply a delay to release. The data in table 7.1 indicate that matrices containing 95 mg ethylcellulose 7 cP had a burst release while matrices containing 285 mg polymer did not.

### 7.3 EFFECT OF PARTICLE SIZE AND VISCOSITY GRADES OF ETHYLCELLULOSE ON DRUG RELEASE

Ritger and Peppas (1987) and Mitchell et al (1993d) reported that smaller particle sizes of **hydrophilic** polymers such as HPMC, generally gave slower release profiles than with large particles sizes. Although **hydrophobic** polymers such as ethylcellulose do not swell on contact with moisture, the effect of their particle size on drug release has not been studied in depth. Because the matrices containing 95 mg or 140 mg ethylcellulose 7 cP did not show the desired sustenance of release (section 7.2), matrices containing 285 mg were more thoroughly investigated.

#### **7.3.1 Experimental**

##### 7.3.1.1 Materials

The materials used in this part of study, and described in section 2.1, were propranolol hydrochloride (<125  $\mu\text{m}$ ), ethylcellulose 7 cP, ethylcellulose 10 cP and magnesium stearate.

### 7.3.1.2 Matrix preparation

For the purpose of achieving different particle size ranges of ethylcellulose 7 cP and ethylcellulose 10 cP, both grades were sieved to produce the <125 µm, 150-250 µm, 250-355 µm and 355-425 µm fractions. All tablets in this study were manufactured as described in section 2.2.4 and contained 160 mg propranolol hydrochloride, 0.75% magnesium stearate as lubricant and 285 mg ethylcellulose 10 cP or ethylcellulose 7 cP. The compaction pressure used was 181.1 MNm<sup>-2</sup>.

### 7.3.1.3 Dissolution methodology

Dissolution was carried out at 37°C, as described in section 2.2.5.

### 7.3.1.4 Analyses of drug release

The same methods as described in section 7.2.1.4 for analyses of drug release were used.

## **7.3.2 Results and discussion**

The release profiles of propranolol hydrochloride from matrices containing 285 mg ethylcellulose 10 cP (figure 7.3) or ethylcellulose 7 cP (figure 7.4) of different particle sizes were generally linear for up to more than 80% drug release when plotted as a function of the square root of time. The release data, analyzed using equations 1.2 and 1.3, are shown in tables 7.2 and 7.3. The matrix tablets which consisted of <125 µm ethylcellulose showed the slowest drug release. As the particle size increased the release rate increased

(values of  $K_3$  in tables 7.2 and 7.3). This may be due to the fact that penetration of water into the matrices was facilitated when the coarser particle size fractions were used. The times for 50% release of the drug to be released ( $T_{50\%}$ ) are also shown in tables 7.2 and 7.3. It is seen that as the particle size of both grades of ethylcellulose increased, the values of  $l$  (lag time) and  $C$  decreased, indicating a burst release of drug with the coarser particle sizes.

Although both ethylcellulose 10 cP and ethylcellulose 7 cP showed similar behaviour, matrices containing ethylcellulose 7 cP showed marginally slower release rates than matrices containing ethylcellulose 10 cP at equivalent particle size. The lowest release rate of  $4.53 \pm 0.03\% \text{ min}^{-1/2}$  was obtained from matrices containing 285 mg ethylcellulose 7 cP compared with  $4.84 \pm 0.07\% \text{ min}^{-1/2}$  from matrices containing ethylcellulose 10 cP. Similar results have been reported by Upadrashta et al (1993) who, using ethylcellulose 10, 20, 45 and 100 cP, reported that a controlled release rate is achieved with lower viscosity grades of ethylcellulose.

The matrices containing  $<125 \mu\text{m}$  ethylcellulose 7 cP remained intact during testing, whereas matrices consisting of coarser particles slowly disintegrated. As the particle size of each ethylcellulose increased, the release exponent (values of  $n$ ) increased and the highest value,  $n = 0.88$ , was obtained for ethylcellulose 10 cP with the 425-355  $\mu\text{m}$  fraction. The data indicate that, since the values of  $n$  were dependent on the particle size, as the particle size



Figure 7.3: The effect of particle size of ethylcellulose 10 cP on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 10 cP. Results are the means  $\pm$  SD of six determinations.

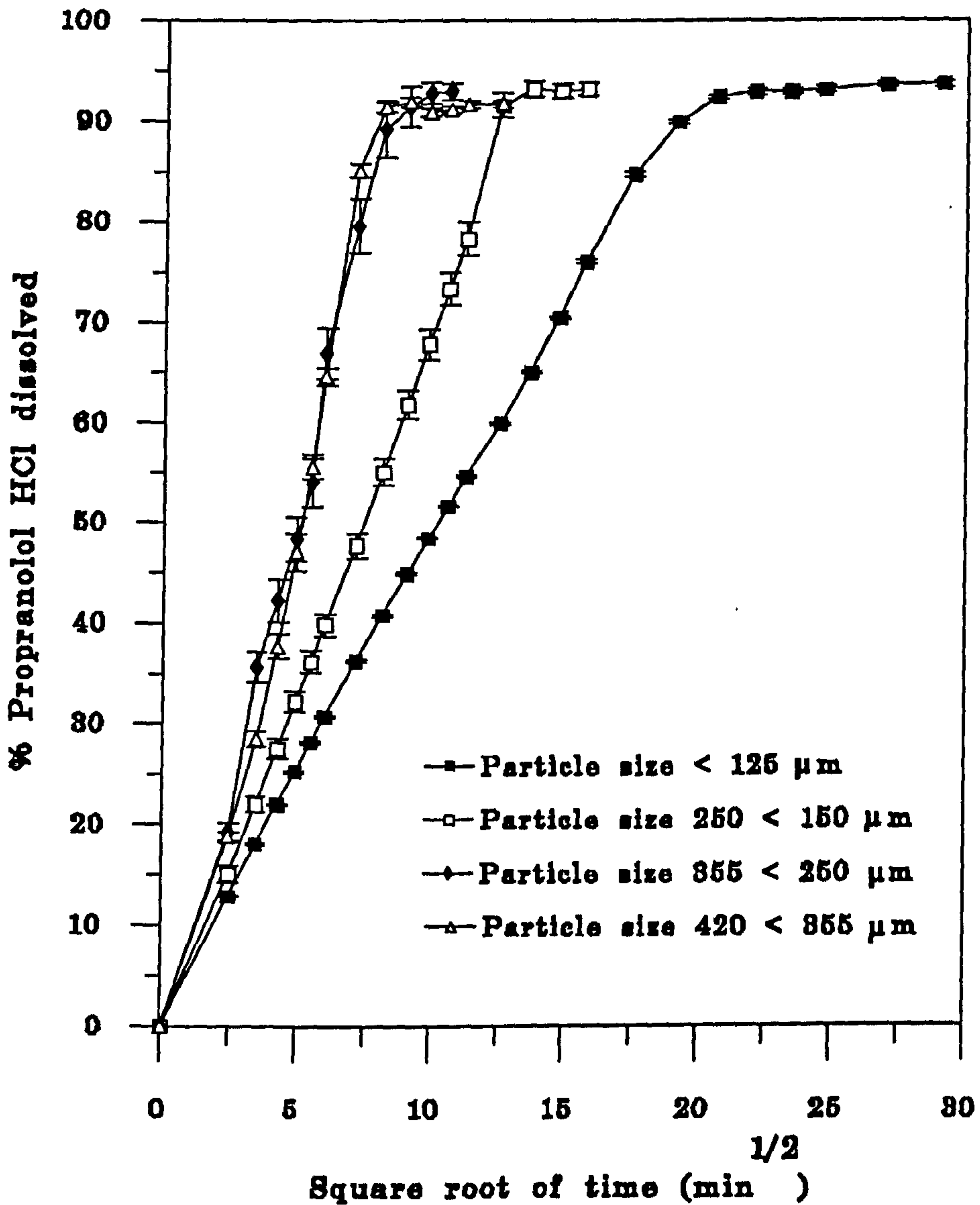


Table 7.2: Effect of particle size of ethylcellulose 10 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 10 cP. Results are the means  $\pm$  SD of six determinations

Particle size $\mu\text{m}$	$T_{50\%}$ minutes $\pm$ SD	Equation 1.2			Equation 1.3		
		$K_2$ (%min <sup>-n</sup> )	n	l (min)	$K_3$ (%min <sup>-1/2</sup> )	C (%)	
425 < 355	26.2 $\pm$ 1.4	2.5	0.88	-3.78	11.91 $\pm$ 0.50	-19.8	
355 < 250	31.9 $\pm$ 2.4	4.9	0.66	-2.10	9.79 $\pm$ 0.61	-8.68	
250 < 150	55.8 $\pm$ 2.5	9.0	0.52	3.35	7.42 $\pm$ 0.06	-2.62	
<125	103.6 $\pm$ 0.4	5.5	0.47	-0.29	4.84 $\pm$ 0.07	2.27	

$K_2$ , n, l,  $K_3$  and C are parameters described by equations 1.2 or 1.3 (section 1.4.1)

Figure 7.4: The effect of particle size of ethylcellulose 7 cP on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations.

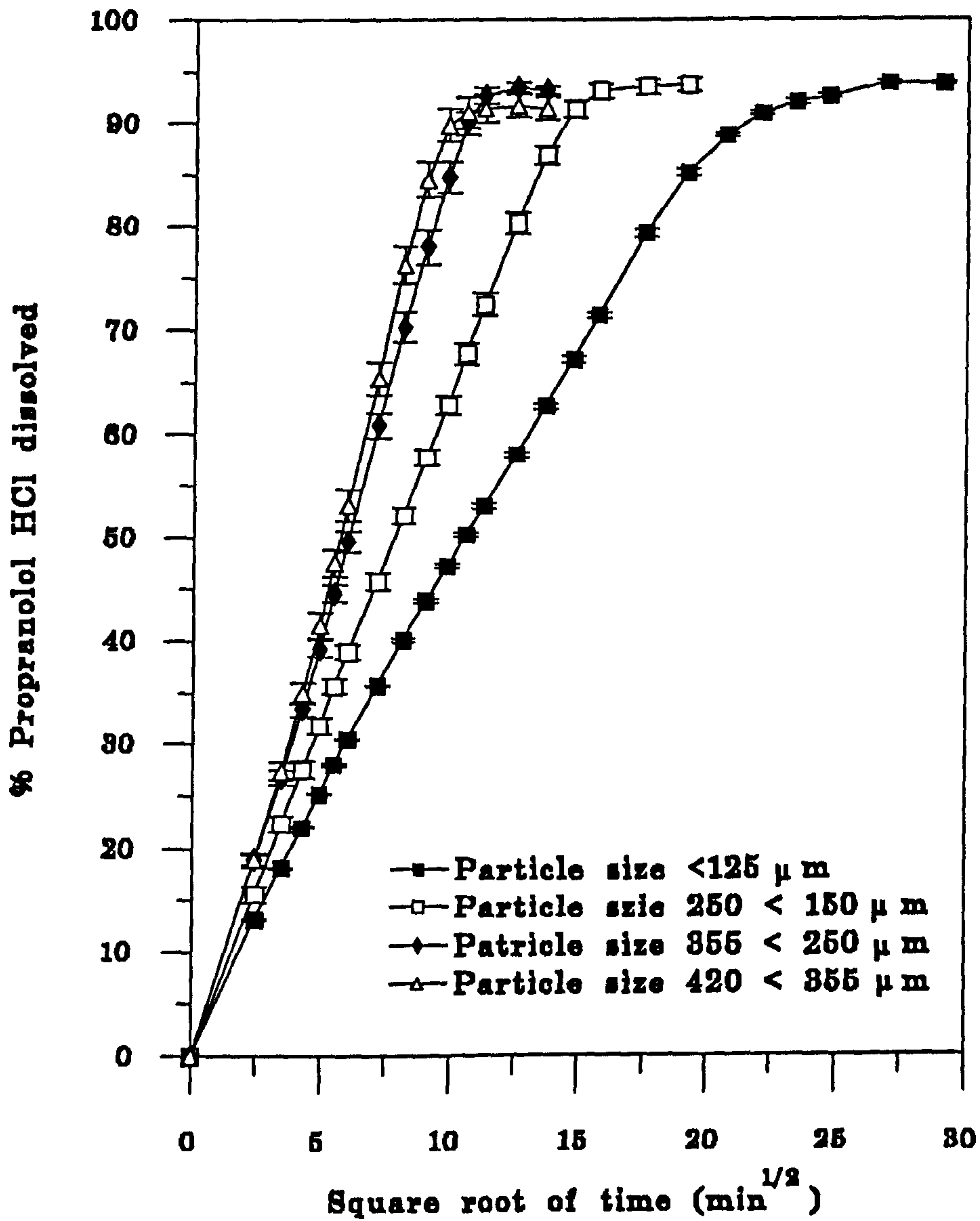




Table 7.3: Effect of particle size of ethylcellulose 7 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations

Particle size $\mu\text{m}$	$T_{50\%}$ minutes $\pm$ SD	Equation 1.2			Equation 1.3		
		$K_2$ (%min <sup>-n</sup> )	n	l (min)	$K_3$ (%min <sup>-1/2</sup> )	C (%)	
425 < 355	32.7 $\pm$ 1.7	6.4	0.59	-1.13	9.39 $\pm$ 0.24	-7.82	
355 < 250	36.5 $\pm$ 0.9	6.2	0.58	-0.76	8.67 $\pm$ 0.17	-4.91	
250 < 150	61.0 $\pm$ 1.9	6.6	0.50	0.24	6.43 $\pm$ 0.17	0.165	
< 125	109.8 $\pm$ 1.1	6.3	0.44	0.82	4.53 $\pm$ 0.03	3.95	

$K_2$ , n, l,  $K_3$  and C are parameters described by equations 1.2 or 1.3 (section 1.4.1)

of ethylcellulose decreased the release became progressively controlled by diffusion. Although the value of  $n$  for coarse particle size of ethylcellulose 10 cP is the desired for near zero order release, the negative value of  $C$  indicates a burst release of drug before control of release is accomplished.

#### 7.4 EFFECT OF COMPACTION PRESSURE ON DRUG RELEASE

It is well known that compaction pressure does not effect drug release rates from matrices containing hydrophilic polymers (Ford et al, 1985a; Conte et al 1993). However, ethylcellulose is thought to deform plastically when subjected to compression (Rekhi and Jambhekar, 1995) and consequently the drug release may be a function of the compaction pressure used to produce the matrices. Therefore, matrix tablets containing 285 mg ethylcellulose 7 cP <125  $\mu\text{m}$  size were chosen for investigation of the effects of compaction pressure on drug release. The reasons for choosing this viscosity grade and particle size of ethylcellulose were that:

a- matrices containing 95 mg or 140 mg of ethylcellulose 7 cP gave a release faster than from matrices containing 285 mg (section 7.2),

b- matrices containing 285 mg ethylcellulose <125  $\mu\text{m}$  size showed a sustained release of propranolol hydrochloride for more than 7 hours (section 7.3),

c- the release rate from matrices containing ethylcellulose 7 cP was slightly lower than from matrices containing ethylcellulose 10 cP (values of  $K_3$  in tables 7.2 and 7.3),

## **7.4.1 Experimental**

### **7.4.1.1 Materials**

Propranolol hydrochloride (<125  $\mu\text{m}$ ), ethylcellulose 7 cP (<125  $\mu\text{m}$ ) and magnesium stearate, used in this part of the study, are described in section 2.1.

### **7.4.1.2 Matrix preparation**

Tablets in this study were manufactured as described in section 2.2.4 and contained 160 mg propranolol hydrochloride (<125  $\mu\text{m}$ ), 0.75% magnesium stearate as lubricant and 285 mg ethylcellulose 7 cP (<125  $\mu\text{m}$ ). Tablets were compressed at pressures ranging from 7.8 to 393.7  $\text{MNm}^{-2}$ . Tablets up to 213.4  $\text{MNm}^{-2}$  pressure (7.9, 39.4, 78.7, 118.1 or 213.4  $\text{MNm}^{-2}$ ) were made on a Manesty F3 single punch machine. In order to avoid damage to the press, tablets made at higher pressures (315.0 or 393.7  $\text{MNm}^{-2}$ ) were compressed using a compaction simulator (ESH testing Ltd., Brierly Hill, U.K.).

### **7.4.1.3 Porosity determination**

The porosities of the matrices were calculated using equation 7.1 (Narisawa et al, 1994).



$$\varepsilon = (1 - P_r / P_t) \times 100$$

Equation 7.1

Where:  $\varepsilon$  = porosity of matrix,  $P_r$  = the apparent density of the compact at any given pressure ( $\text{g/cm}^3$ ),  $P_t$  = the true density of powder ( $\text{g/cm}^3$ ).

$P_t$  was determined using an Air Comparison Pycnometer (Model 930, Beckman Instruments Ltd. U.K.). The mean of three determinations for each batch was used for the true density of powder. The dimensions of the tablets were measured using a screw-gauge micrometer (Moore and Wright, Sheffield) and used to calculate the tablet volume in order to determine  $P_r$  for each tablet. The mean of six determinations was used to determine the porosity of matrices at each compaction pressure.

#### 7.4.1.4 Dissolution methodology

Dissolution was carried out at 37°C as described in section 2.2.5.

#### **7.4.2 Results and discussion**

Figure 7.5 shows the effect of compaction pressure on drug release from matrices containing 285 mg ethylcellulose 7 cP. The data obtained are presented in table 7.4. The release from matrices compressed at 7.8  $\text{MNm}^{-2}$  was very rapid. The dissolution profile from matrices made at 39.4  $\text{MNm}^{-2}$  was biphasic. The rates were  $5.62\% \pm 0.28 \text{ min}^{-1/2}$  for up to 30% release and subsequently  $11.07\% \pm 0.41 \text{ min}^{-1/2}$  up to 80% release. The release rates of matrices compressed at forces between 78.7 and 393.7  $\text{MNm}^{-2}$  were relatively

unaffected by pressure.

As the compaction pressures initially increased, the porosities of matrices decreased and subsequently the release rates (value of  $K_3$  in table 7.4) decreased. The porosity of matrices made at pressures between 78.7 and 393.7  $\text{MNm}^{-2}$  were similar and the values of release exponent ( $n$ ) at this range of compaction pressures were also similar (between 0.43 to 0.46), whereas at 39.4  $\text{MNm}^{-2}$  pressure the porosity and the value of  $n$  were high. Therefore it could be suggested that the porosity of matrices affected the drug release mechanism. Stamm and Tritsch (1986), using ethylcellulose 20 cP, reported that matrices made with low crushing strengths had high porosity and gave quick release of metoclopramide hydrochloride whereas the release profiles of this drug were similar, but lower from matrices made to higher crushing strengths. Higuchi (1963) showed that in the matrix type of delivery system, the porosity and degree of tortuosity in the capillaries influenced drug release rate and reported that the amount of drug per unit of matrix volume decreased with time as dissolution occurred. Similarly, Desai et al (1966) reported that the release data from elastic matrices such as polyvinyl chloride were found to be independent of the compression force which was attributed to a constancy of porosity within the matrix.

The release kinetics and  $T_{50\%}$ s are also shown in table 7.4. The  $T_{50\%}$ s were similar for matrices compressed at 78.7 - 393  $\text{MNm}^{-2}$ . The values of  $n$  suggest that drug release became predominantly diffusional controlled as the

Figure 7.5: The effect of compaction pressure ( $\text{MNm}^{-2}$ ) on the release of propranolol hydrochloride from matrices containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations.

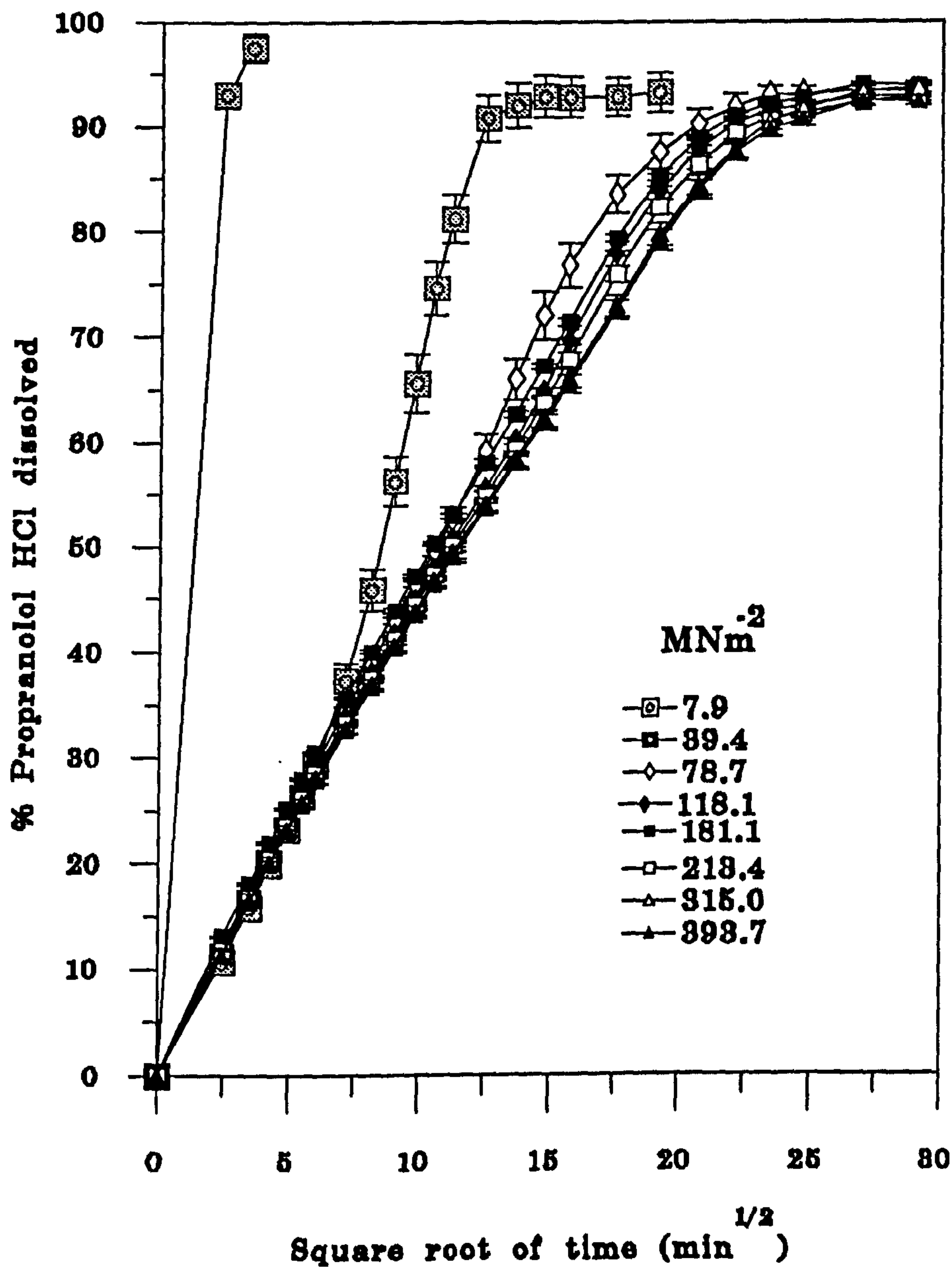




Table 7.4: Effect of compaction pressure of ethylcellulose 7 cP on the dissolution constants from tablets containing 160 mg propranolol hydrochloride and 285 mg ethylcellulose 7 cP. Results are the means  $\pm$  SD of six determinations

Pressure MNm <sup>-2</sup>	Porosity % $\pm$ SD	T <sub>50%</sub> Mins $\pm$ SD	Equation 1.2			Equation 1.3	
			K <sub>2</sub> (%min <sup>-n</sup> )	n	l (min)	K <sub>3</sub> (%min <sup>-1/2</sup> )	C (%)
7.8	37.1 $\pm$ 0.2	< 3	- <sup>a</sup>	-	-	-	-
39.4	17.9 $\pm$ 0.5	72.0 $\pm$ 4.1	0.62	0.99	-13.8	8.15 $\pm$ 0.41	-15.5
78.7	14.2 $\pm$ 0.3	112.7 $\pm$ 1.6	4.54	0.51	-1.6	4.89 $\pm$ 0.15	0.43
118.1	11.5 $\pm$ 0.6	122.5 $\pm$ 1.7	5.40	0.46	-0.1	4.45 $\pm$ 0.06	2.92
181.1	11.4 $\pm$ 0.6	109.8 $\pm$ 1.1	6.31	0.44	0.8	4.34 $\pm$ 0.03	3.95
213.7	9.9 $\pm$ 0.2	125.6 $\pm$ 2.5	5.54	0.44	0.5	4.16 $\pm$ 0.04	3.04
315.0	13.3 $\pm$ 0.1	129.8 $\pm$ 3.3	5.92	0.44	1.7	4.02 $\pm$ 0.06	3.47
393.7	13.5 $\pm$ 0.3	132.2 $\pm$ 2.8	6.12	0.43	1.4	4.13 $\pm$ 0.05	3.48

K<sub>2</sub>, n, l, K<sub>3</sub> and C are parameters described by equations 1.2 or 1.3 (see section 1.4.1); <sup>a</sup> no data due to very fast release

compaction pressure increased. In table 7.4 it may be observed that an increase in compaction pressure caused increase in the values of C or l. Therefore the burst release seen at low compaction pressures was suppressed at higher compaction pressures.

## 7.5 EFFECT OF REPLACEMENT OF ETHYLCELLULOSE BY HYDROXYPROPYLMETHYLCELLULOSE OR SODIUM CARBOXYMETHYLCELLULOSE ON DRUG RELEASE

In swelling systems, the release of a solute (e.g. drug, dye) is controlled by one or more of the following processes namely, the transport of the solvent into the polymer matrix, swelling of the associated polymers, diffusion of the solute through the swollen polymer and erosion of the swollen polymer (Ranga Rao and Padmalatha Devi, 1988). Since ethylcellulose is a hydrophobic polymer and can not swell in a manner similar to HPMC or NaCMC, it was considered that admixture of HPMC or NaCMC with ethylcellulose could change the permeability of the matrix (Porter, 1989) and consequently modify the release rate or, in the case of NaCMC, additionally interact with propranolol hydrochloride.

### **7.5.1 Experimental**

#### 7.5.1.1 Materials

Propranolol hydrochloride (<125  $\mu$ m), ethylcellulose 7 cP (<125  $\mu$ m), HPMC

K4M, NaCMC (Blanose) and magnesium stearate, described in section 2.1, were used in this part of study.

#### 7.5.1.2 Matrix preparation

Tablets were compressed to contain 160 mg propranolol hydrochloride (<125  $\mu\text{m}$ ), 285 mg of total polymers in ratios 1:3, 1:1 or 3:1 of HPMC K4M : ethylcellulose 7 cP (<125  $\mu\text{m}$ ) or NaCMC (Blanose) : ethylcellulose 7 cP (<125  $\mu\text{m}$ ) and 0.75% magnesium stearate and were compressed at 181.1 MNm<sup>-2</sup> as described in section 2.2.4.

#### 7.5.1.3 Dissolution methodology

Dissolution was carried out at 37°C as described in section 2.2.5.

### **7.5.2 Results and discussion**

#### 7.5.2.1 Replacement of HPMC by ethylcellulose

Drug release profiles of tablets prepared from different ratios of HPMC K4M : ethylcellulose 7 cP are shown in Figure 7.6 and the data obtained using equations 1.2 and 1.3 are presented in table 7.5. As the proportion of ethylcellulose in the matrix increased the value of  $T_{50\%}$  decreased and subsequently the release rate increased from  $2.7\% \pm 0.2 \text{ min}^{-1/2}$  (HPMC K4M alone) to  $4.8\% \pm 0.1 \text{ min}^{-1/2}$  (ethylcellulose 7 cP alone). It was surprising that the values of  $n$  did not change when the matrices consisted of an admixture of the two polymers or HPMC alone. This fact confirmed the finding of Ford



Figure 7.6: The effect of HPMC K4M : ethylcellulose 7 cP ratio on propranolol hydrochloride release from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer. Results are the means  $\pm$  SD of six determination.

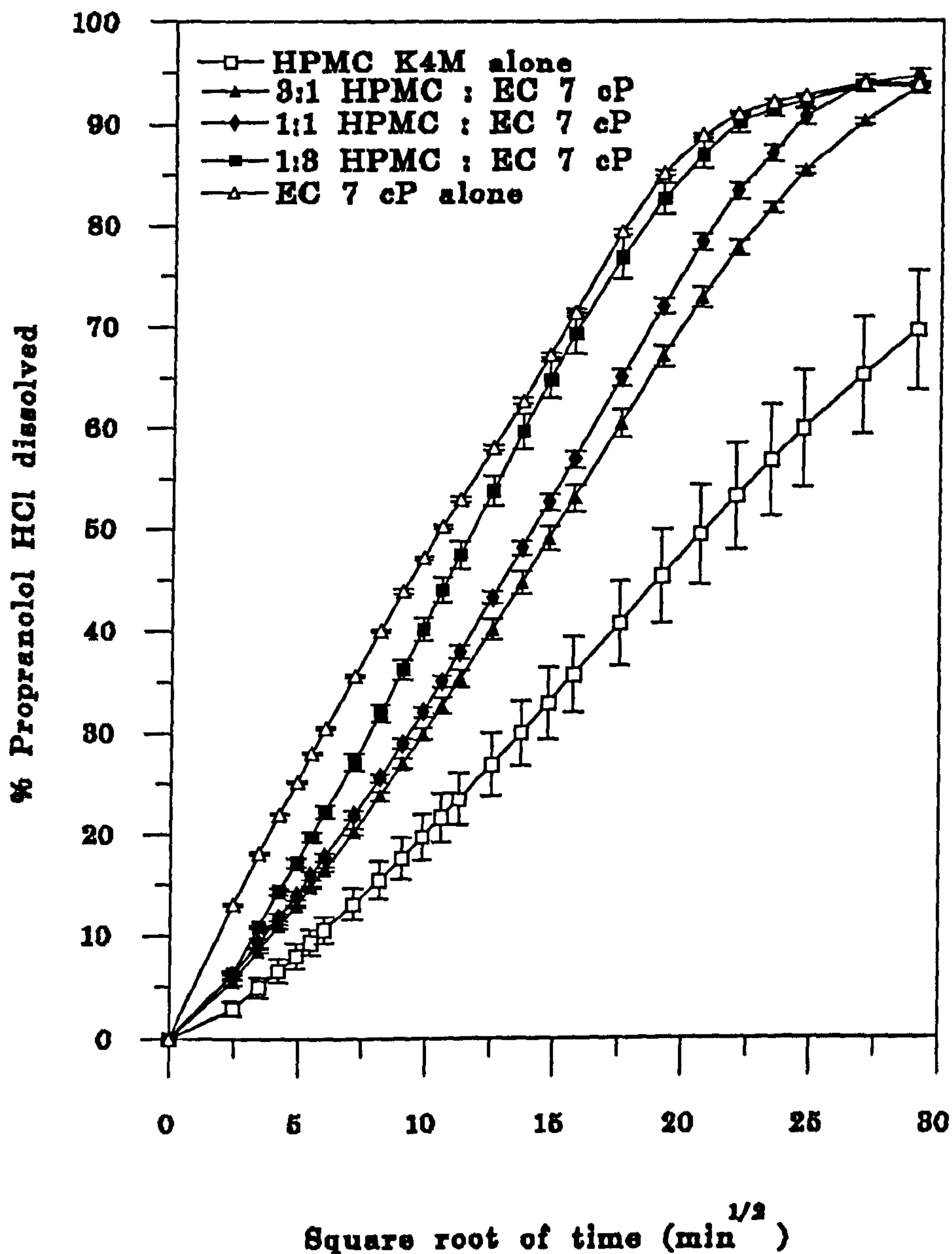


Table 7.5: The effect of HPMC K4M : ethylcellulose 7 cP or NaCMC Blanose : ethylcellulose 7 cP ratio on the dissolution constants from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer based on equations 1.2 and 1.3. Results are the means  $\pm$  SD of six determinations

Polymer	Ratio	$T_{50\%}$ mins $\pm$ SD	Release rate $\text{min}^{-1/2} \pm \text{SD}$	Equation 1.2			Equation 1.3	
				$K_2(\% \text{min}^{-n})$	n	l	$K_3(\text{min}^{-1/2})$	C (%)
HPMC :	1:0	398.7 $\pm$ 12.0	2.7 $\pm$ 0.2	1.42	0.59	5.39	2.64 $\pm$ 0.2	-5.47
	3:1	222.9 $\pm$ 8.8	3.7 $\pm$ 0.1	1.88	0.61	-0.02	3.65 $\pm$ 0.1	-5.08
	1:1	198.3 $\pm$ 4.7	3.9 $\pm$ 0.1	1.98	0.61	-0.50	3.86 $\pm$ 0.1	-4.93
	1:3	129.2 $\pm$ 4.5	4.8 $\pm$ 0.1	2.76	0.59	1.84	4.76 $\pm$ 0.1	-6.11
NaCMC :	1:0	512.9 $\pm$ 18.5	3.5 $\pm$ 0.1	*	*	*	3.48 $\pm$ 0.1	-30.2
	3:1	365.5 $\pm$ 30.3	4.0 $\pm$ 0.3	0.01	1.45	-40	4.05 $\pm$ 0.3	-25.8
	1:1	269.1 $\pm$ 7.8	4.3 $\pm$ 0.1	0.45	0.86	9.19	4.38 $\pm$ 0.1	-18.4
	1:3	30.8 $\pm$ 2.5	7.2 $\pm$ 0.2	*	*1	*	8.43 $\pm$ 0.2	7.85
Ethylcellulose	0:1	109.8 $\pm$ 1.1	4.6 $\pm$ 0.0	6.3	0.44	0.82	4.53 $\pm$ 0.1	3.95

\* data did not fitted in equation 1.2.

et al (1987) who investigated the effect of replacement HPMC by diluents and reported that replacement of portions of HPMC within the matrices by diluents increased the release rates of promethazine hydrochloride, irrespective of whether the diluents were water soluble or water insoluble.

The exponent value from matrix tablets containing ethylcellulose (0.44) indicates that the matrix exhibits mainly diffusional release mechanisms, whereas the exponent values from matrices containing various ratios of HPMC K4M : ethylcellulose (0.59 - 0.62) indicates a coupling of diffusion (case I) and polymer relaxation phenomena (case II). This fact indicates that the presence of HPMC encouraged erosion in the matrices.

Visually, the matrices containing ethylcellulose remained intact during the test and matrices containing HPMC alone swelled. When the matrix tablets consisted of 1:3 HPMC : ethylcellulose, they disintegrated slowly. This phenomenon could be due to the fact that when the proportion of ethylcellulose in the matrix is high, the hydrophilic particles in the matrix were separated from each other and formation of a protective gel layer around the matrix did not occur. As the proportion of HPMC in the matrix increased, the matrix remaining at the end of dissolution became larger.

#### 7.5.2.2 Replacement of NaCMC by ethylcellulose

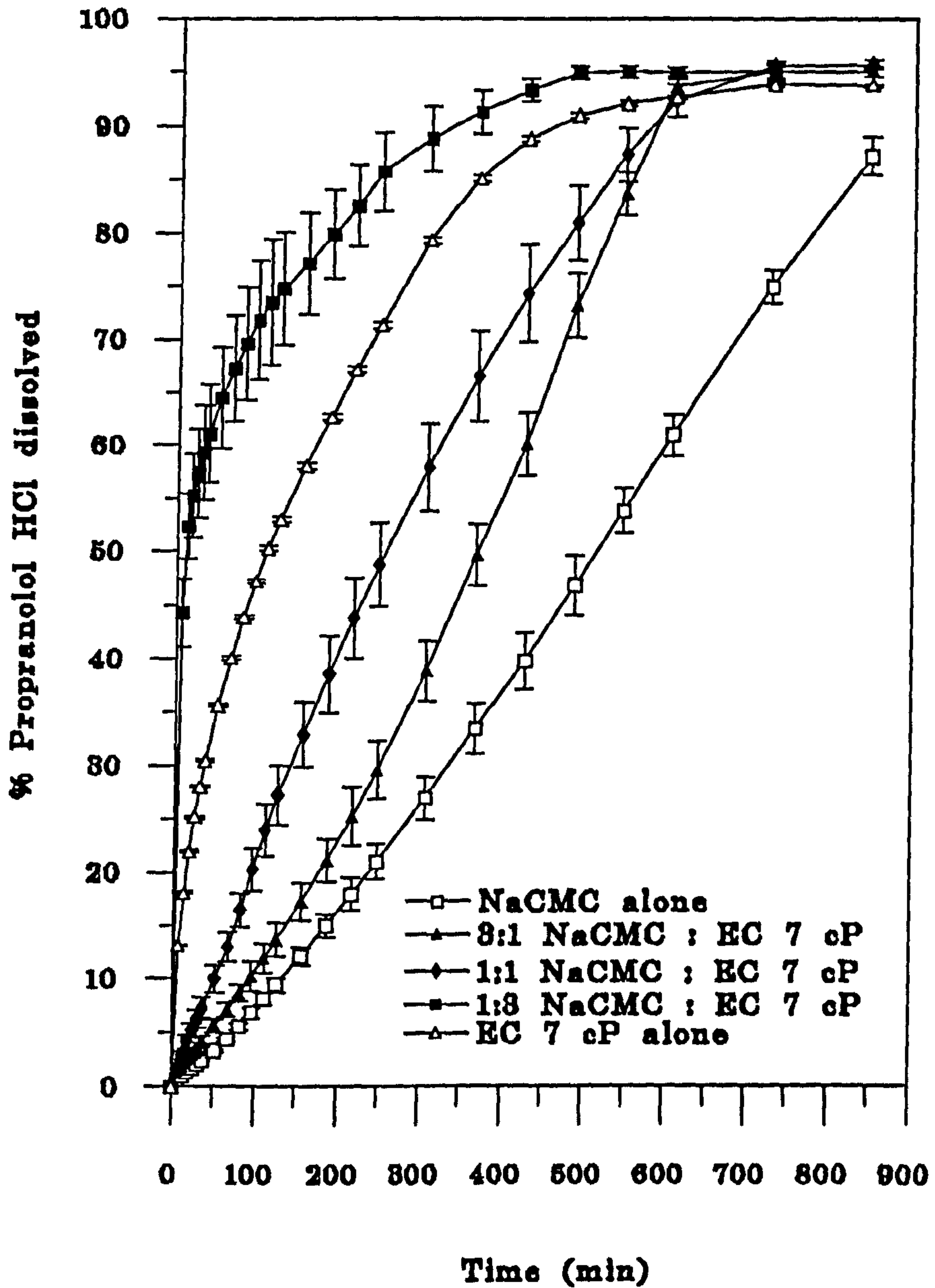
Figure 7.7 shows the data for NaCMC - ethylcellulose matrices. The data obtained by using equations 1.2 and 1.3 (between 5 - 60% drug release) are



presented in table 7.5. Since the release data from matrices containing NaCMC alone or ratio 3:1 NaCMC : ethylcellulose did not fit to equation 1.2, it is omitted in table 7.5. As the ethylcellulose portion in the matrices consisting of NaCMC : ethylcellulose increased, the  $T_{50\%}$  decreased and the release rates ( $K_3$  in table 7.5) increased. When the proportion of ethylcellulose in the matrix tablets was 75% (i.e., 1:3 NaCMC : ethylcellulose) a burst release was observed and more than 45% drug released during the initial 6 minutes of dissolution test. This phenomenon could be explained in the following way: when the proportion of NaCMC in the matrix was low and therefore its particles were separated by non-hydrophilic ethylcellulose particles, the formation of a protective layer by NaCMC (which occurs following water absorption at higher proportions of NaCMC) did not occur effectively. Consequently the drug was released rapidly. The interaction between propranolol hydrochloride and NaCMC which discussed in section 5.3.3 is another reason that caused the slow release from matrices, whereas propranolol hydrochloride could not interact with ethylcellulose.

Matrices containing 3:1 NaCMC : ethylcellulose (25% ethylcellulose content) gave a release exponent value of 1.45 (table 7.5). This value indicates super case-II transport. The reason for this value might be the high swelling nature of the polymer at this ratio (Ranga Rao et al, 1988a; Bain et al, 1991). Addition of ethylcellulose into NaCMC matrices possibly would increase the porosity of the matrix tablets and the matrices swell very fast in contact with water, because the penetration of water into matrices is facilitated.

Figure 7.7: The effect of NaCMC (Blanose) : ethylcellulose 7 cP ratio on propranolol hydrochloride release from matrices containing 160 mg propranolol hydrochloride and 285 mg total polymer. Results are the means  $\pm$  SD of six determinations.



## 7.6 WATER UPTAKE OF ETHYLCELLULOSE, HYDROXYPROPYLMETHYLCELLULOSE AND THEIR MIXTURES

Knowledge of the water uptake by the polymer is necessary to understand the dissolution process. The purpose of this study was to investigate the process of hydration of ethylcellulose 7 cP on its own or in admixture with HPMC, in order to evaluate the release mechanism of propranolol hydrochloride from these matrices.

### **7.6.1 Experimental**

#### 7.6.1.1 Materials

Ethylcellulose 7 cP (<125  $\mu\text{m}$ ) and HPMC K4M, as described in section 2.1, were used.

#### 7.6.1.2 Preparation of wafers

Wafers were made using approximately 10 mg of ethylcellulose (<125  $\mu\text{m}$ ), HPMC K4M or their 1:1 mixture as described in section 2.2.2.4.

#### 7.6.1.3 Evaporation of water from wafers containing HPMC or ethylcellulose

Wafers containing ethylcellulose, after 30 minutes of contact with water (before the scan) were reweighed. The results showed  $32 \pm 1.8\%$  w/w reduction in their weight indicating evaporation of water. Similar tests were carried out for HPMC and NaCMC wafers. The results showed a  $1.6 \pm 0.1\%$



w/w loss due to water evaporation. The reason for this difference might be the ability of HPMC or NaCMC to absorb water and therefore prevent the water from evaporating.

#### 7.6.1.4 Method of determination

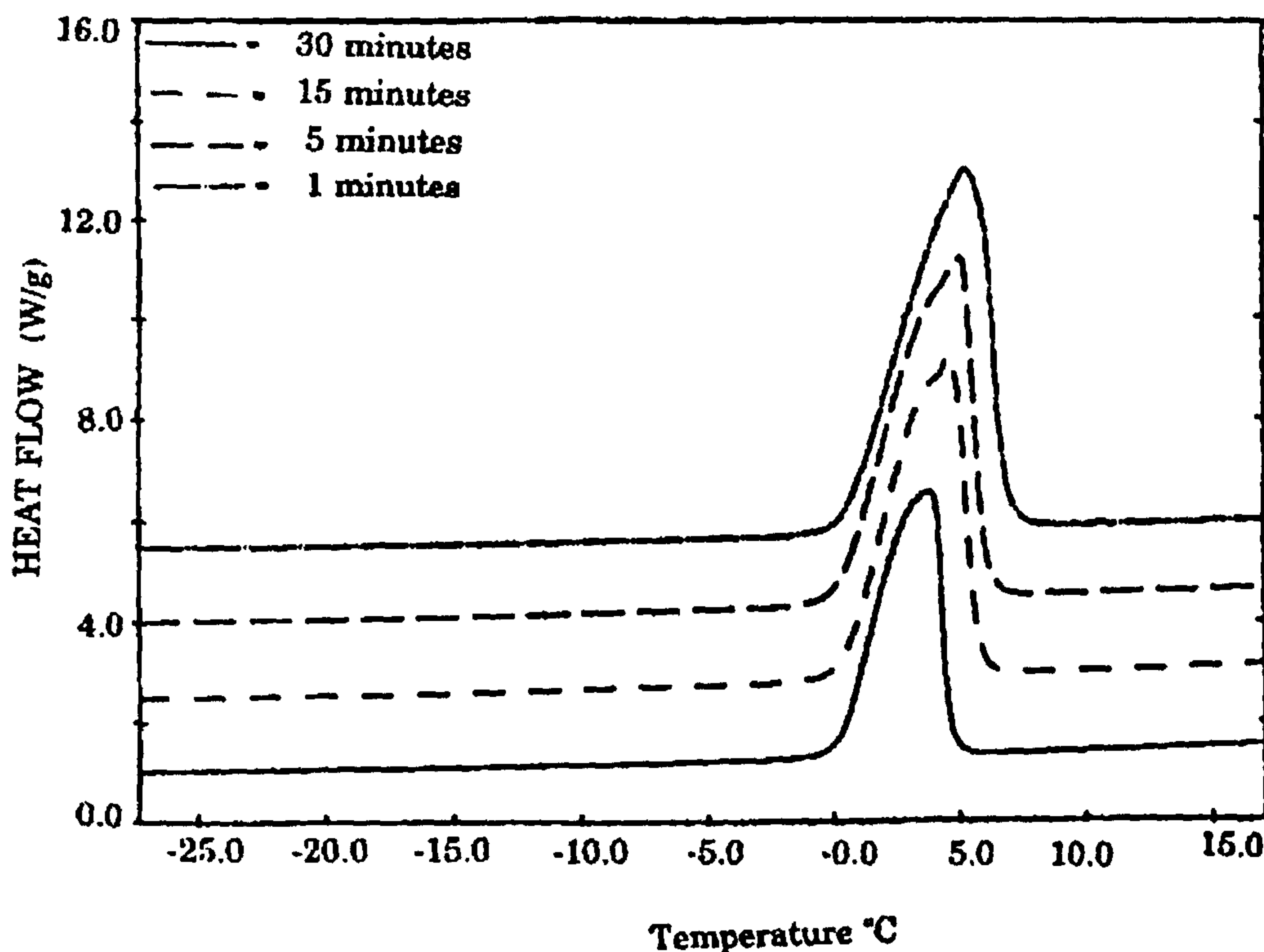
Water uptake by wafers was initially determined by the methods described in section 2.2.2.4. As discussed before, water evaporation occurred and therefore the sample pans containing ethylcellulose were measured after storage prior to analysis. The amounts of water remaining in the pans were re-determined such that water uptake could be calculated accurately.

#### **7.6.2 Results and discussion**

Figure 7.8 shows typical DSC scans of water taken up by wafers containing ethylcellulose 7 cP (<125  $\mu\text{m}$ ). The data of percent water bound are presented in table 7.6. The amount of water apparently taken up increased over the period of 30 minutes. After 5 minutes of contact with water, 7.4% of uptake had occurred. Typical data for water taken up by wafers containing 1:1 HPMC K4M : ethylcellulose are presented in figure 7.9 and table 7.6. Approximately 39% of uptake occurred after 5 minutes of contact of the wafers with water.

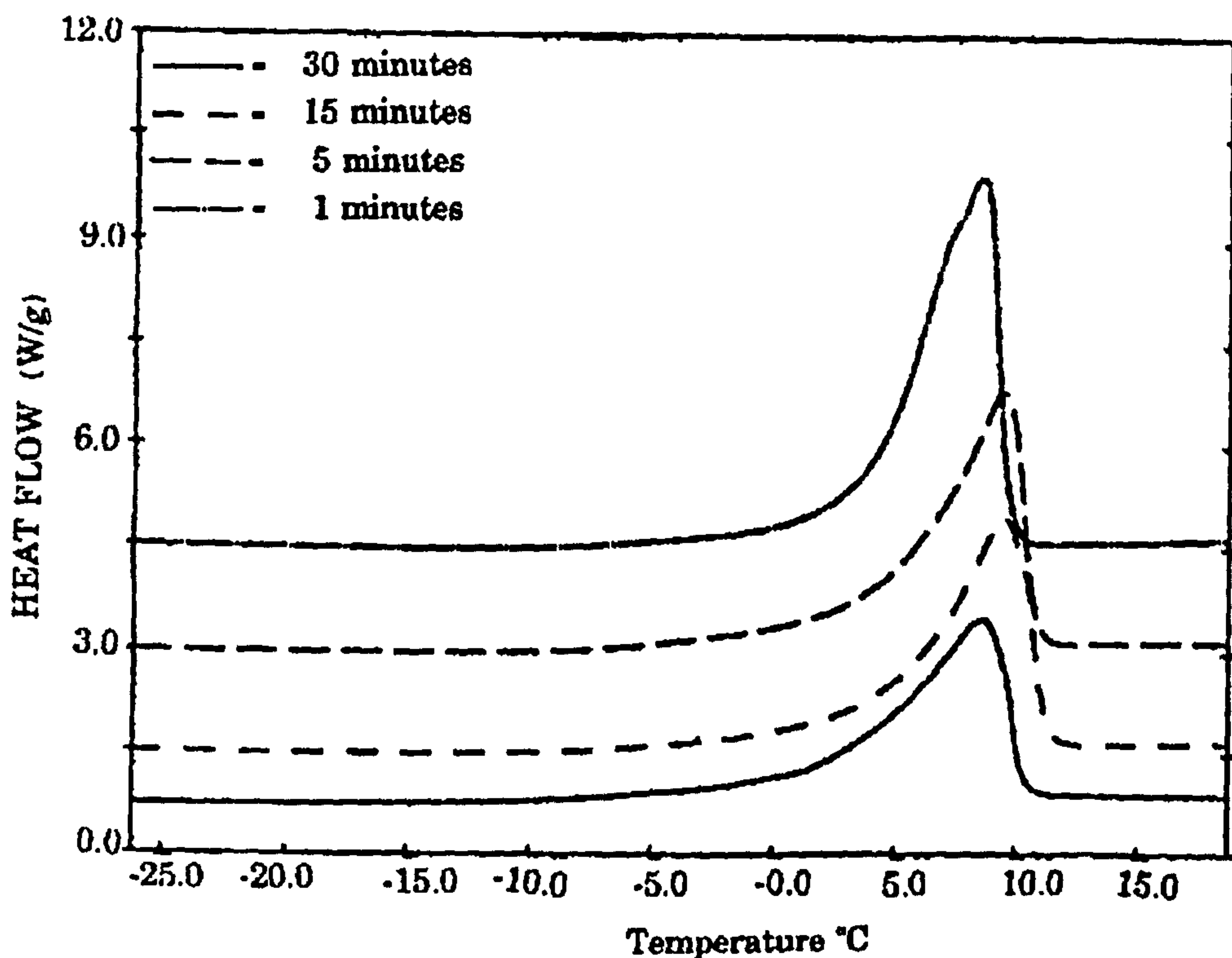
The results of Tukey's test from wafers containing ethylcellulose 7 cP suggest that at ( $p < 0.05$ ), there was no significant difference between the enthalpies of pure water and the enthalpies of discs containing ethylcellulose after

Figure 7.8: DSC scans showing the melting endotherms of free water in contact with ethylcellulose 7 cP discs following storage at 1, 5, 15 or 30 minutes at ambient temperature.



1 minute of contact with water indicating weak ability of ethylcellulose to absorb water. There were significant differences between the percentage of bound water from discs containing ethylcellulose at 1, 5 and 15 minutes of contact with water. However, no significant increase in bound water was observed after 15 minutes indicating saturation of ethylcellulose. There were significant differences between the melting enthalpies of discs containing

Figure 7.9: The DSC scans showing the melting endotherms of free water in contact with discs containing 1:1 HPMC K4M : ethylcellulose 7 cP following storage at 1, 5, 15 or 30 minutes at ambient temperature.



HPMC and ethylcellulose at all periods of time of contact with water.

The data in table 7.6 indicate that discs containing 1:1 HPMC : ethylcellulose absorbed water similar to HPMC K4M at 1 minute whereas, they absorbed water more than HPMC at 5 minutes ( $p < 0.05$ , Tukey's test). The water uptake from discs containing the 1:1 mixture was more than anticipated.



The expected amount of water taken up by these discs after 5 minutes of contact with water, was 19.8% (mean of values in table 7.6) while the actual water uptake observed was about 39%. This suggests that water penetrated these wafers more easily than predicted from the data for the individual polymers. The ethylcellulose particles presumably facilitated water uptake by decreasing the apparent tortuosity of the matrix. However, Tukey's tests showed significant differences between HPMC and the 1:1 mixture at 15 or 30 minutes of contact with water ( $p < 0.05$ ).

Table 7.6: Effect of time on the percent of water bound by 10 mg discs containing HPMC K4M, ethylcellulose 7 cP or their 1:1 mixture (results are the means  $\pm$  SD of three tests).

Time (min)	HPMC K4M	EC 7 cP	1:1 HPMC : EC
0	0	0	0
1	27.5 $\pm$ 2.3	3.4 $\pm$ 0.6	26.0 $\pm$ 1.3
5	32.2 $\pm$ 1.2	7.4 $\pm$ 1.6	39.1 $\pm$ 0.2
15	56.6 $\pm$ 0.4	12.5 $\pm$ 1.7	39.9 $\pm$ 1.2
30	63.6 $\pm$ 1.4	13.6 $\pm$ 1.7	51.2 $\pm$ 1.3

Furthermore, the endotherms in the DSC of water in contact with ethylcellulose were sharp and there was no broadening in their scans (figure 7.8) whereas, the endotherms from wafers containing 1:1 HPMC : ethylcellulose were broad (figure 7.9) which indicates an interaction between water and the polymer. However, the results of water bound to ethylcellulose were similar to those findings of Joshi and Wilson (1993) who reported that moles of non-freezing water per polymer repeat unit for ethylcellulose EC E4 were  $1.6 \pm 0.3$  mole water, whereas the moles of non-freezing water per polymer repeat unit for HPMC E5 were  $6.2 \pm 1.3$ , indicating a high difference in the water absorbing capacity of HPMC compared to ethylcellulose.

## 7.7 CONCLUDING REMARKS

The results confirm that the release rate of propranolol hydrochloride from matrices containing ethylcellulose can be modified using smaller particle sizes and a lower viscosity grade of ethylcellulose. The smaller particle size and the lowest viscosity grade of ethylcellulose gave the slowest release rate. Compaction pressure up to  $39.4 \text{ MNm}^{-2}$  affected the release rates whereas from  $78.7$  to  $393.7 \text{ MNm}^{-2}$  did not affect release rate. This was attributed to the high porosity of the matrices at low compaction pressure. In the matrices containing HPMC K4M : ethylcellulose, as the proportion of ethylcellulose increased the release rates gradually increased. Similar behaviour was seen for matrices containing NaCMC : ethylcellulose except when the portion of ethylcellulose was 75% where the burst release of propranolol hydrochloride

occurred. The admixture of HPMC and ethylcellulose had the ability of absorbing more water. Water bound to ethylcellulose was very low whereas the water bound to mixture of ethylcellulose and HPMC was high at initial stages of uptake. This fact can be attributed to the ease of penetration of water to the wafers containing 1:1 HPMC : ethylcellulose, because addition of ethylcellulose to HPMC would increase the porosity of wafers which enables them to absorb more water.



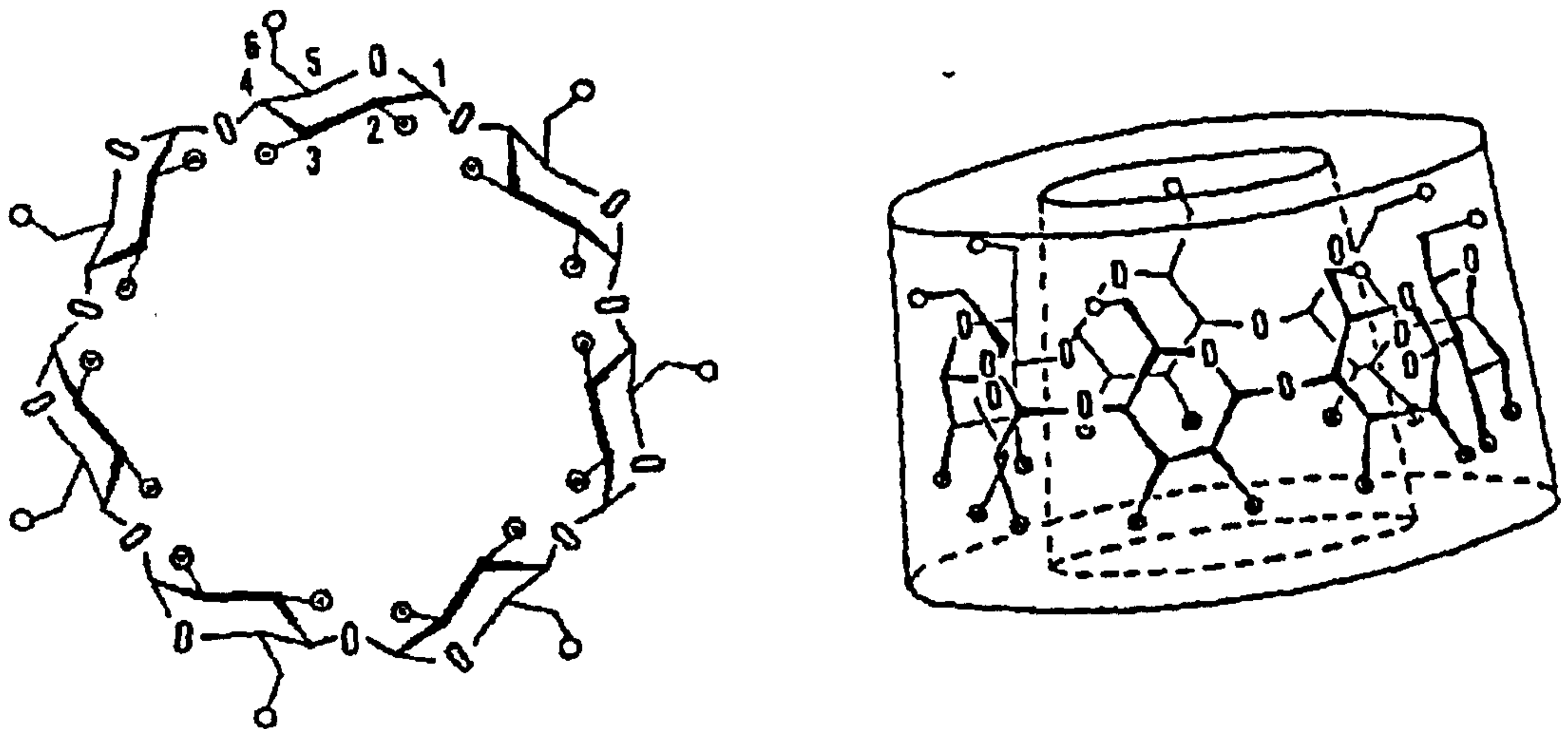
# CHAPTER 8 THE RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING HYDROXYPROPYLMETHYLCELLULOSE AND $\beta$ -CYCLODEXTRIN

## 8.1 INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides having  $\alpha(1-4)$  linked glucose units, which are formed by the enzymatic degradation of amylose. They are well documented for their ability to form inclusion complexes with a wide variety of "guest" molecules (Szetjli, 1982). Cyclodextrins can be produced by the relatively simple technology of fermentation of starch. The most common cyclodextrins are  $\alpha$ ,  $\beta$  and  $\gamma$  cyclodextrins, consisting of 6, 7 and 8 glucose units respectively. All of the CDs are water-soluble, crystalline and non-hygroscopic (Szetjli, 1982). Since all of the free hydroxyl groups are on the outer surface of the ring, the internal cavity of the doughnut-shaped molecule is slightly apolar and the outer surface of a CD molecule is hydrophilic (Szetjli, 1991). Figure 8.1 shows the chemical structure of  $\beta$ -cyclodextrin (left) and its side view or doughnut-shaped molecule (right) (Uekama and Otagiri, 1987). Among the three groups of CDs and a wide variety of their derivatives,  $\beta$ -cyclodextrin is more important than the others because  $\alpha$ -CDs can be used only for small molecules or for the complexation of slim side chains (Szetjli, 1991) and  $\gamma$ -CDs are, at present, too expensive for any practical purposes and could be used to advantage only with large molecules such as macrolides or steroids (Szetjli, 1991). However,  $\beta$ -cyclodextrin, due to its medium diameter

cavity, is suitable for many drugs (Le Bas and Rysanek, 1987).

Figure 8.1: Chemical structure of  $\beta$ -cyclodextrin (left) and its side view (right) (after Uekama and Otagiri, 1987)



Cyclodextrin (CD) and its derivatives can be used for drugs either for complexation or as auxiliary additives (carriers, diluents, solubilizers or tablet ingredients) (Szetjli, 1982; Roy, 1994).  $\beta$ -cyclodextrin ( $\beta$ -CD) and its derivatives also have been used in pharmaceutical formulations to enhance the solubility (Uekama et al, 1990), dissolution rate (Uekama et al, 1983), membrane permeability (Uekama et al, 1983), taste masking (Roy, 1994) or modification of dissolution behaviour of water-insoluble drugs such as naftazone (Giunchedi et al, 1994), through the formation of inclusion complexes with the drugs. However, there are few reports on the use of  $\beta$ -cyclodextrins as excipients for soluble drugs (Duddu et al, 1993).

Armstrong et al (1986) reported that propranolol hydrochloride molecules could make an inclusion complex with  $\beta$ -cyclodextrin. Duddu et al (1993) using propranolol hydrochloride and  $\beta$ -cyclodextrin, confirmed the findings of Armstrong et al (1986). However, it could be assumed that a complex formed by  $\beta$ -cyclodextrin and propranolol hydrochloride which has a molecular weight and size bigger than each of its agents, would modify drug release from matrices. This assumption was based on findings of Korsmeyer et al (1983a) who observed that the release of three drugs, differing widely in their molecular weights, namely potassium chloride (mol. wt. 74.55), phenylpropanolamine hydrochloride (mol. wt. 187.67) and bovine serum albumin (mol. wt. 69000), through poly(vinyl alcohol) matrices. Their results revealed that as the molecular size of the solute increased, the release rate decreased. This part of the study set out to investigate the release of propranolol hydrochloride -  $\beta$ -cyclodextrin complex from HPMC K4M matrices.

### **8.1.1 Aims and objectives**

The main aim was to investigate the release of propranolol hydrochloride from propranolol -  $\beta$ -cyclodextrin complex or from the admixture of  $\beta$ -cyclodextrin and HPMC K4M. Additionally, the water uptake of wafers containing  $\beta$ -cyclodextrin, lactose, 1:1 HPMC :  $\beta$ -cyclodextrin and 1:1 HPMC : lactose were studied in an attempt to elucidate the mechanisms of drug release.



## 8.2 PREPARATION AND CHARACTERIZATION OF $\beta$ -CYCLODEXTRIN COMPLEX

The propranolol hydrochloride -  $\beta$ -cyclodextrin complex was examined by DSC by comparing its scans with those of the pure materials and their physical mixture.

### **8.2.1 Experimental**

#### 8.2.1.1 Materials

$\beta$ -cyclodextrin (<105  $\mu\text{m}$ ) and propranolol hydrochloride were used as described in section 2.1.

#### 8.2.1.2 Preparation of physical mixture of propranolol hydrochloride and $\beta$ -cyclodextrin

1:1 molar ratio of propranolol hydrochloride (1.183 g) and  $\beta$ -cyclodextrin (4.540 g) were mixed in a glass jar using a tumbler mixer for 10 minutes.

#### 8.2.1.3 Preparation of propranolol-cyclodextrin complex

The method used for the preparation of the complex was similar to that used by Duddu et al (1993). The molar ratio of propranolol hydrochloride (2.958 g) and  $\beta$ -cyclodextrin (11.350 g) were dissolved in distilled water (60 mL and 300 mL respectively). The aqueous solution of  $\beta$ -cyclodextrin was heated to 70 °C to produce a clear solution. Then both aqueous solutions of propranolol hydrochloride and  $\beta$ -cyclodextrin were mixed in a 500 mL baker. The solution

was kept overnight in five petri dishes in an oven at 50°C to evaporate the water.

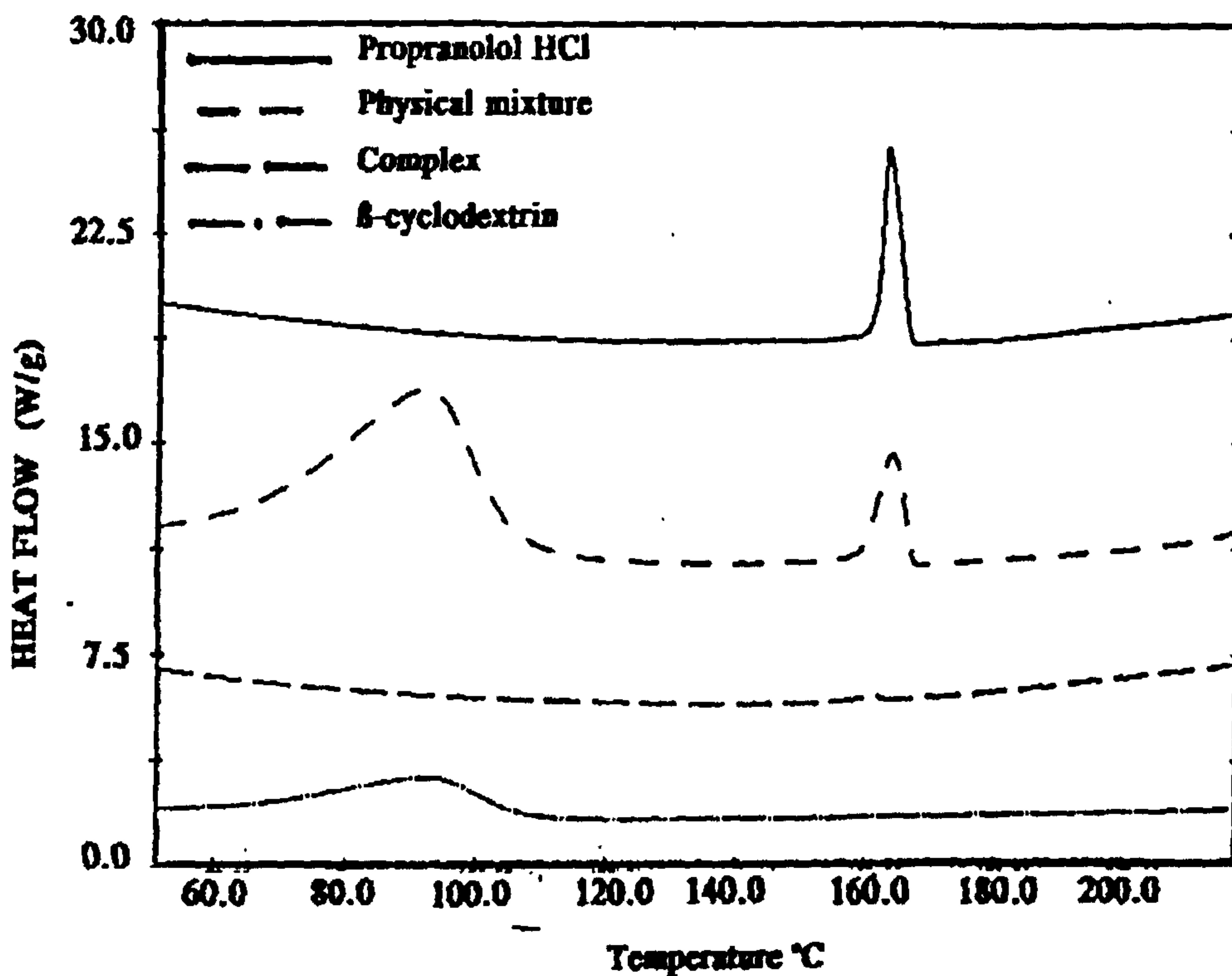
#### 8.2.1.4 Methodology

Samples (5 mg) containing propranolol hydrochloride, physical 1:1 molar mixture of propranolol hydrochloride and  $\beta$ -cyclodextrin (section 8.2.1.2) and the complex of propranolol- $\beta$ -cyclodextrin (section 8.2.1.3) were accurately weighed and placed into aluminum pans (Perkin Elmer, 6.35 mm diameter). Aluminum lids were used to cover the sample without sealing. The samples were heated from 40°C to 300°C at 10°C/min. The heats of fusion of propranolol hydrochloride in the samples were measured, calculated on the basis of the propranolol hydrochloride to be in the samples.

#### **8.2.2 Results and discussion**

Figure 8.2 shows the DSC scans of propranolol hydrochloride,  $\beta$ -cyclodextrin, physical mixture of 1:1 molar propranolol hydrochloride and  $\beta$ -cyclodextrin and the complex. The peak of pure propranolol hydrochloride was at 164°C (enthalpy of  $123.8 \pm 1.2$  J/g). A similar peak was observed for the physical mixture indicating that there was no interaction between propranolol hydrochloride and  $\beta$ -cyclodextrin in solid forms (enthalpy of  $116.6 \pm 4.8$ ). The propranolol hydrochloride and  $\beta$ -cyclodextrin complex showed the complete disappearance of the endothermic peak at about 164°C. These results clearly indicate that there is a difference between the physical mixture and the propranolol hydrochloride -  $\beta$ -cyclodextrin complex. Similar results were

Figure 8.2: DSC scans of propranolol hydrochloride,  $\beta$ -cyclodextrin, physical mixture of 1:1 molar propranolol hydrochloride and  $\beta$ -cyclodextrin and the complex of propranolol- $\beta$ -cyclodextrin following heating from 40°C to 300°C at 10°C/min.



reported by Duddu et al (1993) who used the 1:1 molar ratio of propranolol hydrochloride and  $\beta$ -cyclodextrin in different solid forms (freeze-dried inclusion complex, freeze-dried  $\beta$ -cyclodextrin, freeze-dried d-propranolol and physical mixture of propranolol and  $\beta$ -cyclodextrin). They claimed that the formation of an inclusion complex by freeze-drying was suggested by the absence of the melting endotherm of racemic propranolol hydrochloride at 165°C in the DSC curve of the inclusion complex. The  $\beta$ -cyclodextrin and its



physical mixture with propranolol hydrochloride had peaks around 100 °C which probably were related to water in the samples.

### 8.3 RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING $\beta$ -CYCLODEXTRIN COMPLEX

As mentioned before, in order to produce a bigger molecule of propranolol hydrochloride, that was thought to be able to reduce the drug release, a complex of propranolol -  $\beta$ -cyclodextrin was made. The release of drug from propranolol  $\beta$ -cyclodextrin complex was compared to release of drug from matrices containing physical mixture of propranolol and  $\beta$ -cyclodextrin.

#### **8.3.1 Experimental**

##### 8.3.1.1 Materials

Propranolol hydrochloride (<125  $\mu\text{m}$ ), unseived  $\beta$ -cyclodextrin and its <105  $\mu\text{m}$  fraction and magnesium stearate were used as described in section 2.1.

##### 8.3.1.2 Tablet preparation

Tablets were prepared containing 80 mg propranolol hydrochloride, 307 mg  $\beta$ -cyclodextrin (unsieved and <125  $\mu\text{m}$  fraction in size) and 0.75% magnesium stearate as described in section 2.2.4. This ratio corresponded to the 1:1 molar ratio of propranolol hydrochloride :  $\beta$ -cyclodextrin. Similarly tablets containing 387 mg of the complex of propranolol and  $\beta$ -cyclodextrin (<105  $\mu\text{m}$ ) which contained 80 mg propranolol hydrochloride were also made. All tablets

were compressed at  $182 \text{ MNm}^{-2}$ .

### 8.3.1.3 Dissolution methodology

Dissolution was carried out at  $37^{\circ}\text{C}$  as described in section 2.2.5.

### **8.3.2 Results and discussion**

The release of propranolol hydrochloride from tablets containing the 1:1 molar ratio of unsieved  $\beta$ -cyclodextrin and propranolol hydrochloride was very fast and all drug was released within 15 minutes of the start of the test. Therefore  $\beta$ -cyclodextrin of particle size  $< 105 \mu\text{m}$  fraction was examined. The release remained fast but was slower than the unsieved fraction. A  $T_{50\%}$  of  $14.0 \pm 1.0$  minutes was obtained. Release of propranolol hydrochloride from tablets containing 387 mg of the complex, which contained 80 mg propranolol hydrochloride and 307 mg  $\beta$ -cyclodextrin, was examined and a  $T_{50\%}$  of  $8 \pm 1.2$  minutes was obtained which indicated a faster release than from the physical mixture. Duddu et al (1993) using discs (10 mm diameter) containing 250 mg of the complex with a similar formulation reported that the release was very fast and that the discs dissolved completely within 30 minutes.

## 8.4 RELEASE OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING $\beta$ -CYCLODEXTRIN AND HYDROXYPROPYLMETHYLCELLULOSE K4M

The release of propranolol hydrochloride from HPMC matrices containing  $\beta$ -cyclodextrin was investigated. For comparison, similar formulations

containing lactose instead of  $\beta$ -cyclodextrin were made to see if the complexation of  $\beta$ -cyclodextrin with propranolol hydrochloride had any effect on drug release.

#### **8.4.1 Methodology**

Propranolol hydrochloride (<125  $\mu\text{m}$ ),  $\beta$ -cyclodextrin (<105  $\mu\text{m}$ ), lactose (<105  $\mu\text{m}$ ) and magnesium stearate were used as described in section 2.1. Matrix tablets were prepared containing 80 mg propranolol hydrochloride, 160 mg HPMC K4M and 0, 76.7, 153.5 or 307.0 mg  $\beta$ -cyclodextrin or lactose and 0.75% magnesium stearate as described in section 2.2.4 which were compressed at  $182 \text{ MNm}^{-2}$ . These ratios corresponded to the 0, 0.25, 0.5 or 1 molar ratios of propranolol hydrochloride :  $\beta$ -cyclodextrin respectively. Additionally matrices containing 160 mg HPMC K4M and 387 mg of the complex, were similarly made. Dissolution was carried out at  $37^\circ\text{C}$  as described in section 2.2.5 and equation 1.2 ( $Q=K_2(t-1)^n$ ) was used in the evaluation of the release mechanisms.

#### **8.4.2 Results and discussion**

Figure 8.3 shows the release profiles from matrices containing 80 mg propranolol hydrochloride, 160 mg HPMC K4M and 307 mg  $\beta$ -cyclodextrin or lactose. Figure 8.3 also demonstrates the release of propranolol hydrochloride from matrices containing the complex of propranolol hydrochloride and  $\beta$ -cyclodextrin in admixture with 160 mg HPMC K4M. The data obtained using equation 1.2 are presented in table 8.1.



Figure 8.3: Release profiles from matrices containing 80 mg propranolol hydrochloride, 160 mg HPMC K4M and 307 mg  $\beta$ -cyclodextrin or lactose and matrices containing 160 mg HPMC K4M with 387 mg complex of propranolol -  $\beta$ -cyclodextrin. Results are the means  $\pm$  SD of six determinations.

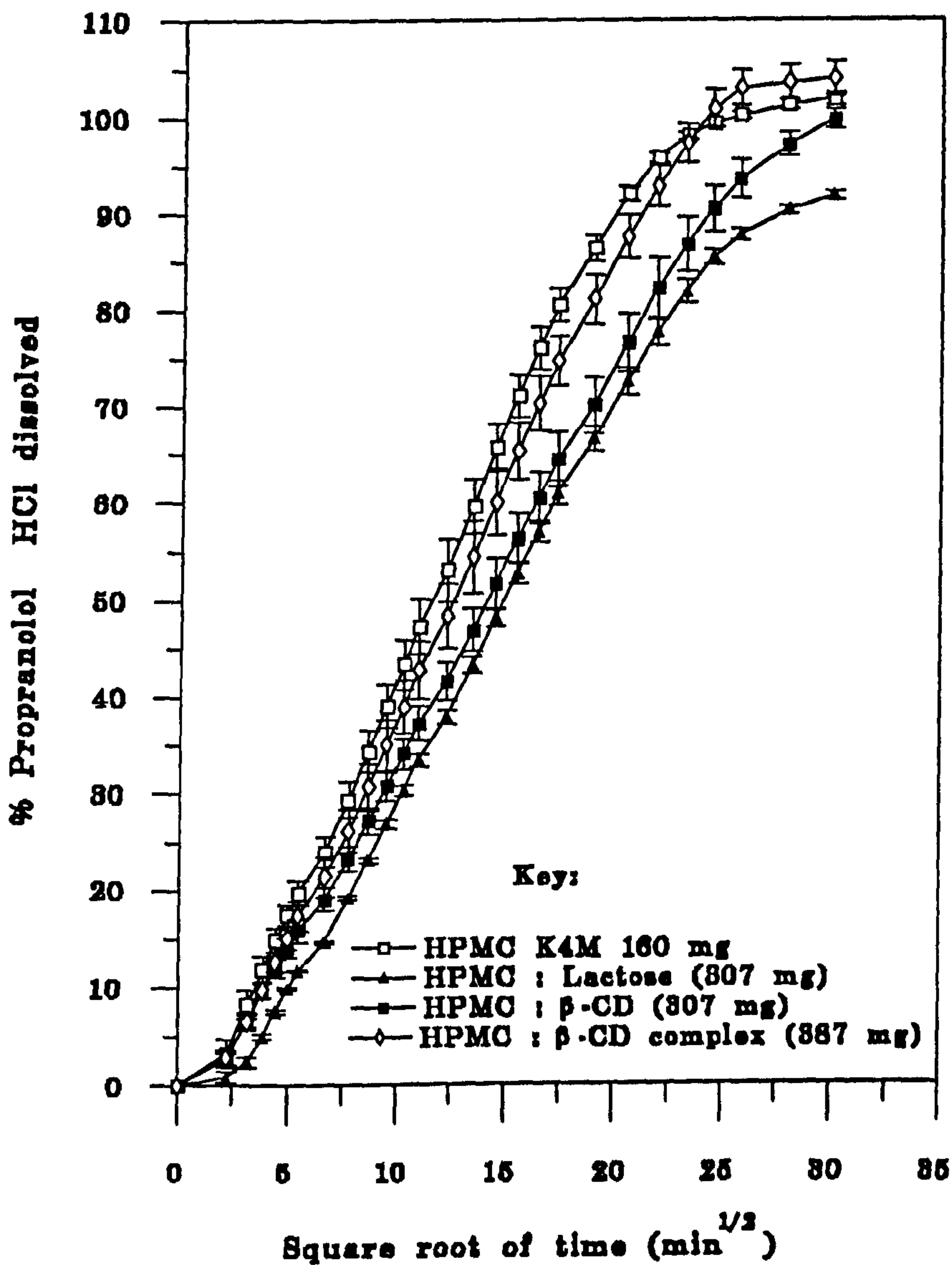


Table 8.1: Estimated values of  $K_2$  (% min<sup>-n</sup>), n, l,  $T_{50\%}$  (hour) and release rates (% min<sup>-1/2</sup>) from matrices containing 80 mg propranolol hydrochloride, 160 mg HPMC K4M and 0, 76.7, 153.5 and 307 mg  $\beta$ -cyclodextrin or lactose (between 5-60% released) based on equation 1.2. Results are the means  $\pm$  SD of six determinations

Content (mg)	$K_2$	n	l	$T_{50\%}$ (hour)	Release rate
<b>HPMC:<math>\beta</math>-CD</b>					
160:0	2.67	0.60	3.40	2.38 $\pm$ 0.22	5.01 $\pm$ 0.1
160:76.7	2.31	0.61	2.65	2.58 $\pm$ 0.23	4.70 $\pm$ 0.1
160:153.5	2.34	0.60	2.90	2.83 $\pm$ 0.16	4.52 $\pm$ 0.1
160:307.0	2.05	0.61	2.60	3.47 $\pm$ 0.30	4.04 $\pm$ 0.2
<b>HPMC:Lactose</b>					
160:76.7	2.57	0.61	0.15	2.11 $\pm$ 0.10	4.94 $\pm$ 0.1
160:153.5	2.56	0.60	3.84	2.52 $\pm$ 0.30	4.81 $\pm$ 0.2
160:307.0	2.15	0.60	5.61	3.26 $\pm$ 0.12	4.17 $\pm$ 0.1
$\beta$ -CD-propranolol complex*			-	0.13 $\pm$ 0.02	-
HPMC: $\beta$ -CD-PH**	2.21	0.62	3.99	2.63 $\pm$ 0.28	4.73 $\pm$ 0.1

\* =387.0 mg  $\beta$ -cyclodextrin-propranolol complex, \*\* =387.0 mg complex + 160 mg HPMC K4M.

Data in table 8.1 indicate that as the  $\beta$ -cyclodextrin or lactose in the matrices increased the release rates decreased. Matrices containing the molar ratio of  $\beta$ -cyclodextrin and propranolol hydrochloride gave the slowest release rate ( $4.04\% \text{ min}^{-1/2}$ ) compared with matrices containing HPMC K4M alone ( $5.01\% \text{ min}^{-1/2}$ ). The values of release exponents were between 0.60 - 0.62, suggesting that the release of propranolol hydrochloride is controlled by both diffusion of the drug through the hydrated matrix and the erosion of the matrix itself (Peppas and Sahlin, 1989). It is seen that in spite of high difference in  $\beta$ -cyclodextrin content in the matrices (table 8.1) the value of n did not change dramatically. This result was similar to findings of Ford et al (1987) who investigated the effect of adding soluble or insoluble excipients in HPMC matrices and reported that despite the vast differing solubility between used materials the release exponent did not change. Drug release from matrices containing the complex was faster than from the other matrices at the same composition, indicating that propranolol in the complex was more freely able to dissolve. This was contrary to what had been expected and the reason is unknown and needs more thorough investigation. However, one possible explanation is that the size of the complex particles used in this study ( $<105 \mu\text{m}$ ) was small. The particle size of the propranolol hydrochloride in the complex would be considerably smaller than the size of propranolol hydrochloride in the physical mixture. This could consequently result in faster drug release than expected.

For further investigation of the release of drug from these matrices, the



solubilities of propranolol hydrochloride in aqueous  $\beta$ -cyclodextrin solutions and the water uptake of discs composed of  $\beta$ -cyclodextrin, lactose, 1:1 HPMC :  $\beta$ -cyclodextrin or 1:1 HPMC : lactose were determined.

## 8.5 PHASE-SOLUBILITY STUDIES

The method of Higuchi and Connors (1965) was used to determine the solubility of propranolol hydrochloride in different molar ratios of aqueous  $\beta$ -cyclodextrin solutions.

### **8.5.1 Experimental**

#### 8.5.1.1 Materials

Propranolol hydrochloride and  $\beta$ -cyclodextrin as described in section 2.1 were used.

#### 8.5.1.2 Methodology

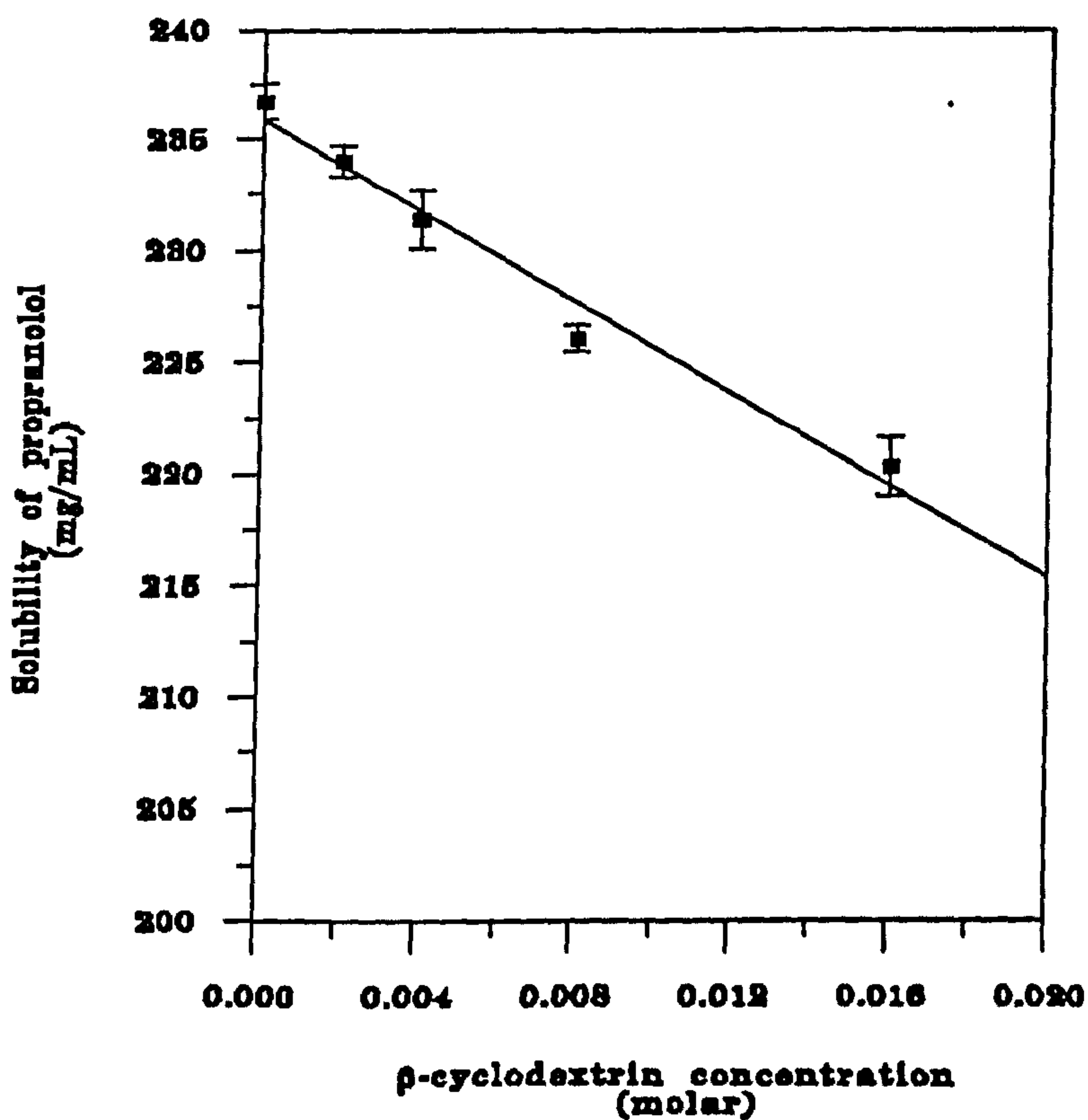
Excess amounts of propranolol hydrochloride (2 g) were weighed into 20 mL test tubes, to which were added 5 mL of distilled water containing various concentrations of  $\beta$ -cyclodextrin (0.001-0.016 M). The tubes were shaken at  $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$  in a water bath (Companstat 882942, England). After 48 hours, the supernatant was filtered through a Whatman No. 1 filter. One mL of the sample was adequately diluted with distilled water and analyzed spectrophotometrically at 288 nm. The amount of dissolved propranolol was calculated from equation 2.1 (section 2.2.3.1). Determinations were carried

out in triplicate.

### 8.5.2 Results and discussion

The phase solubility diagram obtained for propranolol hydrochloride with  $\beta$ -cyclodextrin is shown in figure 8.4. The solubility of propranolol hydrochloride decreased as the  $\beta$ -cyclodextrin concentration increased.

Figure 8.4: The effect of  $\beta$ -cyclodextrin concentration on the solubility of propranolol hydrochloride (results are the means  $\pm$  SD of three determinations)



A number of investigators have reported that  $\beta$ -cyclodextrin enhances the solubility of poorly soluble drugs such as benzodiazepines (Uekama et al, 1983) and piretanide (Uekama et al, 1990). The decrease observed in the solubility of propranolol hydrochloride with increasing  $\beta$ -cyclodextrin content might be due to an interaction between them. Armstrong et al (1986) reported that since the molecule of propranolol hydrochloride is almost completely included in the cavity of  $\beta$ -cyclodextrin, the solubility of the complex of propranolol and  $\beta$ -cyclodextrin would be influenced more by the interaction of the water molecules with  $\beta$ -cyclodextrin than by their interaction with the drug. Since the solubility of propranolol is more than that of  $\beta$ -cyclodextrin (Szetjli, 1982), this result confirmed the theory of Armstrong et al (1986) that the solubility of soluble drugs depends on the solubility of  $\beta$ -cyclodextrin. The solubility of propranolol hydrochloride is almost 2.5 times more than that of  $\beta$ -cyclodextrin.

#### 8.6 WATER UPTAKE BY WAFERS CONTAINING $\beta$ -CYCLODEXTRIN, LACTOSE OR 1:1 HYDROXYPROPYLMETHYLCELLULOSE : $\beta$ -CYCLODEXTRIN OR LACTOSE

Since the water uptakes of polymers or excipients could affect drug release, DSC was used to evaluate and determine the uptake of water into matrices containing  $\beta$ -cyclodextrin alone or its admixture with HPMC in the ratio 1:1. For comparison, the water uptakes of lactose and 1:1 HPMC : lactose were also determined.



## **8.6.1 Experimental**

### **8.6.1.1 Materials**

$\beta$ -cyclodextrin (<105  $\mu\text{m}$ ), HPMC K4M and lactose (<105  $\mu\text{m}$ ) were used as described in section 2.1.

### **8.6.1.2 Preparation of wafers**

Wafers containing approximately 10 mg of  $\beta$ -cyclodextrin, 1:1  $\beta$ -cyclodextrin : HPMC, lactose, or 1:1 lactose : HPMC were made and tested as described in section 2.2.2.4.

### **8.6.1.3 Methodology**

The water uptake was determined according to the methods described in section 2.2.2.4.

## **8.6.2 Results and discussion**

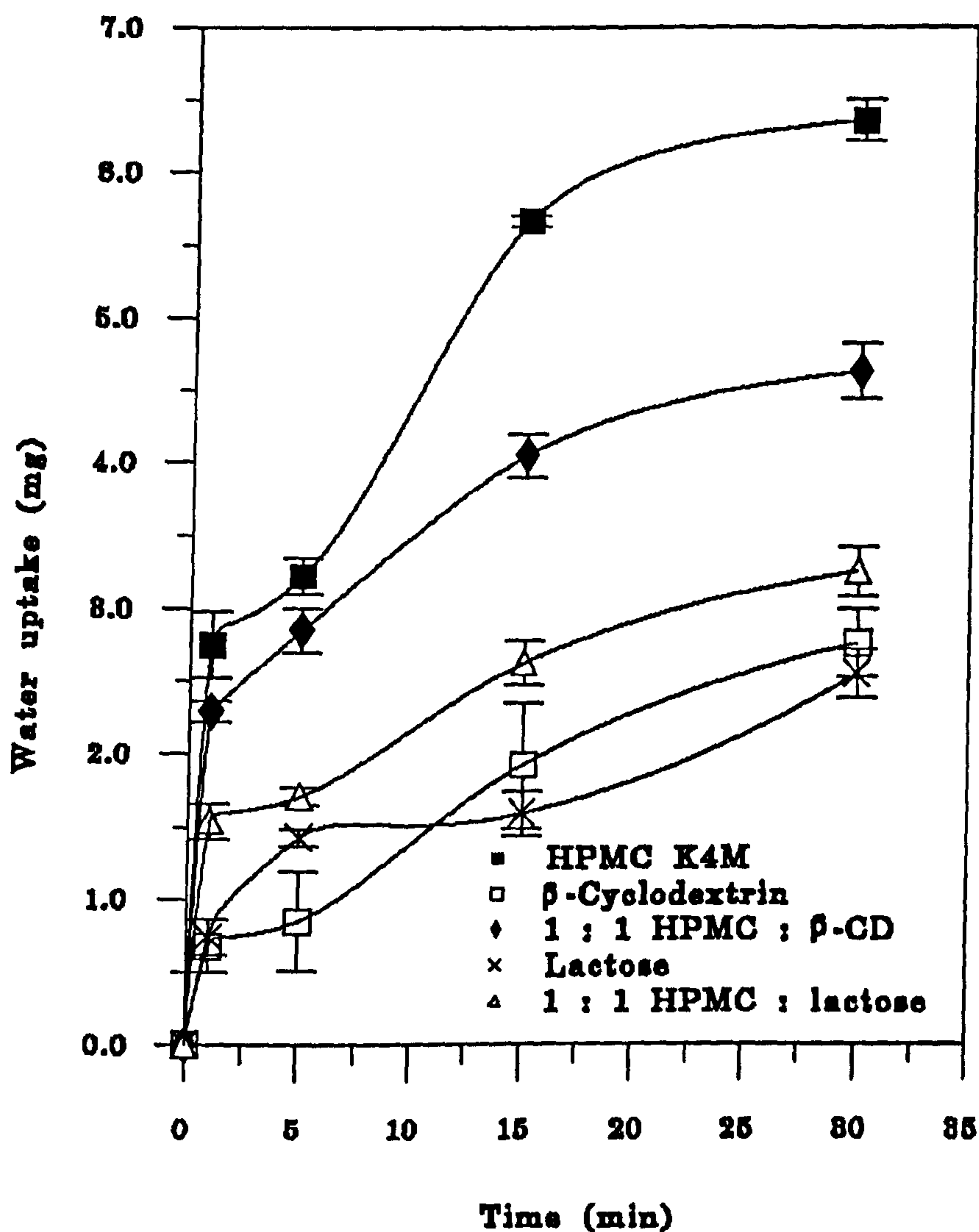
Figure 8.5 shows the mean values (mg) for the bound water from discs containing 10 mg HPMC K4M,  $\beta$ -cyclodextrin, lactose, 1:1 HPMC :  $\beta$ -cyclodextrin and 1:1 HPMC : lactose at ambient as a function of time. These results show that the water uptake by HPMC was faster than with the other samples. Mixtures of 1:1 HPMC :  $\beta$ -cyclodextrin or 1:1 HPMC : lactose hydrated in a manner intermediate to the individual materials. An initial rapid water uptake occurred in the  $\beta$ -cyclodextrin-HPMC wafers that slowed down after 5 minutes. Similar behaviour was obtained from discs containing

HPMC and ethylcellulose (section 7.6). As mentioned before, the increase in water uptake might be due to the ease of penetration of water to these wafers. Replacement of lactose instead of  $\beta$ -cyclodextrin slowed down the water uptake by the wafers. This was probably due to the greater solubility of lactose compared to  $\beta$ -cyclodextrin which prevents water from being absorbed by the HPMC.

Tukey's test on the data from wafers containing HPMC K4M,  $\beta$ -cyclodextrin, lactose, 1:1 HPMC :  $\beta$ -cyclodextrin and 1:1 HPMC : lactose was carried out. There were generally significant differences between the melting enthalpies after 1, 5, 15 or 30 minutes of contact with water ( $p < 0.05$ ) with the exceptions that, no significant differences were observed at 1 and 5 minutes between HPMC and 1:1 HPMC :  $\beta$ -cyclodextrin and there were also no significant differences at 1, 15 or 30 minutes between  $\beta$ -cyclodextrin and lactose.

The water uptake from wafers containing 1:1 mixture of HPMC: $\beta$ -cyclodextrin was greater than predicted from the uptake of the individual polymers. This was similar to that of HPMC : ethylcellulose wafers which was discussed in section 7.6.2. The 1:1 HPMC : lactose showed different behaviour to the 1:1 HPMC :  $\beta$ -cyclodextrin wafers. The water uptake from wafers containing 1:1 HPMC : lactose was less than predicted. This difference might be due to the different characteristics of the two ingredients. Since  $\beta$ -cyclodextrin is less soluble than lactose, when it is mixed with HPMC, there would be less competition to absorb water. In a mixture of HPMC and lactose, the lactose

Figure 8.5: The effect of time on the amount of water bound by 10 mg discs containing HPMC K4M (■),  $\beta$ -cyclodextrin (□), lactose (x), 1:1 HPMC :  $\beta$ -cyclodextrin (◆), 1:1 HPMC : lactose ( $\Delta$ ) from an unbound 10 mg quantity of distilled water at ambient. Results are the means  $\pm$  SD of three determinations.





retards the uptake of water by HPMC due to its own high solubility, presumably increases the tortuosity of the hydrating gel.

### 8.7 CONCLUDING REMARKS

Although the drug release from HPMC matrices containing the physical mixture of propranolol hydrochloride and  $\beta$ -cyclodextrin was fast, it was slower than from those matrices containing the complex at the same conditions. The dissolution profiles of these matrices decreased as the  $\beta$ -cyclodextrin increased. This fact is attributed to increase in surface area of the matrices which was caused by increasing the amount of  $\beta$ -cyclodextrin in the matrices. Replacement of lactose instead of  $\beta$ -cyclodextrin at the same content showed slightly faster release than matrices containing  $\beta$ -cyclodextrin. The solubility of propranolol hydrochloride decreased in the presence of  $\beta$ -cyclodextrin. When they were mixed with HPMC, their water uptakes were dependent on their solubilities.  $\beta$ -Cyclodextrin facilitated the penetration of water into the discs containing 1:1 HPMC :  $\beta$ -cyclodextrin. This was similar to the water uptake of discs containing 1:1 HPMC : ethylcellulose.

## CHAPTER 9 GENERAL DISCUSSION

### 9.1 INTRODUCTION

During the last two decades, cellulose ethers have become popular as the basis for use as controlled-release dosage forms. Their ease of compression, non-toxic nature, their ability to accommodate a large percentage of drug and the negligible influence of processing variables on the release from their matrices are some of the reasons for their popularity (Doelker, 1987). Hydroxypropylmethylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC) are the most popular cellulose ethers and were selected for this study. Three different viscosity grades of NaCMC namely NaCMC (Blanose), NaCMC (P 800) and NaCMC (P 350) were investigated as well as ethylcellulose, which is a hydrophobic polymer, and  $\beta$ -cyclodextrin as adjuncts to provide sustained release of propranolol hydrochloride from oral matrix systems.

Propranolol hydrochloride, a non-selective  $\beta$ -blocker antihypertensive drug, has a short elimination half life of three hours and an extensive saturable first-pass hepatic metabolism, which make it a suitable candidate to be delivered at a controlled rate (Martindale, The Extra Pharmacopoeia, 1993).

Matrix delivery systems are finding increasing application in the areas of controlled-release of pharmaceutical due to their potential use as simple

inexpensive devices capable of releasing a drug at a controlled rate. One disadvantage of matrix system is that it can not produce zero-order drug release (Baveja et al, 1987; Grass and Robinson, 1990). The release profiles of freely soluble drugs from hydrophilic matrix systems normally follow a square root of time relationship, i.e., the release rate decreases with time (Ranga Rao and Padmalatha Devi, 1988). This fact has been proven by many researchers (Ford et al, 1985b; Baveja et al, 1988a; Mitchell et al, 1993a; Perez-Marcos et al, 1994) who showed that the release of propranolol hydrochloride from matrices containing HPMC was dependent on the square root of time and did not produce zero-order release. Since zero-order release of a drug is the most appropriate release pattern (Baveja, 1987; Silber et al, 1988), attempts were made to formulate propranolol hydrochloride to give a zero-order release by using combinations of polymers. The main aim was to find out under which circumstances and to what extent varying the ratio of polymers could be of assistance in controlling drug release and providing a zero-order release.

## 9.2 RELEASE MECHANISMS OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING ONE POLYMER

### **9.2.1 HPMC K4M matrices**

Initially propranolol hydrochloride (160 mg) was formulated into matrices containing 57, 71, 95, 140 or 285 mg HPMC K4M. The release rates decreased as the polymer content increased. This finding is similar to the



findings of Ford et al (1985b), Ranga Rao et al (1990) and Mitchell et al (1993a). Matrices containing only HPMC K4M provided a sustained release of propranolol hydrochloride which was dependent on the square root of time where the correlation coefficients were  $> 0.997$  for the release data. This confirmed the reports of Ford et al (1985a, b) and Baveja et al (1988a) who claimed that drug release from HPMC matrices followed square root of time relationships.

Two mathematical models were used to calculate release exponents ( $n$ ) from matrices containing HPMC K4M. Equation 1.2 ( $Q=K_2(t-l)^n$ ) produced by Ford et al (1991) gave lower sum of squares of errors compared with the simple equation 1.1 ( $Q=K_1t^n$ ) produced by Korsmeyer et al (1983a). Thus equation 1.2, which included a lag time, best described the release of propranolol hydrochloride from matrices containing HPMC K4M. The results confirmed the findings of Ford et al (1991) who stated that a lag time must be used when determining release exponents.

The values of release exponent ( $n$ ) from matrices containing different amounts of HPMC K4M were in the range of 0.59 and 0.69, indicating that the release of propranolol hydrochloride was controlled by diffusion and erosion of the matrix. Ford et al (1987) and Ranga Rao et al (1990) reported similar values of  $n$  of 0.64 and 0.63 for propranolol hydrochloride release from matrices containing HPMC K15M and HPMC K4M matrices, respectively.

It is generally thought that HPMC matrices are physico-chemically inert. However, cloud point determination showed that an interaction took place between HPMC and propranolol hydrochloride. It was observed that adding propranolol hydrochloride to HPMC gels caused an increase in the cloud point, which suggests that the solubility of HPMC was increased and/or less water was required for its hydration. Mitchell et al (1993a) demonstrated that factors such as the cloud point of the HPMC K15M may influence the performance and properties of the gel layer around the matrix and subsequently modify the drug release. Therefore, increase in solubility of HPMC by adding propranolol hydrochloride would cause faster formation of a gel layer, which is necessary for achieving controlled release. These results were in agreement with reports of Rassing (1985) and Rassing and Davis (1986) who reported that water penetration into HPMC matrices was faster if drugs or detergents were present.

Using differential scanning calorimetry (DSC), it was observed that 100 g HPMC K4M required  $6.4 \pm 0.3$  moles of water for full hydration ( $12.3 \pm 0.5$  moles water per PRU). This result was different from those results obtained by Ford and Mitchell (1995) and Joshi and Wilson (1993). The reason for the difference between the results from water distribution test in this study and those obtained by Ford and Mitchell (1995) (8.5 moles water per PRU) and Joshi and Wilson (1993) ( $6.2 \pm 1.3$  moles water per PRU) could be due to different polymer types and the concentration of the gels previously examined (section 4.4). However, DSC clearly showed that when propranolol

hydrochloride was added to HPMC K4M gels, the water required for full hydration of polymer decreased. This was in agreement with the several findings of Ford and Mitchell (1995).

It is well known that the most important factor in drug release is the water uptake of the polymers which relates to the rate at which the gel layer forms around the matrix (Ford and Mitchell, 1995). DSC was used to determine the water uptake of HPMC at ambient and at 37°C. It was observed that HPMC wafers after 30 minutes contact with water at 37°C, absorbed 29% more water than at ambient.

In conclusion, dissolution of propranolol hydrochloride from HPMC matrices is controlled or characterized by:

- \* both diffusion and erosion mechanisms ( $0.59 < n < 0.69$ ),
- \* the increased solubility of HPMC caused by the addition of propranolol hydrochloride.

### **9.2.2 NaCMC matrices**

The release data obtained from the different viscosity grades of NaCMC, indicated that NaCMC behaved differently to HPMC. As the polymer content increased, the release kinetics of the drug became more dependent on time rather than the square root of time. Since most of formulations in this study were dependent on the square root of time, the release rates for NaCMC matrices were calculated based on square root of time.



Matrices containing 57 or 71 mg NaCMC disintegrated during the dissolution testing whereas matrices containing HPMC of similar content did not. This fact could be due to the higher solubility of NaCMC compared with HPMC (Klug, 1971; Doelker, 1987). However, the strong interaction between propranolol hydrochloride and NaCMC might be the main reason for the disintegration of matrices with low polymer content. In section 5.3.3 it was shown that as the NaCMC content decreased, the ability of propranolol hydrochloride to occupy the sites occupied by sodium atoms in the PRU of NaCMC increased. Therefore, in matrices with low polymer content, the whole polymer in the matrix could bind to the propranolol and, due to the insolubility of the produced mass, the matrix disintegrated.

The effects of the viscosity grade of polymers on drug release from compressed delivery systems have been studied by various researchers (Huber and Christenson, 1968; Lapidus and Lordi, 1968; Alderman, 1984; Ford et al, 1985a, b; Baveja et al, 1988a; Wan et al, 1991; Colombo et al, 1992 and Cheong et al, 1995). The viscosity of a polymer solution is an indication of its molecular weight. Alderman (1984) claimed that increasing the molecular weight of a polymer in matrix formulations increases the gel layer formed at the surface of the matrix and therefore made it more resistant to erosion. However, as the viscosity of NaCMC increased (the rank order of viscosity was NaCMC Blanose > NaCMC P 800 > NaCMC P 350) the release rate, into water, from matrices containing 285 mg polymer decreased from  $5.2\% \text{ min}^{-1/2}$  (for NaCMC P 350) to  $3.1\% \text{ min}^{-1/2}$  (for NaCMC

Blanose). Therefore, it could be concluded that the viscosity grades of NaCMC affected the drug release. This behaviour was found to be in contrast to HPMC matrices, e.g., Ford et al (1985a) examined HPMC K100, HPMC K4M, HPMC K15M and HPMC K100M and reported that HPMC K100 (low viscosity grade) gave the highest release rate of propranolol hydrochloride whereas the other three grades, which had higher viscosities, behaved similarly. Bonferoni et al (1992) also confirmed the finding of Ford et al (1985a) about matrices containing HPMC and meanwhile claimed that the viscosity of NaCMC affected drug release.

It was observed that the initial burst of drug release, which was seen in the case of HPMC matrices (figure 3.11), was suppressed by using NaCMC of equivalent content. This finding was similar to that of Padmalatha Devi et al (1989) who showed that tablets containing NaCMC, with or without HPMC, lacked an initial burst release of drug. This fact probably is due to the ability of NaCMC to interact with propranolol hydrochloride and produce an insoluble complex.

The release data from matrices containing NaCMC were fitted into equation 1.1 ( $Q=Kt^n$ ). As the polymer content increased the value of release exponent increased. Matrices with low polymer content (57, 71 and 95 mg), due to their fast release, did not generate enough release data to allow estimation of the release mechanisms. Matrices containing 285 mg NaCMC (Blanose, P 800 and P 350) gave near zero order release ( $1.18 > n > 1.05$ ) and the



viscosity of polymer did not appear to affect the value of  $n$ . When the polymer content decreased from 285 mg (i.e., 140 or 95 mg) the effect of viscosity grade of NaCMC on the value of  $n$  was clearly observed. Although the values of the release exponents from matrices containing 285 mg NaCMC alone were in a range indicating near zero-order release into water, fast release of drug from these matrices into 0.1 M hydrochloric acid indicated that the matrices containing NaCMC alone were unsuitable.

Using differential scanning calorimetry (DSC), it was shown that 100 g NaCMC (Blanose) required a minimum  $6.0 \pm 0.4$  moles water per 100 g of polymer for full hydration. It seems that NaCMC probably requires less water for hydration than HPMC.

When propranolol hydrochloride was added to NaCMC gels, a precipitate was produced, indicating an interaction between them and possibly the formation of a complex. The formation of the complex was confirmed by DSC and dialysis. DSC showed a weak interaction between propranolol hydrochloride and NaCMC in their physical mixture and strong interaction following addition of water to the physical mixture.

A study on the erosion of the matrices confirmed that those containing NaCMC showed a faster erosion compared to HPMC matrices. This was in agreement with the findings of Bonferoni et al (1992). When propranolol hydrochloride was added to the matrices containing NaCMC, it provided a



reduction in erosion which was probably due to the insolubility of the complex formed between NaCMC and propranolol hydrochloride. The importance of this interaction between propranolol hydrochloride and NaCMC was proved by replacing propranolol hydrochloride by lactose, which is soluble and does not interact with NaCMC. This resulted in an increase in the rate of erosion of the matrices.

To confirm the role of erosion in matrices, the release of sodium ions from matrices containing NaCMC and also various matrices (1:1 HPMC : NaCMC, NaCMC : propranolol hydrochloride, NaCMC : lactose) was determined. The addition of propranolol hydrochloride or lactose to NaCMC caused an increase in the release of sodium ions. The probable reasons for the increases in sodium release by both propranolol and lactose are different. Propranolol hydrochloride, due to the formation of its complex with NaCMC, would facilitate the release of sodium ion whereas, the addition of lactose, due to its solubility, increased the porosity of matrices. The increased porosity eased the penetration of water and subsequently increased the erosion of matrices containing lactose and NaCMC.

In conclusion, dissolution of propranolol hydrochloride from NaCMC matrices is controlled or characterized by:

- \* formation of a complex between NaCMC and propranolol hydrochloride,
- \* a wide range of release exponents ( $0.33 < n < 1.18$ ),

\* the viscosity grade of NaCMC,

\* a reduction in erosion of matrices.

### **9.2.3 Ethylcellulose matrices**

Matrices containing ethylcellulose had different characteristics to matrices composed of HPMC or NaCMC. As the polymer content increased from 95 to 285 mg the release exponent ( $0.49 > n > 0.44$ ) remained almost unchanged, indicating that the polymer content did not affect the mechanisms of drug release from ethylcellulose matrices. This was in contrast to matrices containing of HPMC or NaCMC. The release mechanism from matrices containing ethylcellulose was via diffusion. Similar results from matrices containing propranolol hydrochloride : ethylcellulose 14 cP in the ratios of 10:90, 30:70 and 50:50% w/w were reported by Sangavi and Shiravandekar (1994). The smaller particle size and the lowest viscosity grade of ethylcellulose gave the slowest release rate. This was in agreement with the findings of Upadrashta et al (1993). Compaction pressure up to  $39.4 \text{ MNm}^{-2}$  affected the release rates whereas from  $78.7$  to  $393.7 \text{ MNm}^{-2}$  did not. This was attributed to the high porosity of the matrices at low compaction pressure which facilitated the penetration of water into the matrices.

Water uptake by ethylcellulose discs were very low (13.6%) compared to HPMC discs (63.6%) after 30 minutes of contact with water (table 7.6). Good (1981) stated that polymers which do not absorb significant amounts of

solvent are thought to release their enclosed drug via a pure diffusion mechanism involving a thin diffusion layer near the polymeric surface. The data perhaps supports the role of diffusion in ethylcellulose matrices.

In conclusion:

- \* the release mechanism was by diffusion ( $0.49 > n > 0.44$ ),
- \* the polymer content did not affect the release mechanism,
- \* the small particle size and the lowest viscosity grade of ethylcellulose gave the slowest release rate of propranolol hydrochloride.
- \* compaction pressure did not affect the release rate,
- \* the water uptake by ethylcellulose was very low.

### 9.3 RELEASE MECHANISMS OF PROPRANOLOL HYDROCHLORIDE FROM MATRICES CONTAINING TWO POLYMERS

#### **9.3.1. Matrices containing HPMC : NaCMC**

One interesting characteristic of gels containing admixtures of HPMC and NaCMC is undoubtedly the synergistic increase in the viscosity of their gels. Baveja & Ranga Rao (1986) were the first to suggest the use of these properties, by combining both anionic (NaCMC) and non-ionic (HPMC) cellulose ethers in matrix tablets, to produce a zero order release of soluble drugs.



A zero-order release of propranolol hydrochloride was generally not produced by matrices containing only NaCMC or HPMC. Therefore propranolol hydrochloride was used in matrices at different ratios of HPMC and NaCMC. Near zero-order release was only achieved within a narrow range of HPMC : NaCMC ratios.

As mentioned before, the release exponent from matrices containing different amounts of HPMC K4M was in the range of 0.59 and 0.69 whereas, the release mechanism from matrices containing NaCMC or its mixture with HPMC was very complicated and dependent on the polymer content. Similar observations were reported by Ranga Rao et al (1990). Bonferoni et al (1992), using salbutamol sulphate incorporated in mixtures of three viscosity grades of HPMC (HPMC K4M, HPMC K15M and HPMC K100M) and two viscosity grades of NaCMC (Blanose 7LFD and Blanose 7HFD), similarly reported complex release mechanisms from matrices composed of admixtures of HPMC and NaCMC.

The gels containing the various grades of NaCMC, had higher viscosities compared to those of HPMC K4M gels of similar concentrations. No relationship existed between the release rates from matrices containing HPMC and NaCMC of similar content. In mixtures containing HPMC and NaCMC, the viscosities of gels in the range of 0.0 - 0.05% w/w were intermediate between those of the two individual polymers, indicating that at low polymer content there was probably little interaction between the

polymer molecules. For gels containing 0.1 - 0.5% w/w polymer, the viscosities increased with increase in the proportion of NaCMC (Blanose) and were higher than produced from gels of HPMC or NaCMC alone. The increase in viscosities from gels containing admixtures of the two polymers, clearly showed that a synergistic increase in viscosity occurred above a critical concentration.

The cloud points in gels containing 1:1 HPMC : NaCMC was lower than from HPMC gels of similar concentration while gels containing NaCMC did not show any cloud points below 75°C. The decrease in cloud point was attributed to an interaction between the carboxyl groups of NaCMC and the hydroxyl groups of HPMC which provided a competition for the distribution of water in the gels.

In conclusion, the most important factors affecting dissolution of propranolol hydrochloride from matrices containing both HPMC and NaCMC were:

- \* the increase in viscosity of gels containing HPMC and NaCMC due to the interaction between them,
- \* the insoluble complex formed by the interaction between NaCMC and propranolol hydrochloride,
- \* the HPMC : NaCMC used in the matrix,
- \* the viscosity grade of NaCMC.

### **9.3.2 Matrices containing HPMC : ethylcellulose**

In the matrices containing HPMC K4M : ethylcellulose, as the proportion of ethylcellulose increased the release rates gradually increased. The values of the exponent  $n$  from matrices containing HPMC : ethylcellulose in the ratios of 1:0, 3:1, 1:1 and 1:3 appeared not to vary from the range of 0.59-0.61, indicating that both diffusion of the drug and the erosion of the matrix, contributed to the release of propranolol hydrochloride.

The water bound to discs containing 1:1 HPMC : ethylcellulose at initial stages of contact with water was high, possibly due to the increase in permeability of wafers containing 1:1 HPMC : ethylcellulose caused by ethylcellulose. However, after 15 minutes of contact with water, wafers containing HPMC absorbed more water than their 1:1 mixture.

In conclusion,

- \* the ratio of 1:3, 1:1 or 3:1 ethylcellulose : HPMC did not change the release mechanism ( $0.59 < n > 0.61$ ),
- \* addition of ethylcellulose to HPMC caused an increase in permeability of the matrices,
- \* wafers containing 1:1 HPMC : ethylcellulose absorbed water more than predicated.

### **9.3.3 Matrices containing NaCMC : ethylcellulose**

In contrast to matrices containing HPMC : ethylcellulose, major differences



in drug release were observed on changing the NaCMC : ethylcellulose ratio. At the ratio of 3:1 NaCMC : ethylcellulose, a value of 1.45 for the release exponent was obtained, indicating super case II transport. Some studies postulated that such high values are due to the high swelling nature of a polymer (Ranga Rao et al, 1988a; Bain et al, 1991). This swelling nature is caused by the addition of ethylcellulose to NaCMC, while ethylcellulose alone did not swell. Addition of ethylcellulose into NaCMC matrices possibly would increase the porosity of the matrix tablets and the matrices would swell quickly on contact with water, because the penetration of water into matrices was facilitated.

Since the data obtained from matrices containing NaCMC alone and the 1:3 NaCMC : ethylcellulose ratio did not fit into equation 1.2 (see section 3.2.2), equation 1.3 ( $Q=Kt^{1/2}+C$ ) was used for comparison of release rates from matrices. It was observed that as the proportion of ethylcellulose increased upto 75% of the polymer content, the release rates increased.

#### **In conclusion**

- \* addition of ethylcellulose to NaCMC, increased the permeability of its matrices and subsequently the matrices swelled rapidly,**
- \* replacement of NaCMC by ethylcellulose in the matrices, decreased the interaction between propranolol hydrochloride and NaCMC and subsequently increased the release rate of drug.**

#### 9.4 MATRICES CONTAINING HPMC : $\beta$ -CYCLODEXTRIN

It was hoped that the formation of a complex of propranolol hydrochloride and  $\beta$ -cyclodextrin, due to the increase in molecular weight and size of the complex compared with propranolol hydrochloride, would reduce the release of propranolol hydrochloride from HPMC matrices. Drug release from tablets containing the physical mixture of  $\beta$ -cyclodextrin and propranolol hydrochloride was fast, but was slower than from tablets containing the complex of  $\beta$ -cyclodextrin and propranolol hydrochloride (section 8.3).

The dissolution rates of propranolol hydrochloride (80 mg) incorporated in matrices containing 160 mg HPMC K4M and 0, 0.25, 0.5 and 1 molar ratios of  $\beta$ -cyclodextrin, decreased as the  $\beta$ -cyclodextrin content increased. This was attributed to the increase in the surface area of the matrices. Replacement of  $\beta$ -cyclodextrin by lactose in matrices led to slightly faster release rates than equivalent  $\beta$ -cyclodextrin content. This fact probably is due to the increase in the porosity of the matrices containing HPMC and lactose.

The values of release exponents from all matrices containing HPMC K4M and  $\beta$ -cyclodextrin or lactose, were between 0.60 - 0.62, suggesting that the release of propranolol hydrochloride is controlled by both diffusion of the drug through the hydrated matrix and the erosion of the matrix itself (Peppas and Sahlin, 1989). This result was similar to findings of Ford et al (1987) who investigated the effect of adding soluble or insoluble excipients

in HPMC matrices and reported that despite the vast differing solubility between used materials, the release exponent did not change. Drug release from matrices containing HPMC K4M and the complex of propranolol- $\beta$ -cyclodextrin was slightly faster than from samples containing HPMC K4M and the equivalent physical mixture of propranolol hydrochloride and  $\beta$ -cyclodextrin, indicating that drug release from the physical mixture and the complex were also similar. This was contrary to the assumption that a big molecule of complex would reduce drug release.

Water uptake determination by wafers containing  $\beta$ -cyclodextrin, lactose, 1:1 HPMC K4M :  $\beta$ -cyclodextrin or 1:1 HPMC : lactose, showed that lactose and  $\beta$ -cyclodextrin had the lowest water uptake due to their high solubilities. When they were mixed with HPMC,  $\beta$ -cyclodextrin caused HPMC to absorb more water while lactose prevented it from absorbing water.

In conclusion,

- \* the incorporation of  $\beta$ -cyclodextrin or lactose into the matrices decreased the release rates of propranolol hydrochloride,
- \* admixture of  $\beta$ -cyclodextrin with HPMC increased the amount of water taken up initially while the admixture of lactose with HPMC caused less water than expected to be taken up.



## 9.5 EFFECT OF pH ON DRUG RELEASE

Since a tablet is first introduced into the acidic medium of stomach, the influence of pH on drug release must not be ignored. Therefore, the release of propranolol hydrochloride from matrices containing HPMC : NaCMC in different media was investigated. The release rates of propranolol hydrochloride from matrices containing 285 mg HPMC showed slight increases when dissolution media was changed from distilled water to 0.1 M hydrochloric acid, whereas a significant increase in release rates from matrices containing solely NaCMC were observed. This fact was attributed to the insolubility of NaCMC at acidic media. As mentioned before, drug release from matrices containing NaCMC in 0.1 M hydrochloric acid was very fast and more than 70% of drug released within 2 hours and all drug released during 3 hours. However the data suggested that matrices containing NaCMC alone are not suitable for soluble drugs. A similar statement was made by Ranga Rao et al (1988a) who claimed that NaCMC alone is not an ideal polymer to prepare sustained release matrix formulations.

Only slight differences in the release rates of propranolol hydrochloride from matrices containing different viscosity grades of NaCMC admixture with HPMC was observed into 0.1 M hydrochloric acid. This fact indicates that the interaction between propranolol hydrochloride and NaCMC, due to the insolubility of NaCMC at 0.1 M hydrochloric acid, could not occur. These matrices (1:1 HPMC : NaCMC) showed a significant difference in release

rates into distilled water, indicating that the synergistic increase in viscosity of gels containing HPMC and NaCMC only occurred in distilled water.

As the pH increased, the difference between release of drug from matrices with different viscosity grades of NaCMC was more obvious. The reason for this difference might be due to the solubility of propranolol hydrochloride which has a pKa of 9.5 (Clark's Isolation and Identification of Drugs, 1986). Therefore, the solubility of propranolol hydrochloride will decrease as the pH of medium increases. Thus, the drug release would be reduced. Similarly the NaCMC would become ionized and the differences in viscosity grade could be reflected in changes in dissolution rate.

In conclusion,

- \* the interaction between propranolol hydrochloride and NaCMC was at its minimum into 0.1 M hydrochloric acid,
- \* the solubility of propranolol hydrochloride was at its minimum into borate buffer solution pH 9.4,
- \* the interaction between propranolol hydrochloride and NaCMC was at its maximum into distilled water or at higher pHs.

## CHAPTER 10 CONCLUSIONS AND RECOMMENDATIONS FOR FURTHER WORK

### 10.1 CONCLUSIONS

Hydroxypropylmethylcellulose and sodium carboxymethylcellulose as hydrophilic polymers, ethylcellulose as a hydrophobic polymer and  $\beta$ -cyclodextrin as an adjunct were used in the preparation of matrix tablets to examine sustained release of propranolol hydrochloride, as a model water soluble drug.

Zero-order release of propranolol hydrochloride was obtained from matrices containing 285 mg polymer at the 3:1 ratio of NaCMC (Blanose) : HPMC K4M. The reason for this might be related to factors such as the interaction between propranolol hydrochloride and NaCMC and the synergistic increase in the viscosity of gels containing admixtures of HPMC and NaCMC.

Viscosity determination took place in a concentration range which would be found when matrices had completely dissolved into 1000 mL dissolution media. A synergistic increase in viscosity of gels containing HPMC and NaCMC occurred above a certain concentration. Addition of propranolol hydrochloride to HPMC caused an interaction which increased the cloud point and salted-in HPMC. Addition of propranolol hydrochloride to NaCMC, produced a precipitate which made matrices more resistant to



erosion.

Although it is generally thought that HPMC or NaCMC are inert and free from problems, this study showed interactions occurred between HPMC or NaCMC and propranolol hydrochloride. NaCMC matrices alone were not suitable for producing a sustained release of propranolol hydrochloride, because when at low pHs, failure to provide controlled release was apparent.

Differential scanning calorimetry was used to determine of water uptake by the polymers. The water uptake of wafers containing HPMC, NaCMC and their 1:1 mixture was high, whereas the water uptake of ethylcellulose was very low. The effect of addition of ethylcellulose,  $\beta$ -cyclodextrin and lactose on water uptake from wafers containing HPMC was investigated. Both ethylcellulose and  $\beta$ -cyclodextrin caused HPMC to absorb more water while lactose prevented it from absorbing water.

## 10.2 RECOMMENDATIONS FOR FURTHER WORK

1. Since the addition of propranolol hydrochloride to NaCMC produced a complex, further investigation of this complex is recommended. Possibly a particular ratio of NaCMC : propranolol hydrochloride will produce a solid which may be appropriate for the sustained release of propranolol hydrochloride.

2. In this study only matrices made by direct compression were investigated. Wet granulation, producing the complex of propranolol-CMC prior to dissolution, might lead a desirable formulation, therefore preparation of matrices using wet granulation from HPMC, NaCMC and propranolol hydrochloride for future studies is recommended.
3. Hydrophobic cyclodextrin derivatives such as ethylated  $\beta$ -cyclodextrin are reported to be useful as slow-release carriers for water-soluble drugs such as diltiazem hydrochloride (Horiuchi et al, 1990) and isosorbide dinitrate (Hirayama et al, 1988). Therefore the release of propranolol hydrochloride from ethylated  $\beta$ -cyclodextrin should be investigated prior to possible inclusion into HPMC matrices.
4. The extension of this study to other drugs which are not hydrochloride salts and do not react with NaCMC should be investigated.
5. Non-ionizable drugs could allow a thorough investigation of the influence of blends containing NaCMC and HPMC in matrix tablets.

## APPENDIX 1

### BUFFER SOLUTIONS FORMULAE

The following buffers were prepared for the dissolution tests determined in this thesis.

Composition of different buffer solutions used in this study are as follows:

#### **1- Buffer phosphate pH 6.8**

0.1 M hydrochloric acid	750 mL
0.2 M tribasic sodium phosphate	250 mL

0.2 M tribasic sodium phosphate ( $\text{Na}_3\text{PO}_4$ ) was prepared by dissolving 32.79 g tribasic sodium phosphate in 1 litre distilled water.

#### **2- Buffer phosphate pH 7.4**

0.2 M monobasic potassium phosphate solution	250 mL
0.1 M sodium hydroxide	195.5 mL
Water to	1000 mL.

0.1 M sodium hydroxide was prepared by dissolving 4 g sodium hydroxide in 1 litre distilled water. 0.2 M monobasic potassium phosphate solution ( $\text{KH}_2\text{PO}_4$ ) was prepared by dissolving 27.22 g monobasic potassium phosphate in 1 litre distilled water.



### **3- Borate buffer pH 9.4**

0.2 M Boric acid and potassium chloride	250 mL
0.1 M sodium hydroxide	160.5 mL
Water to	1000 mL

0.2 M Boric acid and potassium chloride were prepared by dissolving 12.37 g boric acid ( $\text{H}_3\text{BO}_3$ ) and 14.91 g potassium chloride (KCl) separately in distilled water, mixed and then diluted with distilled water to 1000 mL.

The pHs of all buffers were determined by pH meter and adjusted to the desired pH, by using 2 M hydrochloric acid or 2 M sodium hydroxide.

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## Advanced studies

One-day course on Microsoft Windows 3.1 and one-day course on Cricket Graph for Windows, held at Liverpool John Moores University, 1993.

## **Conference attendance**

1. **British Pharmaceutical Conference, Reading, 1993.**
2. **British Pharmaceutical Conference, London, 1994.**
3. **Liverpool School of Pharmacy Research Seminar, 1994.**
4. **Attending all seminars at the School of Pharmacy, Liverpool John  
Moors University**



## **PUBLISHED COMMUNICATIONS AND PRESENTATIONS**

The following have been published or presented in advance of this thesis.  
Copies may be found in the pocket at the end of this thesis:

1. The release of propranolol hydrochloride from matrices containing sodium carboxymethylcellulose and hydroxypropylmethylcellulose.

Dabbagh, M.A., Ford, J.L., Rubinstein, M.H., Hogan, J.E.

Presented to the British Pharmaceutical conference (Reading, 1993)

Published: *J. Pharm. Pharmacol.* 45 (1993) 1134.

2. Release of propranolol hydrochloride from mixed cellulose matrices.

Hogan, J.E., Ford, J.L., Dabbagh, M.A., Rubinstein, M.H.

Presented: 21<sup>st</sup> International Symposium on Controlled Release of Bioactive materials, (Nice-France, 1994).

Published: *Proc. Intern. Symp. Control. Rel. Bioact. Mater.* 21 (1994) 732-733.

3. Effect of polymer particle size and compaction pressure on drug release from matrices containing ethylcellulose

Dabbagh, M.A., Ford, J.L., Rubinstein, M.H., Hogan, J.E.

Presented to the British Pharmaceutical conference (London, 1994)

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4. The effects of viscosity grade of sodium carboxymethylcellulose on drug release from matrix tablets

Ford, J.L., Dabbagh, M.A., Rubinstein, M.H., Hogan, J.E.

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5. An assessment of the performance of matrices containing hydroxypropylmethylcellulose, sodium carboxymethylcellulose and propranolol hydrochloride

Ford, J.L., Dabbagh, M.A., Rubinstein, M.H., Hogan, J.E.

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