

**USE OF HYPROMELLOSE AND
HYDROXYPROPYL CELLULOSE TO DEVELOP
AN AGE APPROPRIATE PLATFORM
TECHNOLOGY FOR THE ADMINISTRATION OF
MEDICINES TO CHILDREN**

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Abstract

There is a significant need for research and development into paediatric medicines. The absence of suitable medicines or critical safety and efficacy information, poses significant risks to a particularly vulnerable patient population. The paediatric population is made up of a wide range of individuals of substantially varied physical size, weight and stage of physiological development. Some commonly used excipients may be unsuitable for use in children; and some dosage forms may be undesirable to the paediatric population. There is a need for a dosage form platform that is designed to meet the needs of the paediatric patient. The dosage form should offer dose flexibility, dose accuracy, afford acceptable taste of undesirable tasting drug substances and be suitable for administration to all paediatric sub groups. To ensure affordability and thus enhance access to medicines for children in developing countries or emerging markets, the dosage form should be simple to manufacture without the need for specialised equipment.

Spray-drying was investigated to co-process a functional polymer, hypromellose, with a model drug substance, paracetamol, to enhance the functionality of the polymer and to taste mask the paracetamol. Though hypromellose was successfully spray-dried it was not possible to spray-dry hypromellose with paracetamol. The viscosity of aqueous solutions of hypromellose played a key role in determining the grade and concentration of hypromellose that could be successfully spray-dried. Temperature was used to reduce viscosity of hypromellose solutions but careful temperature control is required to avoid reaching the gelation temperature of the hypromellose.

The effect of temperature on aqueous hydroxyl propylcellulose (HPC) solutions showed that heating causes a reduction in solubility of HPC in water which results in its precipitation and the formation of liquid crystals. Consequently, the aqueous HPC solutions appear 'cloudy' and their viscosity decreases. The temperature at which these changes occur is referred to as the 'cloud-point'. The effect of temperature on aqueous HPC solutions containing drug is dependent on the properties of the drug. Paracetamol decreased the temperatures of dehydration and onset of precipitation and ranitidine hydrochloride increased the temperatures of dehydration and precipitation. This is probably associated with a salting in effect.

HPC was used to form films which disintegrate in <30 seconds but are able to retard dissolution rate of paracetamol. HPC may be used to form films which meet the pharmacopoeial content uniformity criteria typically applied to oral dosage forms. HPC films have application for administering drugs to paediatric or geriatric patients by disintegrating in the mouth and so overcoming swallowing difficulties; potentially providing taste masking and aiding absorption across the oral cavity.

HPC films offer significant benefits to the paediatric population. The manufacturing process is simple and transportation is easy as secondary packs are likely to be less bulky than currently used for tablets. The films may also be suitable for administering combinations of drugs in the same dosage form by layering or by combining the drugs at the HPC solution stage. For these reasons the HPC films may have particular application for diseases in the developing world and meet many requirements associated with WHO and other global regulatory guidelines.

“To accomplish great things we must not only act, but also dream; not only plan but also believe.”

Anatole France, 24th December 1896

This thesis is dedicated

In Loving Memory of Dad

and to

Mum, Louise, and Chloe

for their continuous love, support, encouragement and inspiration

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CONTENTS

Title Page	
Abstract	ii
Quote	iii
Dedications	iv
Acknowledgments	v
Content	vii
List of Figures	xv
List of Tables	xviii
List of Abbreviations and Units	xx
Appendices	xxii
Chapter 1 Introduction	1
1.1 General Introduction	1
1.2 Challenges Associated with Developing Paediatric Medicines	3
1.2.1 Physiological and pharmacological challenges	3
1.2.1.1 Pre-term new-born infants	3
1.2.1.2 Full-term new-born infants	4
1.2.1.3 Infants and toddlers (28 days to 23 months)	6
1.2.1.4 Children (2 – 11 years)	6
1.2.1.5 Adolescents	7
1.2.2 Ethical challenges	7

1.2.3	Formulation challenges	12
1.2.3.1	Toxicity issues of some common excipients in paediatric formulations	12
1.2.3.2	Palatability challenges	16
1.2.3.3	Dysphagia challenges	19
1.2.3.4	Examples of paediatric formulations	20
1.3	Aims and Objectives	23
 Chapter 2 Materials and Theoretical Background to Analytical Techniques Used		 24
2.1	Materials	24
2.1.1	Drug substances	24
2.1.1.1	Paracetamol	25
2.1.1.2	Ranitidine hydrochloride	27
2.1.2	Polymers	29
2.1.2.1	Hypromellose	29
2.1.2.2	HPC	31
2.1.3	Other materials	33
2.1.3.1	Purified water	33
2.2	Analytical Techniques	34
2.2.1	Determination of viscosity	34
2.2.2	Ultraviolet spectrometry	35

2.2.3	Hot stage microscopy	37
2.2.4	Dissolution testing	38
2.2.5	Disintegration testing	39
2.2.6	Scanning Electron Microscopy (SEM)	40
2.2.7	Differential Scanning Calorimetry (DSC)	41
2.2.8	Thermal Gravimetric Analysis (TGA)	41
 Chapter 3 Preparation of Polymer Solutions for Characterisation, Spray-Drying and Film Formation		43
3.1	Preparation of Polymer Solutions	43
3.1.1	Preparation of hypromellose solutions	43
3.1.2	Preparation of HPC solutions	44
3.2	Preparation of Drug Polymer Solutions/Dispersions	45
3.2.1	Preparation of hypromellose drug solutions/dispersions	45
3.2.2	Preparation of HPC drug solutions/solutions	45
 Chapter 4 Feasibility of Spray-drying Aqueous Hypromellose Solutions		47
4.1	Introduction	47
4.2	Materials and Methods	48
4.2.1	Preparation of aqueous hypromellose solutions	49

4.2.2	Physical appearance of aqueous hypromellose solutions	49
4.2.3	Viscosity determination of aqueous hypromellose solutions	49
4.2.4	Spray-drying of aqueous hypromellose solutions	50
4.2.4.1	Process overview	51
4.2.4.2	Development of a spray-drying process for aqueous solutions of hypromellose	53
4.2.5	Characterisation of spray-dried hypromellose	54
4.2.5.1	Physical appearance by Scanning Electron Microscopy	54
4.2.5.2	Viscosity testing	55
4.3	Results and Discussion	56
4.3.1	Preparation and physical appearance of aqueous hypromellose solutions	56
4.3.2	Viscosity determination of aqueous hypromellose solutions	57
4.3.3	Spray-drying of aqueous hypromellose solutions	61
4.3.3.1	Development of a spray-drying process for aqueous solutions of hypromellose	61
4.3.3.2	Characterisation of spray-dried hypromellose	62
4.3.3.3	Physical appearance by Scanning Electron Microscopy	62
4.3.3.4	Viscosity testing	68
4.4	Conclusion	71

Chapter 5 Preparation and Viscosity Determination of Aqueous Hypromellose Dispersions Containing Paracetamol 72

5.1	Introduction	72
5.2	Materials and Methods	72
5.2.1	Preparation of aqueous hypromellose dispersions containing paracetamol	72
5.2.2	Physical appearance of aqueous hypromellose dispersions containing paracetamol	73
5.2.3	Viscosity determination of aqueous hypromellose dispersions containing paracetamol	73
5.3	Results and Discussion	74
5.3.1	Preparation and physical appearance of the aqueous hypromellose dispersions containing paracetamol	74
5.3.2	Viscosity determination of aqueous hypromellose dispersions containing paracetamol	74
5.4	Conclusion	77

Chapter 6 Investigating the Influence of Temperature on Physical Properties of Aqueous Solutions of HPC 78

6.1	Introduction	78
6.2	Materials and Methods	78
6.2.1	Preparation of aqueous solutions of HPC	79
6.2.2	UV transmission measurement of aqueous solutions of HPC	79

6.2.3	Viscosity determination of aqueous HPC solutions	80
6.2.3.1	Viscosity determination using small sample adaptor	80
6.3	Results and Discussion	82
6.3.1	Preparation of aqueous HPC solutions	82
6.3.2	UV transmission data for aqueous HPC solutions	83
6.3.3	Viscosity data for aqueous HPC solutions	85
6.4	Conclusion	92

Chapter 7 Investigating the Influence of Temperature and Drug Substance on Aqueous Solutions of HPC 93

7.1	Introduction	93
7.2	Materials and Methods	93
7.2.1	Preparation of aqueous HPC solutions	95
7.2.2	UV transmission measurement of aqueous HPC solutions	95
7.2.3	Viscosity determination of aqueous HPC solutions	95
7.2.3	UV transmission measurement of aqueous HPC solutions	95
7.2.4	Hot stage microscopy of aqueous HPC solutions	96
7.3	Results and Discussion	96
7.3.1	Preparation of aqueous HPC solutions containing drug substances	96
7.3.2	UV transmission data for HPC solutions containing drug substances	96
7.3.3	Viscosity data for HPC solutions containing drug substances	100

7.3.4	Hot stage microscopy for HPC solutions containing drug substances	103
7.4	Conclusion	106
Chapter 8 HPC Film Preparation and Characterisation		107
8.1	Introduction	107
8.2	Materials and Methods	107
8.2.1	Manufacture of HPC films	108
	8.2.1.1 Development of drying process	109
8.2.2	Characterisation of films	109
	8.2.2.1 Film weight	110
	8.2.2.2 Film thickness	110
	8.2.2.3 Disintegration of films	110
	8.2.2.4 SEM analysis of films	110
	8.2.2.5 Dissolution and assay of films	111
	8.2.2.6 DSC	113
	8.2.2.7 TGA	113
8.3	Results and Discussion	114
8.3.1	Manufacture of Films	114
8.3.2	Film Characterisation	117
	8.3.2.1 Film weight and film thickness	117
	8.3.2.2 Film disintegration testing	118

8.3.2.3 SEM analysis of films	121
8.3.2.4 Dissolution of paracetamol from HPC films	122
8.3.2.5 Film assay testing	126
8.3.2.6 Thermal analysis of films	127
8.4 Conclusion	132
Chapter 9 General Discussion	133
9.1 Rationale and Aim	133
9.2 Co-processing by spray-drying	134
9.3 Investigating the Influence of Temperature on Aqueous Solutions of HPC	136
9.4 HPC Film Preparation and Characterisation	138
Chapter 10 General Conclusions and Recommendations for Further Work	140
10.1 General Conclusions	140
10.2 Recommendations for Further Work	142
References	143
Appendices	xxii

LIST OF FIGURES

Chapter 2

Figure 2.1	Chemical structure of paracetamol	25
Figure 2.2	Chemical structure of ranitidine hydrochloride	27
Figure 2.3	Chemical structure of hypromellose	30
Figure 2.4	Chemical structure of HPC	32
Figure 2.5	The behavior of Newtonian fluids	34
Figure 2.6	Schematic diagram of hot stage microscope sample holder	38

Chapter 4

Figure 4.1	Principle components of a spray-drying process	51
Figure 4.2a	The effect of temperature on the viscosity of 5 %w/w hypromellose E5LV solutions	59
Figure 4.2b	The effect of temperature on the viscosity of 20 %w/w hypromellose E5LV solutions	59
Figure 4.2c	The effect of temperature on the viscosity of 5 %w/w hypromellose E15LV solutions	60
Figure 4.2d	The effect of temperature on the viscosity of 5 %w/w hypromellose E50LV solutions	60
Figure 4.3	SEM of E5LV non spray-dried hypromellose powder (Scale bar indicates 500 μm)	63
Figure 4.4	SEM of E5LV non spray-dried hypromellose powder (Scale bar indicates 200 μm)	64
Figure 4.5	SEM of E5LV non spray-dried hypromellose powder (Scale bar indicates 50 μm)	64
Figure 4.6	SEM of E5LV non spray-dried hypromellose powder (Scale bar indicates 20 μm)	65
Figure 4.7	SEM of E5LV non spray-dried hypromellose powder (Scale bar indicates 10 μm)	65
Figure 4.8	SEM of E5LV spray-dried hypromellose powder (Scale bar indicates 500 μm)	66

Figure 4.9	SEM of E5LV spray-dried hypromellose powder (Scale bar indicates 200 μm)	66
Figure 4.10	SEM of E5LV spray-dried hypromellose powder (Scale bar indicates 50 μm)	67
Figure 4.11	SEM of E5LV spray-dried hypromellose powder (Scale bar indicates 20 μm)	67
Figure 4.12	SEM of E5LV spray-dried hypromellose powder (Scale bar indicates 10 μm)	68

Chapter 6

Figure 6.1	The effect of temperature on per-cent transmission for aqueous solutions of HPC	84
Figure 6.2	The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC EXF	85
Figure 6.3	The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC LXF	86
Figure 6.4	The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC JXF	86
Figure 6.5	The effect of temperature on viscosity of solutions containing 5 %w/w HPC GXF	87
Figure 6.6	Phase diagram for HPC solutions proposed by Webowyj and Gray 1980	90

Chapter 7

Figure 7.1	The effect of temperature on per-cent transmission of 5 %w/w EXF HPC Solutions containing different concentrations of paracetamol	98
Figure 7.2	The effect of temperature on per-cent transmission of 5 %w/w EXF HPC Solutions containing different concentrations of ranitidine	98
Figure 7.3	The effect of temperature on viscosity of 5 %w/w EXF HPC	100

	Solutions containing different concentrations of ranitidine	
Figure 7.4	The effect of temperature on viscosity of 5 %w/w EXF HPC	102
	Solutions containing different concentrations of paracetamol	
Figure 7.5	Still images obtained from the hot stage microscope of HPC polymer solution containing 15 mg/g paracetamol heated at various temperatures	103

Chapter 8

Figure 8.1	PTFE coated ampoule cap used as a casting plate	108
Figure 8.2	Effect of drying time on 15 mg/g paracetamol film samples dried at 40°C, 60°C and 80°C	114
Figure 8.3	Film disintegration time and time to dissolve for HPC films without drug substance and HPC films containing 5 mg/g and 15 mg/g paracetamol	119
Figure 8.4	SEM images of placebo and 15 mg/g paracetamol film surface	121
Figure 8.5	Mean (n = 3) paracetamol release from 5mg/g films dried at various conditions and compared to 5 mg paracetamol (powder) in purified water	123
Figure 8.6	Mean (n = 3) paracetamol release from 15mg/g films dried at various conditions and compared to 15 mg paracetamol (powder) in purified water	123
Figure 8.7	TGA plot for HPC film containing no drug substance	128
Figure 8.8	DSC plot for HPC film containing no drug substance	128
Figure 8.9	TGA plot for HPC film containing 5 mg/g paracetamol	129
Figure 8.10	DSC plot for HPC film containing 5 mg/g paracetamol	129
Figure 8.11	TGA plot for HPC film containing 15 mg/g paracetamol	131
Figure 8.12	DSC plot for HPC film containing 15 mg/g paracetamol	131

LIST OF TABLES

Chapter 1

Table 1.1	Example of commercially available paediatric dosage forms designed for oral delivery	22
-----------	--	----

Chapter 2

Table 2.1	Materials used in investigation	24
Table 2.2	Recommended paracetamol dose ranges according to age	26
Table 2.3	Recommended IV paracetamol dose ranges according to weight	26
Table 2.4	Physico-chemical properties of paracetamol	27
Table 2.5	Recommended ranitidine dose ranges according to age	28
Table 2.6	Physico-chemical properties of ranitidine	29
Table 2.7	Details of methocel grades selected	31
Table 2.8	HPC grade material properties	33

Chapter 4

Table 4.1	Aqueous hypromellose solutions considered	48
Table 4.2	Quantitative composition of aqueous hypromellose solutions (per 500g of solution)	48
Table 4.3	Spray-drying process parameters used	54
Table 4.4	Assessment of spray-drying solution suitability based on polymer grades and polymer concentrations	56
Table 4.5	Viscosity method parameters and mean viscosity data	58
Table 4.6	Viscosity method parameters and mean viscosity data of polymer solutions prepared using non spray-dried and non spray-dried hypromellose	69

Chapter 5

Table 5.1	Quantitative composition of drug-polymer dispersion (per 500g of solution)	73
-----------	--	----

Table 5.2	Viscosity method parameters and mean viscosity data for 5 %w/w hypromellose E5LV containing 15 %w/w paracetamol at 25°C and 40°C	74
-----------	--	----

Chapter 6

Table 6.1	Quantitative composition of aqueous HPC solutions (per 500g of solution)	79
Table 6.2	Viscometer spindle type and speed used for viscosity testing	81
Table 6.3	HPC polymer grades, concentrations considered and occurrences of gelling	83

Chapter 7

Table 7.1	Active polymer solutions considered	94
Table 7.2	Quantitative composition of paracetamol aqueous HPC solutions (per 500g of solution)	94
Table 7.2	Quantitative composition of ranitidine aqueous HPC solutions (per 500g of solution)	95

Chapter 8

Table 8.1	Polymer and drug solution concentrations used to produce films	108
Table 8.2	Summary of dissolution method parameters	112
Table 8.3	Summary of on-line UV analysis	112
Table 8.4	Drying conditions employed for HPC film manufacture	115
Table 8.5	Physical appearance of films produced from solutions prepared in Table 8.1	116
Table 8.6	The impact of drying conditions on film weight and film thickness	118
Table 8.7	Theoretical composition of 5 mg/g and 15mg/g paracetamol HPC films	126
Table 8.8	Assay data obtained for films prepared using HPC solutions containing 5 mg/g and 15 mg/g paracetamol	126

LIST OF ABBREVIATIONS AND UNITS

ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AUC	Area Under the Curve
BP	British Pharmacopeia
C _{MAX}	Concentration Maximum
CNS	Central Nervous System
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency (Formerly EMEA)
EP	European Pharmacopeia
EU	European Union
FDA	Food and Drug Administration
HCl	Hydrochloride
HPC	Hydroxypropyl Cellulose
HPMC	Hydroxypropyl methyl cellulose
ICH	International Conference on Harmonisation
MAFF	Ministry of Agriculture, Fisheries and Food
NaOH	Sodium hydroxide
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PAS	Pediatric Advisory Subcommittee
PILs	Patient Information Leaflets
RCPCH	Royal College of Paediatrics and Child Health
SEM	Scanning Electron Microscope
TGA	Thermal Gravimetric Analysis
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
UV	Ultra Violet
WHO	World Health Organisation

UNITS

%	percentage
Kg	kilogram
g	gram
mg	milligram
µg	microgram
Daltons	unit of mass
mL	millilitre
L	litre
m ³	cubic metre
s	seconds
min	minute
hrs	hours
wks	weeks
nm	nanometre
mm	millimetre
cm	centimetre
°C	degrees Celsius
pH	measure of acidity or basicity
w/v	weight per volume
cP	centipoises
w/w	weight per weight
rpm	revolutions per minute
bar	unit of pressure
mbar	millibar

1 INTRODUCTION

1.1 General Introduction

One in five children (3 million) within the United Kingdom has a long standing illness or disability (Martin 2004). Many, if not most, of these disadvantaged children will use medication on a long term basis that is either unlicensed for paediatric use or has not been scientifically studied within this patient population. Around 90 % of babies in neonatal intensive care, 70 % of patients in paediatric intensive care, and almost 70 % of children in hospital in Europe receive at least one unlicensed or off-label medicine during a hospital stay (Conroy 2003).

The majority of marketed drugs are either not labelled, or inadequately labelled, for intended use in paediatric patients. Approximately, 80 % of listed product information labels (PILs) in the US either disclaimed usage or lacked specific dosing information for paediatric use. Less than 30 % of drugs approved by the Food and Drugs Administration (FDA) were authorised for paediatric use. Additionally, only 38 % of new medicinal products, which were potentially of benefit in paediatric therapy, were initially labelled for paediatric use (Goldkind 2004).

A lack of vital, supporting information often prompts conservatism from paediatricians who often choose to prescribe existing, established medications (Standing and Tuleu 2005). Though these products may have well established safety profiles, their efficacy may be marginal, and be potentially less effective than the newer drugs, which lack relevant safety data.

Children are not young adults and due to many physiological, regulatory, ethical and practical reasons, effective adult doses of newly approved medicinal products cannot necessarily be reduced based on a simplistic, relative mg/kg body weight basis alone (Cella et al 2010)

In an attempt to encourage pharmaceutical companies to invest in the research and development of paediatric medicines, regulatory agencies such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the US,

published regulations forcing companies to consider the development of medicines for children (EMA 2006 and FDA 2003).

Paediatric formulations must provide dose flexibility, accurate dosing, have acceptable taste and be designed to enhance patient compliance. Further investigation into the development of 'Paediatric Friendly' formulations is required.

1.2 Challenges Associated with Developing Paediatric Medicines

There are many aspects to be considered when developing paediatric medicines. Due to the complexity of this patient population, it is critical that the patient is considered at the outset of the development of the dosage form.

1.2.1 Physiological and pharmacological challenges

Children are not just small adults; either from a biological or pharmacological development perspective (Bowles et al 2010). However, it is often overlooked that the paediatric patient population is not a homogenous sub-group either, and can be sub-classified, based on very real physiological (size, and developmental biology) and pharmacological differences (RCPCH 1999) as follows:

- Pre-term new-born infants i.e. born before gestation date
- Full term new-born infants (0-27 days where day '0' is day of birth)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12-16/18 years, but dependent on region)

1.2.1.1 Pre-term new-born infants

It is not possible (except in rare cases e.g. vaccines, antidotes, Baker 2007) to extrapolate the efficacy of medicinal products from studies in adults to predict efficacy in paediatrics. However, even studies in older paediatric patients can be difficult to meaningfully extrapolate to preterm new-born infants (ICH 2000).

Clinical study design considerations that need to be evaluated include:

- (1) difficulties in assessing study outcomes
- (2) small patient numbers at each centre and very real centre differences (based on care, experience and infrastructure)

(3) small pharmacokinetic sampling (the total blood volume of a 0.5 kg preterm infant is 40ml) necessitating enhanced sampling and preparation techniques and more sensitive analytical methodologies

(4) weight and age (gestational and postnatal)

More worryingly, this sub-category of the paediatric population is also not homogenous, as there are huge developmental differences between a 25-week gestation new-born (0.5 kg) from the much heavier 30-week gestation newborn (1.5 kg) (Kearns et al 2003 and Rakhmanina and van den Anker 2006). Important developmental, biological and pharmacological features that need to be considered when administering medicines to preterm paediatric patients include:

(1) rapid changes of pharmacology and physiology necessitating unique dosing regimens

(2) the immaturity of the renal and hepatic clearance mechanisms, and of the blood-brain barrier (this has the potential for all administered drugs to penetrate into the central nervous system (CNS), not just those that are reported to have high CNS permeability in adults)

(3) protein binding and displacement issues (in particular, bilirubin)

(4) opportunities (often inadvertent) for transdermal absorption of drugs

(5) unique neonatal susceptibilities, e.g. retinopathy and unique neonatal disease states, e.g. respiratory distress syndrome.

1.2.1.2 Full-term new-born infants

Although more mature, 'full term newborn infants' is a similar sub-class to preterm newborn infants in terms of relative maturity to an adult. Drugs that demonstrate high protein binding in adults are often more freely available in neonates due to the competitive binding seen between albumin and bilirubin (elevated in neonates). The displacement of bilirubin can cause CNS toxicity as the blood-brain barrier is still not fully mature. This is a particular problem with sulphonamides (Choonara 2009).

The hepatic and renal clearance mechanisms are rapidly developing during the first month after birth and consequently, hepatically-cleared drugs are extracted more slowly, so drug doses and resultant efficacy need to be carefully monitored and potentially altered on a daily (or near daily) basis, e.g. phenytoin, phenobarbitone. The body water, fat content and high surface area to weight ratio of new-born paediatric patients indicate that the volumes of distribution of drugs may be significantly different to older paediatric or adult patients (Duke and Urquhart 1997). As a consequence water soluble drugs are diluted to a greater extent in neonates resulting in the potential requirement to increase dose to produce the desired plasma concentration.

One of the most important differences between paediatric and adult patients is oxygen consumption which, in infants may exceed 6 ml/kg/min, twice that of adults (Rusy and Usaleva 1998). There are physiological adaptations in paediatric cardiac and respiratory systems to meet this increased demand. Both induction and emergence from anesthesia are more rapid in children than in adults. This is probably because of a smaller lung functional residual capacity per unit body weight and a greater tissue blood flow, especially to the key organs (brain, heart, liver and kidney). These organs in adults account for 10 % of body weight versus 22 % in neonates (Rusy and Usaleva 1998).

Similarly, oral absorption is less predictable than in older paediatric or adult patients. In the early days after birth, neonates are achlorohydric, with gastric pHs being much higher than in the majority of Caucasian adults. As a consequence, the absorption of acid labile drugs may be enhanced, e.g. proton-pump inhibitors whereas, the absorption of fat soluble drugs may be reduced, for example fat soluble vitamins (Duke and Urquhart 1997). Additionally, the selection of delayed release formulations, which rely on pH sensitive enteric coated formulations, should be cautiously considered for use in neonates. There are many examples in the literature of unanticipated toxic effects from limited clearance and resultant accumulation of drugs in this class of infants; for example, chloramphenicol grey baby syndrome (Mulhall et al 1983). In contrast, established toxicology profiles may be less applicable to this patient sub-set; for example, aminoglycosides are safe and effective in neonates (Nestaas et al 2005), whereas nephrotoxicity is commonly

encountered from these drugs in older patient sub-sets (Giacioia and Schentag 1986).

1.2.1.3 Infants and toddlers (28 days to 23 months)

This is a period of very rapid growth and maturation. Oral absorption becomes much more reliable, adult gastric pH is achieved by 23 months, and clearance mechanisms are maturing rapidly (but with significant intra-subject variability); and with clearance (based on a mg/kg basis) often exceeding that seen in adults. This is a result of the liver being up to 50 % greater (as a percentage of total body weight) than in adults. As a consequence the administered doses for hepatically-cleared drugs may need to be higher than in adults. The rates of gastric emptying and general gut motility fall during infancy and early childhood. Although, the extent of drug absorption is usually not impacted, the rate may be i.e. the maximum blood plasma concentration (C_{max}) increases, but the area under the blood plasma concentration versus time curve (AUC) remains the same. Consequently, sustained release formulations should be used with caution during childhood (Duke and Urquhart 1997).

1.2.1.4 Children (2-11 years)

The clearance pathways of most drugs have matured in this sub-class; however, clearance values again often exceed adult values, and are often dependent on the maturation of specific metabolic pathways. Neonates and children have greater surface area to weight ratios and thinner stratum cornea than adults (Werfel et al 1998). Consequently, there is a greater potential for high systemic exposure and subsequent adverse events from topical application of drugs. Of particular importance to the study of drugs in this sub-class is the impact on growth and development. Drugs that are CNS-active can adversely affect psychomotor skills in pre-school/school age groups and impact on the efficacy end-points. The impact of the drug on the child can be monitored using developmental end points, such as growth, weight gain or school performance.

Though rectally administered drugs can produce variable and erratic systemic absorption, administration of drugs via the rectal route can be especially useful to treat the very young, who can experience difficulties swallowing solid oral dosage

forms, and which, thereby avoids the need for injections or in emergency use, such as prolonged fitting, e.g. rectal diazepam (EMA 2013).

Puberty can impact on the efficacy of metabolising enzymes, which significantly impacts on the administered dose on a mg/kg basis, of certain drugs, for example, theophylline (Conroy 2003). Puberty is highly variable and is different in the sexes; girls maturing earlier (as young as 9 years) and more rapidly.

Children often benefit from drugs with intrinsically long half-lives or modified release dosage forms as they can be administered once-daily. For example, the compliance and ethical issues of teachers and carers administering certain medicinal products should not be under-estimated, e.g. Ritalin (Drug and Alcohol Education and Prevention Team 2005).

1.2.1.5 Adolescents

The impact of any medicinal product on the physical, mental or sexual maturation of this paediatric sub-class should be considered. As with late-phase infants, the impact on puberty is important. In particular, the impact on hormones (especially sex hormones), sexual activity and the need for contraception or pregnancy testing can be important factors in clinical trial design. Several disease states are influenced by hormonal changes, for example, changes of frequency and severity of asthma and migraine (Salam et al 2006). However, non-compliance is particularly acute in this age range and recreational drug use, for example, of alcohol, tobacco, cocaine, ecstasy, etc., is unfortunately, becoming more prevalent (Williams et al 2002).

1.2.2 Ethical challenges

There is a growing body of opinion within the world-wide community that children (and their parents) have the right to properly researched and regulated medicines (Davies 2004). Unfortunately, there is an equally strong lobby that considers experimentation on children (particularly, placebo-controlled study designs) to be unethical; and for this to be ultimately a potentially profitable exercise, to be morally indefensible. Consequently, the availability of financial incentives, in terms

of patent life extensions and exclusivity, for industry to develop paediatric medicines in the US and EU is viewed by some as setting an unwanted precedent.

Before undertaking any paediatric research, an investigator needs to ensure that such research cannot be done in adults, with the results being extrapolated to children. The overarching purpose of paediatric research is to obtain knowledge, applicable to the wider needs of the paediatric community.

Paediatrics are a particularly vulnerable patient group. As such, special measures and precautions are required to protect the participants (or their parents, if they are of an age where informed consent is not practicable) from undue risks. Some of the issues perceived by parents (Martin 2004) include:

- (1) risks (both known and unknown)
- (2) discomfort to the child, especially from invasive treatments
- (3) disruption to routine and to family schedules
- (4) financial impact
- (5) incentive to change (if current regimen is working well)
- (6) poor communication, both in terms of on-going issues and feedback on trial results
- (7) scepticism on the real goals of the researchers (more focussed on the research, rather than the treatment and care of the child).

However, rights and duties are 'two sides of the same coin'. If there is a strong lobby for accessibility to paediatric medicines *via* well designed and controlled, clinical studies, is there an associated duty for families to become involved in such trials? Unfortunately, even world-renowned ethics advisors are at a loss to answer this key question (Davies 2004).

However, participation in any clinical trial involves the issue of risk/benefit, which needs to be carefully evaluated by the overseeing Independent Ethics Committee and Institutional Review Boards. These organisations should ensure that participation in such studies is free from inappropriate inducements, and any

reimbursement and subsistence costs are appropriate. Since in the majority of cases, participants in paediatric studies are unable to provide informed consent, this must be obtained from parents or guardians. However, in all cases participants should be made aware of their rights to withdraw from the trial at any time; except in those very rare instances where the welfare of the participant would be placed in jeopardy by failing to participate, or continuing to participate in the clinical programme (FDA 2001a).

Minimising the risk to the participants should be the principal objective, even if the whole community benefits; and every effort should be made to anticipate or reduce known risks. There should be full awareness of the known pharmacology, toxicology, safety and efficacy of the medicinal product prior to the initiation of the study. In addition, studies should be conducted by trained paediatricians, with knowledge of, and experience of dealing with adverse events in paediatrics. The number of participants should be as low as is commensurate with appropriate study designs, and processes for ensuring rapid termination of a study should be in place, should additional, unanticipated risks emerge. Approaches to reduce invasive procedures and minimise the number and volume of samples for subsequent pharmacokinetic evaluation, should form part of the study protocol (EMA 2005).

The various regulatory agencies also evaluate the risk to the child of participating in the paediatric clinical trial. In the UK, the Royal College of Paediatrics and Child Health (RCPCH) define the perceived risk as minimal, low and high risk (McIntosh et al 2000). However, in the latter two categories the RCPCH argue that such research deserves serious ethical consideration, but provide no further guidance. In contrast, in the US, the control of risk is divided into four categories;

- (1) minimal risk
- (2) minor increase over minimal risk
- (3) no direct benefit
- (4) direct benefit

The whole area of paediatric medicine is more extensively regulated in the US (FDA 2001b).

The US Food and Drug Administration (FDA) under the auspices of the Pediatric Advisory Subcommittee (PAS) have taken steps to reassure the general public that the safety of participating children is of paramount concern (Woodcock 2001). The PAS have addressed several of ethical issues, including:

- (1) children as volunteers, versus paediatric patient studies
- (2) placebo controlled trials
- (3) clinical trial design and data analysis.

To provide specific additional safeguards for children, to ensure compliance with the Children's Health Act of 2000, and to coordinate these regulations with Health and Human Services regulations, the FDA introduced Additional Safeguards for Children in Clinical Investigations of FDA Regulated Products (FDA 2001b).

The factors affecting the need for paediatric investigation of either an established drug, or a newly developed drug, and the nature of this clinical programme are varied (Richey et al 2012). They include:

- (1) the seriousness of the condition requiring treatment
- (2) the prevalence of that condition in the paediatric sub-set
- (3) whether the medicine is 'first in its class', or another representative of an established class of compounds
- (4) the availability and suitability of alternative treatments especially the safety and efficacy of these alternative treatments
- (5) the need to develop paediatric specific end-points in the therapeutic disorder
- (6) unique safety concerns
- (7) research that indicates that there could be unique paediatric applications for this medicinal product
- (8) the likely age ranges of the paediatric population
- (9) the need for paediatric formulation development

Pharmaceutical companies developing medicinal products in new therapeutic indications are often viewed from the outside as considering clinical studies in children to be an unattractive, non-viable or non-profitable option (Conroy et al 2000). However, industry has long recognised the need for paediatric medicines and for nearly a decade has been calling for medicines to be licensed to children of specific age ranges, for the publishing of paediatric clinical research guidelines and for regulatory guidance in this area (The Association of British Pharmaceutical Industry (ABPI) 1996).

Unfortunately, there are issues for the pharmaceutical industry in this area. Despite the numbers of children affected in the developed world the paediatric market is still comparatively small. It has been estimated that the cost of a paediatric development plan for a new medicinal product is in the order of \$20 million, and for an existing product, that could equate to a poor, or even negative, return on investment (Tiner 2004). The objectives of the proposed regulations in the EU and US are to improve the overall health and welfare of children, by increasing research, development and approval of paediatric medicinal products. However, it is not clear that the existing incentives will lead to more paediatric research in the EU, as the EU patent extension period is no improvement on the current US position. Although there are some incentives to encourage the generic industry to carry out more research, or develop new paediatric dosage forms on older established products, the generic industry has no record of innovative research to fall back on, which may hamper future development. This is obviously unfortunate as there are often large knowledge gaps with the existing products as many of them have been used 'off-label' and there is no incentive to publish this information, particularly when there is often no obvious advancement in the particular field of research.

In the US, the paediatric exclusivity provision has been highly effective, with industry responding positively, and with resultant extensive paediatric health benefits. In the 3-year period covering implementation of the guidance to 2001, there were 218 paediatric proposals from industry 188 Written Requests from FDA, 77 incomplete letters issued in place of a Written Request, and 95 amendments to Written Requests after negotiations between FDA and industry. This resulted in the submission of 34 products (which included paediatric studies as part of the NDA

submission), of which 28 products (82 %) were granted paediatric exclusivity. The complete list can be found on an FDA website (FDA 2013) and include drugs for the treatment of HIV, diabetes, hypertension, obsessive compulsive disorders, allergies, juvenile rheumatoid arthritis and seizures. It has been estimated that industry had completed 80 % of the paediatric studies requested by FDA, which is in contrast to the 15 % completion rate in the 6-year period before the initiation of the paediatric exclusivity provision (Woodcock 2001).

1.2.3 Formulation challenges

1.2.3.1 Toxicity issues of some common excipients in paediatric formulations

One of the greatest medicinal tragedies of the last century (diethylene glycol poisoning) was prompted in many ways by the need to develop 'child-friendly' dosage forms (Geiling and Cannon 1938). At that time clinical safety of new medicines and new formulations was not required; nor was there an extensive safety data base on existing or novel excipients. In the resulting tragedy 107 patients died of diethylene glycol poisoning, many of them children (Steinbrook 2002) and hence the Best Pharmaceuticals for Children Act (BPCA) became public law in the US in 2002 (FDA 2002).

A safety database exists for established excipients commonly used in pharmaceutical products intended for adults, and new excipients are required to undergo extensive animal safety testing before they can be used in clinical studies. However, the toxicity of some common excipients, like lactose, may differ across the various paediatric sub-groups and between paediatrics and adult patient groups (Edge et al 2005).

One of the direct consequences of the need for oral liquid preparations (that children typically find easiest to swallow), is that taste-masking which often relies on sweeteners, is essential. Aspartame is used as an intense sweetener in beverages, food products, and in pharmaceutical preparations. It enhances flavour systems and can be used to taste-mask unpleasantly bitter tasting characteristics of common drugs. A number of adverse events, e.g. headaches and seizures, has been

reported following the consumption of large quantities of aspartame in beverages (Golightly et al 1988; Butchko and Kotsonis 1989). Although, aspartame has been blamed for hyperactivity in children; a double-blind study of 48 pre-school children who were dosed with diets containing 38 ± 13 mg/kg body weight of aspartame for three weeks, showed no appreciable adverse behaviour or impact on cognitive function (Wolraich et al 1994).

The development of multi-dose oral liquid and parenteral preparations also necessitates the requirement for preservative(s) to prevent microbial contamination.

Benzyl alcohol is an antimicrobial preservative used in cosmetics, food, and in a wide range of pharmaceutical preparations including oral liquid and parenteral preparations. Although widely utilised, its use has been associated with some fatal adverse reactions when given to neonates (Gershanik et al 1981). It is now recommended that its use as a parenteral preservative for new born infants is discontinued. The fatal toxic syndrome in low birth weight premature children was attributed to the use of benzyl alcohol as a preservative in solutions used to flush-out umbilical catheters (Brown et al 1982; Gershanik et al 1982; McCloskey et al 1986). The FDA subsequently recommended discontinuation of this practice and of the use of medicinal products containing preservatives in neonates (FDA 1982; Belson 1982).

Sodium benzoate is an antimicrobial preservative used in cosmetics, food, and in a wide range of pharmaceutical preparations. It has been shown to elicit non-immunological contact reactions, including urticaria and this should be taken into account when formulating paediatric products (Nair 2001). In addition, it is recommended that parenteral combinations of caffeine and sodium benzoate should not be used in neonates (Edwards and Voegeli 1984).

Thiomersal is an antimicrobial preservative used in cosmetics, soft contact lens solutions, and in some pharmaceutical preparations. However, its use is declining owing to its toxicity and there are suggestions for discontinuing its use in eye drops (Ford et al 1985) and vaccines (Cox and Forysth 1988; Seal et al 1991; Noel et al 1991). In both the US and EU, regulatory bodies have recommended that its use in

vaccines, particularly paediatric vaccines is discontinued (APA 1999; EMEA 1999). In recent years public pressure groups have tried to link thimerosal in paediatric vaccines with autism but this claim was unsubstantiated and repudiated by regulatory agencies (Department of Health 2001).

Propyl gallate is a widely used antioxidant in cosmetics, foods, and in a wide range of pharmaceutical preparations. Although, propyl gallate has strong sensitising potential in animals, there are few reports of adverse events in humans but these include methemoglobinemia in neonates (Nitzan et al 1979).

Oral Liquid formulations are often complementarily coloured and flavoured to aid in paediatric patient acceptance and long term compliance. For instance, a paediatric formulation might be taste-masked using banana flavour (a particular favourite of many young children), which would be complemented by the addition of a yellow colorant. One such colorant (FD&C Yellow No. 5 or tartrazine) has long been the subject of much controversy centred around its safety profile, and its possible link with hives (reported incidences of 0.001 %) and hyperactivity in children (Ward et al 1990). In the US, any prescription drug containing tartrazine, is labelled: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic reactions (including bronchial asthma) in certain susceptible persons." (Mroz 2003)

Generally, concerns over the safety profile of colorants in pharmaceuticals and foods are associated with hypersensitivity and hyperactivity (Bell 1991; Lévesque et al 1991; Dietemann-Molard et al 1991), especially in children (Pollock et al 1989).

Poorly soluble drugs are often prepared as oral suspensions, and are frequently co-formulated with surfactants to aid in the wetting of the drug, and in its subsequent dissolution. Docusate sodium, an anionic surfactant, is widely used in pharmaceutical preparations as a wetting agent, dissolution aid and as laxative and faecal softeners. However, the levels of docusate sodium should be strictly controlled in medicinal products to prevent unwanted incidences of diarrhoea, especially in infants. The adult dose (500 mg) is over six times the amount administered to children of 6-months (75 mg) and older (Guidott 1996).

Polyoxyethylene sorbitan fatty acid esters (Polysorbates 20, 40 and 60) are used as emulsifying agents, non-ionic surfactants, solubilising agents, wetting, dispersing

and as suspending agents. Polysorbates are generally regarded as non-toxic and non-irritant materials; however, they have been associated with serious adverse events, including some deaths, in neonates who were administered with vitamin E intravenous preparations (Alade et al 1986; Balistreri et al 1986).

Carrageenan is a naturally occurring gel base or suspending agent derived from seaweed extracts. Carrageenan is generally considered to be non-toxic and non-irritating, except in parenteral preparations. However, because of its ability to induce inflammatory responses in animals, the UK Food Advisory Committee did recommend the removal of carrageenan as an additive in infant food formulas (Ministry of Agriculture, Fisheries and Food (MAFF) 1992).

Lactic acid is used in beverages, food, cosmetics and pharmaceuticals. In topical cosmetics it is used as a skin softener. In food and beverages it is used as a preservative. It is usually present as the racemate (RS); but in some cases the S isomer predominates. Lactic acid is the naturally occurring endpoint of anaerobic metabolism of carbohydrates so is usually viewed as being non-toxic at the levels used in typical formulations. However, there is evidence that neonates have difficulty in metabolising the R isomer; and hence this isomer and the racemate should not be used in infant formulas for children less than 3 months old (World Health Organisation (WHO) 1974).

Almond oil is used as an emollient in infant skin-care preparations. Although, typically regarded as non-toxic and non-irritant there has been one case reported in the literature of a 5-month old child developing contact dermatitis, which was attributed to the topical application for a 2 month period to the cheeks and buttocks (Guillet and Guillet 2000).

Mineral oil is used as an emollient, lubricant or oleaginous vehicle. The most serious adverse event caused by this excipient is lipoid pneumonia caused by inhalation of the oil as it does not elicit the cough reflex. With the reduction in the use of this excipient in intra-nasal formulations the incidence of lipoid pneumonia has decreased (Owen 2005). However, this condition has been associated with the use of mineral oil in cosmetics in an adolescent (Becton et al 1984) and in

ophthalmic formulations (Prakesh and Rosenow 1990). It is recommended that this excipient is not used in paediatric formulations.

Peanut oil is used as a food additive and as a solvent in intra-muscular injections. Some workers have suggested that the use of peanut oil in childhood (infant formula and topical preparations) can lead to later episodes of hypersensitivity, and therefore should be discontinued (Monerat-Vautrin et al 1991; Brown 1991; De Montis et al 1993; Lever 1996; Wistow and Bassan 1999).

Propylene glycol is a general solvent and antimicrobial preservative used in a wide range of pharmaceutical preparations including oral liquid, topical and parenteral preparations. Its use in large volumes in children is discouraged, and it has been associated with CNS adverse events, especially in neonates (Martin and Finberg 1970; Arulanantham and Genel 1978; MacDonald et al 1987).

Lactose occurs widely in dairy products and is used in infant feed formulas. In pharmaceutical preparations it is widely used as a diluent in tablets and capsules, in lyophilised powders, and as a carrier in dry powder inhalation products. Lactose intolerance occurs when there is a deficiency in the intestinal enzyme lactase. This enzyme is normally present at high levels at birth, declining rapidly in early childhood. Hypolactasia (malabsorption of lactose) can thus occur at an early age (4-8 years) and varies among different ethnic groups (Suarez and Saviano 1997). It is unlikely that severe gastrointestinal adverse events could result from ingestion of medicinal products in adults, but it is less clear if this is equally applicable in infants.

Talc is commonly used as a dusting powder and historically has been used as both a glidant and lubricant. Although, generally regarded as non-toxic when orally ingested, inhalation of talc causes irritation and severe respiratory distress in children (Pairaudeau et al 1991).

1.2.3.2 Palatability challenges

Taste is the most important parameter governing paediatric patient compliance. Unfortunately, undesirable palatability is one of the most important formulation challenges encountered with the majority of drug substances (Tuleu 2009, Cram et al 2009). Several approaches have been utilised to overcome this issue including

the use of flavours, sweeteners, amino acids, polymer coating, conventional granulation, lipids; including lipid emulsions and liposomes, lecithins, complexes with cyclodextrins and ion-exchange resins, salts, and polymeric materials.

The use of flavours, generally in combination with artificial sweeteners, is by far the most commonly utilised approach in paediatric formulations; but is not the most successful for highly soluble or very bitter drugs. Artificial flavours (grape, cherry, raspberry, etc.) have been used to mask the taste of some saline drugs (Lankford and Becker 1951). The combination of an effervescent citrate couple in combination with cream and orange flavours was used to mask the bitter taste of chlorpheniramine and phenylpropylamine (Brideau 1995), lemon flavour was used to mask the taste of famotidine (Wehling and Schuehle 1993a); whilst cherry flavour was used to mask the flavour of paracetamol (Wehling and Schuehle 1993b). Vitamin B oral solutions, inosinate and fruit flavours (particularly, orange) are reported to have been used to have improved taste (Kobayashi et al 1992).

Monosodium glyceryrrhizinate, an artificial sweetener with a longer acting sweetness, and flavours has been utilised to improve the bitter taste of guaifenesin (Fawzy et al 1998). Low levels of ammonium glyceryrrhizinate are used to mask the bitter tastes of chewable multivitamin and analgesic tablet formulations, cough and cold syrups, and oral antibiotics (Kurtz and Fuller 1993). Sorbitol, sodium saccharin, sodium glutamate and vanilla flavours have been used to produce palatable solutions of theophylline (Maegaki et al 1993).

Lipids can be used to coat the buccal cavity (including the taste buds) and reduce the flavour threshold of bitter tasting molecules. Cimetidine can be taste-masked by granulation with the lipid lubricant, glyceryl monostearate (Gottwald et al 1991). Similarly, gabapentin can be mixed with gelatine, partially hydrogenated soybean oil and glyceryl monostearate (Chau and Cherukuri 1991). Palatable syrups of carbetapentane citratem, diphenylhydramine, paracetamol and noscapine can be prepared using glycerine, polyglycerine fatty acid esters and triglycerides (Miura et al 1992).

Formulations using lecithin, or related compounds can improve the taste of bitter drugs. Soybean lecithin has been used to mask the unpleasant taste of the

antibiotic, talampicillin (Kinoshita and Shibuya 1987). Similarly, suspensions of phosphatidic acid and β -lactoglobulin, suppress the bitter tastes of caffeine, quinine and papaverine (Kasturagi and Kurihara 1993).

Coating of bitter tasting drugs with hydrophilic agents provides one of the most straightforward approaches to taste masking. The unpleasant taste of ibuprofen in a suspension formulation, can be taste masked (Motola et al 1995) using a mixture of sodium carboxymethyl cellulose and sweeteners (sucrose, sorbitol and glycerine). The bitter tasting antibiotic, amoxicillin, can be taste-masked by granulating with microcrystalline cellulose, and then mixing with hydroxypropylcellulose (Olthoff et al 1988). Tripolidine, can be taste-masked using hydroxypropylcellulose, sweeteners and flavours (McCabe et al 1992).

A variety of proteinaceous excipients has been utilised to improve palatability. Various analgesics, hormones, enzymes, antibiotics, vitamins and dietary fibres have been taste-masked using prolamine coatings; without impacting on bioavailability. Amprilose was taste-masked by coating with calcium gluconate and sodium alginate; the latter forming a gel on contact with water and effectively masking unpleasant tastes (Nanda et al 2002). A gel-based sweet was developed to improve the taste of paediatric paracetamol (Toraishi et al 1988). Sodium alginate mixed with ibuprofen and added drop-wise to a calcium chloride solution gives a colourless and tasteless gel (Andou et al 1998). The bitter taste of the antibiotic clairithromycin can be taste masked by granulation with carbopol and polyvinyl pyrrolidone (Saleki and Keski 1997).

Complexation is a well-documented approach to taste masking. Complexes of ibuprofen, hydroxypropyl- β -cyclodextrin and sweeteners improved the palatability of ibuprofen solutions (Motola et al 1991). The strong bitter taste of carbetapentane was decreased significantly following complexation (1:1) with cyclodextrins (Kurasumi et al 1991). Similarly, bitter tasting drugs can be complexed with ion exchange resins (Elder 2005). Polystyrene based cationic exchange resins (Indion CRP-244 and 254) have been utilised to complex bitter tasting drugs; diphenhydramine, chlorpheniramine, ephedrine, noscapine, and amphetamine (Manek and Kamat 1981). The strong cationic exchange resin Amberlite IRP-69 can

be used to mask the taste of the bitter tasting drugs like paroxetine (Elder et al 2000).

Low solubility salts (dibenzylethylenediamine and bis-ethylenediamine) of penicillin and the magnesium salt of aspirin are tasteless (Nanda et al 2002). Similarly, the magnesium salts of dihydrocodeine, methylephedrine and chlorphenniramine, together with sweeteners are palatable (Nishikawa and Hyashi 1993).

1.2.3.3 Dysphagia challenges

The anatomy of the buccal cavity within a paediatric patient is not a scaled down version of that of an adult and differences exist between neonates and older children, as well as between children and adults. The differences include (Evans-Morris 1998):

- (1) the oral cavity is small in a neonate and is completely filled by the tongue
- (2) neonates have a set of sucking pads in the cheeks
- (3) the soft palate and epiglottis are in contact at rest, providing an additional valve at the back of the oral cavity
- (4) the larynx and hyoid cartilage are both higher in the neck and closer to the back of the epiglottis, providing additional protection to the airway
- (5) the eustachian tube runs horizontally from the middle ear to the nasopharynx (rather than the vertical angle found in older children and adults).

Although, most medicinal products are developed as solid oral dosage forms, typically tablets and capsules (Rubinstein 1988) more than 25 % of adult patients have difficulty in swallowing (dysphagia) these type of medicinal products, and for paediatric and geriatric populations the percentages are much higher. Children over the age of five years can usually swallow a tablet and those as young as three years can be taught, particularly where they suffer from chronic illnesses. Standard tablets (without functional film coats) may be halved (if there is a break-line) or crushed (Richey et al 2012). However, due to difficulties encountered by children with swallowing, alternative formulations, such as oral liquids, oral suspensions,

elixirs, drops, dispersible and chewable tablets are often required. Injectable solutions can be dosed orally, e.g. phytomenadione injection (Duke and Urquhart 1997).

1.2.3.4 Examples of paediatric formulations

Customised paediatric drug products must be carefully designed to overcome the challenges described. As for adults, the most commonly used route of administration is the oral route, but other routes that may be considered are topical, rectal, nasal, inhaled or intravenous. Some of these routes may offer specific advantages for the paediatric population for example, the rectal and topical routes both overcome issues associated with dysphagia and palatability.

Traditionally, liquid oral products have been used to treat children as these offer dose flexibility and avoid swallowing difficulties but these product types also pose many formulation challenges including potential chemical, physical and microbiological stability and taste issues (Nunn and Williams 2005)

As described, unfortunately in many cases, there is a need to manipulate adult medicines when a paediatric product is unavailable. Examples of manipulation include the crushing or splitting of tablets, opening capsules, cutting suppositories, or administering products designed for intravenous routes via alternative routes. Such practical solutions have been used to influence the design of customised oral paediatric formulations where oral liquid formulations are undesirable or non-developable (Richey et al 2012).

For example, a novel fixed dose combination tablet containing zidovudine and lamivudine has been developed as rectangular tablets with multiple fraction bars enabling the units to be split into 8 subunits enabling dose flexibility by weight (Kayitare et al 2009).

Additionally, the concept of emptying capsules has driven the development of granules for dispersion. Instead of being filled into capsules for single unit dosing, the granules are filled into sachets and designed to be dispersed immediately prior to administration e.g. Singulair®.

The use of mini-tablets to overcome swallowing difficulties associated with children has also been explored. Tablets of 3mm diameter were dosed to pre-school children (2 to 6 years) with some success (Thomson et al 2009). Such formulations could be used to dose immediate release or modified release formulations and could be directly associated with the adult formulation.

Other types of solid oral formulations that may enhance compliance within the paediatric population are oral dispersible tablets, films, and melt formulations. Examples of commercially available paediatric products and the associated dosage form type are provided in Table 1.1.

Table 1.1 Examples of commercially available paediatric dosage forms designed for oral delivery.

Product/ Brand	Drug substance	Dosage format	Route of Administration
Nurofen Meltlets	Ibuprofen	Rapidly disintegrating Tablets	Oral
Diclofenac Effervescent Tablets, Hermes (diclofenac)	Diclofenac	Effervescent Tablets	Oral
Aspirin QuickMelts (aspirin)	Aspirin	Orally Dissolving Tablets	Oral
Paracetamol Chewable Tablets, CLL (acetaminophen)	Acetaminophen	Chewable Tablets	Oral
LipiGestic HPuraMed Tension Headache (USA)	Aspirin	Sublingual gel	Sublingual
Junior Strength Motrin	Ibuprofen	Chewable Tablets	Oral
Advil PM	Diphenhydramine Citrate, Ibuprofen	Caplets, Liquid filled capsules	Oral
Childrens Advil Suspension Children's Advil-Flavored(USA)	Ibuprofen	Suspension	Oral
Nexcede	Ketoprofen	Oral soluble film	Oral
Nurofen for Children - Strawberry Flavoured Fever & Pain Relief	Ibuprofen	Liquid	Oral

1.3 Aims and Objectives

The aim of this study is to develop a simple polymeric paediatric dosage form offering dose accuracy, dose flexibility whilst also addressing challenges associated with swallowing difficulties.

This work evaluates the spray drying of hypromellose and paracetamol to determine if spray drying of these materials is feasible and if co-processed material may offer advantages over the binary mixing of polymer with drug substance.

The effect of temperature on aqueous solutions of hypromellose and hydroxyl propylcellulose is evaluated to determine if temperature may be used to reduce viscosity of polymer solutions. The effect of temperature on aqueous solutions of HPC and HPC solutions containing paracetamol and ranitidine hydrochloride (ranitidine hydrochloride will be referred to as 'ranitidine' throughout this thesis) is investigated using UV transmission and viscosity testing.

These data are then used to develop HPC polymer films containing paracetamol and ranitidine. HPC films are characterised to assess the potential use of polymer films as a paediatric dosage form platform.

2. MATERIALS AND THEORETICAL BACKGROUND TO ANALYTICAL TECHNIQUES USED

A list of the materials, suppliers and theoretical background to analytical techniques used throughout the project is provided below. Where appropriate, specific details associated with materials or methods used are provided in the relevant Chapters.

2.1 Materials

Details of the materials used throughout the project are provided in Table 2.1.

Table 2.1 Materials used in investigation

Material	Grade	Supplier	Batch Number
Paracetamol	-	GlaxoSmithKline, UK	0709000128
Ranitidine Hydrochloride	-	GlaxoSmithKline, UK	K076008
Hypromellose	E5LV	Dow Chemical Company, US	TA24012409
	E15LV		UC27012408
	E50LV		UI14012401
HydroxyPropyl Cellulose (HPC)	EXF	Ashland Inc., US	65645
	GXF		66643
	HXF		68745
	JXF		76799
	LXF		77019
	MF		74311
Polyethylene Glycol	400	Dow Chemical Company, US	XE1901AAKC

2.1.1 Drug substances

Two drug substances were considered for this project; paracetamol and ranitidine. The rationale for selection of these drugs together with a summary of their pharmacological application and batch details are provided here. As the data in Table 2.4 and Table 2.6 illustrate each drug has a 'slightly bitter' taste and therefore pose palatability challenges in the development of a paediatric dosage form. These data also show that the two drugs have different solubilities, enabling the impact of drug solubility to be assessed in the experiments conducted in this investigation.

2.1.1.1 Paracetamol

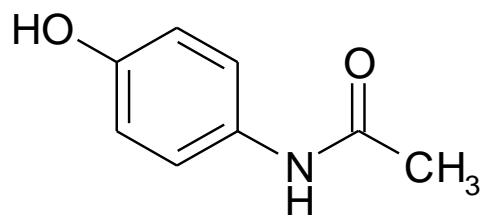


Figure 2.1 Chemical structure of paracetamol

Paracetamol (Figure 2.1) a para-aminophenol derivative, has analgesic and antipyretic properties and weak anti-inflammatory activity. It is given orally or as a rectal suppository for mild to moderate pain and for fever. It may also be given by intravenous infusion for the short-term treatment of moderate pain, particularly after surgery, and of fever. Paracetamol is often the analgesic or antipyretic of choice, especially in the elderly and in patients in whom salicylates or other NSAIDs (non steroidal anti-inflammatory drugs) are contra-indicated. For example, asthmatics, patients with a history of peptic ulcer, and children (Brayfield 2013). Potential advantages of paracetamol over other NSAIDs are a much lower incidence of commonly encountered gastro-intestinal and renal side effects (Wilson 2000).

Though commonly used to treat fever and pain in children, paracetamol is also recognised by the European Medicines Agency (EMA) as a drug substance for which greater research in paediatrics is required. In particular, research into the 'safety and efficacy in pre-terms' and 'the efficacy and safety of a loading dose' is identified as being required.

Paracetamol is widely available in a range of formulations including suspensions, tablets, and melt formulations. The usual oral and rectal dose is 0.5 to 1 g every 4 to 6 hrs up to a maximum of 4 g daily in adults (or children over 12 years). In the UK, the licensed doses of paracetamol for pain and fever in children, given according to age, are shown in Table 2.2.

Table 2.2 Recommended paracetamol dose ranges according to age (Brayfield 2013).

Route	Age					
	28 to 32 wks	>32 wks	1 to 3 months	3 to 12 months	1 to 5 years	6 to 12 years
Oral	20 mg/kg as a single dose then 10 to 15 mg/kg every 8 to 12 hrs if necessary up to a maximum of 30 mg/kg daily	20 mg/kg as a single dose then 10 to 15 mg/kg every 6 to 8 hrs if necessary up to a maximum of 60 mg/kg daily	30 to 60 mg every 8 hrs	60 to 120 mg	120 to 250 mg	250 to 500 mg
Rectal	20 mg/kg as a single dose then 15 mg/kg every 12 hrs if necessary to a maximum of 30 mg/kg daily	30 mg/kg as a single dose then 20 mg/kg every 8 hrs if necessary to a maximum of 60 mg/kg daily	30 to 60 mg every 8 hrs	60 to 125 mg	125 to 250 mg	250 to 500 mg

These doses may be given every 4 to 6 hrs if necessary up to a maximum of 4 doses in 24 hrs.

Doses by intravenous infusion in children are calculated according to body-weight and shown in Table 2.3. Doses are usually administered over 15 minutes (Brayfield 2013):

Table 2.3 Recommended IV paracetamol dose ranges according to weight (Brayfield 2013).

Route	Weight			
	<10kg	10 to 33kg	33 to 50kg	>50kg
IV	Single doses of 7.5 mg/kg every 4 or more hrs to a maximum of 30 mg/kg daily. IV paracetamol has not been studied in premature neonates	Single doses of 15 mg/kg every 4 or more hrs to a maximum of 60 mg/kg or 2g daily (whichever is less).	Single doses of 15 mg/kg every 4 or more hrs to a maximum of 60 mg/kg or 3g daily (whichever is less).	Adult doses

The recommended doses of paracetamol for children may result in sub-therapeutic blood concentrations, and that an initial loading dose should be given, followed by regular doses up to the recommended maximum daily dose. However, the appropriate maximum daily dose remains controversial, and there is obvious concern given the risks of overdose.

Paracetamol was sourced from GSK and has the physico-chemical properties given in Table 2.4:

Table 2.4 Physico-chemical properties of Paracetamol (El-Obeid and A-Badr 1985)

Attribute	Value
Alternative generic names	Acetaminophen
pKa	9.5
Molecular weight	151.16
Appearance	White, crystalline powder
Odour	Odourless
Colour	White
Taste	Slightly bitter
Melting point	169 to 170.5 °C
Solubility	Sparingly soluble in water (30 to 100 parts solvent for one part soluble by weight) Freely soluble in alcohol (1 to 10 parts solvent for one part soluble by weight) A saturated aqueous solution has a pH of about 6

2.1.1.2 Ranitidine hydrochloride

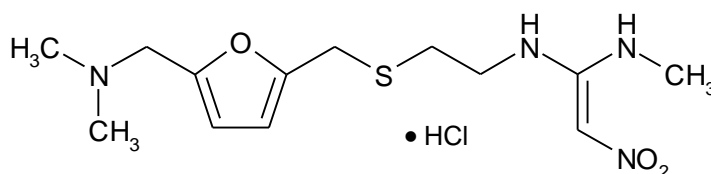


Figure 2.2 Chemical structure of ranitidine hydrochloride

Ranitidine (Figure 2.2) is a histamine H₂-antagonist which may be given orally or parenterally by the intravenous or intramuscular routes to inhibit gastric acid secretion. Ranitidine may be used to treat benign gastric and duodenal ulceration, duodenal ulcers associated with *Helicobacter pylori* infection, gastro-oesophageal

reflux disease, and stress ulceration of the upper gastrointestinal tract (Brayfield 2013). Ranitidine hydrochloride is the most commonly used salt form of ranitidine.

Dosing is dependent upon disease type but in adults oral dosing is generally 150 mg to 300 mg twice a day (Brayfield 2013).

Ranitidine is used in children to heal duodenal and gastric ulcers and to prevent stress ulceration in critically ill patients. It is licensed in children, although indications, age ranges, and doses may vary from country to country (Table 2.5). When given orally, ranitidine is licensed from ages 3 to 11 years and over 30kg body-weight in the UK, and from 1 month to 16 years in the USA.

Table 2.5 Recommended ranitidine dose ranges according to age (Brayfield 2013)

Route	Age				
	Neonates	1 to 6 months	6 months to 3 year	3 to 11 years (UK) 1 month to 16 years (US)	12 to 18 years
Oral	2 mg/kg three times a day (max 3 mg/kg).	1 mg/kg three times a day (max 3 mg/kg).	2 to 4 mg/kg twice a day	4 to 8 mg/kg daily as 2 doses, up to a max of 300 mg daily for 4 to 8 weeks for duodenal and gastric ulcers. 5 to 10 mg/kg daily in 2 doses to a maximum of 600 mg daily for gastro-oesophageal reflux disease.	Adult doses
IV	0.5 to 1 mg/kg every 6 to 8 hrs OR 30 to 60 µg/kg/hrs (up to 3 mg/kg/day)	1 mg/kg (to a max of 50 mg) every 6 to 8 hrs by slow IV injection or intermittent infusion at 25 mg/hrs OR 125 to 250 µg/kg/hrs by infusion.			

Though commonly used to treat reflux oesophagitis, benign gastric and duodenal ulceration, and prophylaxis of duodenal ulceration in children, ranitidine is also recognised by the European Medicines Agency (EMA) as an drug substance for which greater research in paediatrics is required. In particular, the EMA indicate

that research into the ‘the development of an age appropriate alcohol free formulation for use in neonates’ is required which suggests that an age appropriate dosage form containing ranitidine is not currently available.

Ranitidine was sourced from GSK and has the physico-chemical properties given in Table 2.6:

Table 2.6 Physico-chemical properties of ranitidine (Hohnjec et al 1986)

Attribute	Value
Alternative generic names	Ranitidine Hydrochloride
pKa	2.7 and 8.2
Molecular weight	350.9 (HCl) 314.4 (Base)
Salt conversion factor	1 part of free base equivalent to 1.116 of HCl salt
Appearance	White or pale yellow, crystalline powder
Odour	Practically odourless
Colour	White or pale yellow
Taste	Slightly bitter
Melting point	140 °C
Solubility	Freely soluble in water (1 to 10 parts solvent for one part soluble by weight) Sparingly soluble in alcohol (30 to 100 parts solvent for one part soluble by weight) A 1 % solution in water has a pH of 4.5 to 6

2.1.2 Polymers

Hydrophilic polymers are used routinely in pharmaceutical dosage forms as they are safe and well tolerated and offer excellent functionality. Polymers can be used as suspending agents in oral suspensions; as controlled release polymers in oral sustained release matrix tablets and as film formers in film coatings.

Two hydrophilic polymer types were considered for this project; Hypromellose and HydroxyPropylCellulose (HPC). The rationale for selection of these polymers together with a summary of their pharmaceutical application, chemical properties and relevant details of the specific grades of hypromellose and HPC investigated in this project are provided here.

2.1.2.1 Hypromellose

Hypromellose is one of the most commonly researched and frequently utilised polymers in pharmaceutical product development, having many applications including; modified release matrix tablets, binder in granulation processes, viscosity enhancing in suspension products and as a film forming agent in coatings.

Hypromellose is a polypropylene ether of methyl cellulose derived from cotton or wood pulp and contains a basic repeating structure of anhydroglucose units. It is a non-ionic, hydrophilic, swellable polymer with a pH of 5 to 8 (1 %w/v). The chemical structure of hypromellose is shown Figure 2.3.

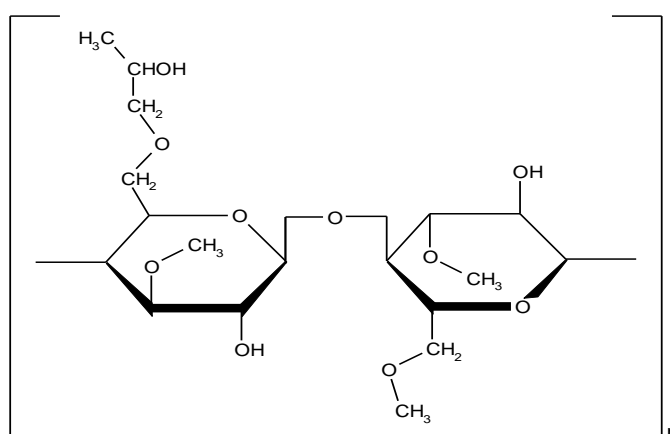


Figure 2.3: Chemical structure of hypromellose

The physicochemical properties of hypromellose are affected by i) its methoxyl group content ii) its hydroxypropoxyl group content and iii) its molecular weight or degree of polymerisation (Dow 2013). A number of grades of hypromellose are available based upon these three characteristics of its chemistry. The United States Pharmacopoeia (USP) recognises 4 different types of hypromellose based upon the methoxyl and hydroxypropoxyl substitution of the molecule. These different types are classified as hypromellose 1828, hypromellose 2208, hypromellose 2906 and hypromellose 2910. The first two digits indicate the percentage number of methoxyl groups and the last two digits indicate the percentage number of hydroxypropoxyl groups e.g. hypromellose 2208 contains 22 % of methoxyl groups and 8 % hydroxypropoxyl groups.

Hypromellose may be further characterised according to the viscosity of a 2 %w/v at 25°C aqueous solution of the particular polymer. The viscosity serves as a measure for the average chain length of the polymer, the degree of polymerisation and

provides a relative indication of the molecular weight (Jumel et al 1995). A range of viscosity grades of hypromellose 2208 and 2910 is available and provides good flexibility for achieving desired function within the dosage form. Some manufacturers are also able to supply ‘fine grade’ material. Due to their finer polymer particle size, the polymer particles are able to hydrate and solubilise more readily (Mitchell and Balwinski 2007). Finer grade material may offer advantages to its function within dosage forms, e.g. a more rapidly hydrating gel layer in matrix tablets.

Hypromellose (Methocel[®]) supplied by The Dow Chemical Company (Midland, Michigan, USA) was used in this investigation. The particular grades of Methocel[®] chosen for this investigation are shown in Table 2.7. The Methocel grades are categorised according to viscosity of the polymers at 2 % aqueous solution (Table 2.7).

Table 2.7 Details of Methocel[®] grades selected (Dow 2013)

Methocel [®] Grade	Viscosity (as 2 % w/w aqueous solution)	Particle Size ¹
E5LV	5cP (4cP to 6cP)	100 % pass through 30 mesh screen; 99 % pass through 40 mesh screen
E15LV	15cP (12cP to 16cP)	
E50LV	50cP (40cP to 60cP)	

Note

1. Particle size of polymer is presented as provided by The Dow Chemical Company. 30 mesh screen is equivalent to 595 µm and 40 mesh is equivalent to 400 µm. 99 % by mass of the polymer will pass through a 400 µm screen.

2.1.2.2 HPC

HPC is a non-ionic, water soluble, partially substituted poly(hydroxypropyl) cellulose ether, available in a range of molecular weights, viscosities and particle sizes. HPC is manufactured by reacting alkali cellulose with propylene oxide at elevated temperatures and pressures. The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each

anhydroglucose monomer unit of the cellulose chain (Fulzele and Hamed 2013). The chemical structure of HPC is shown in Figure 2.4.

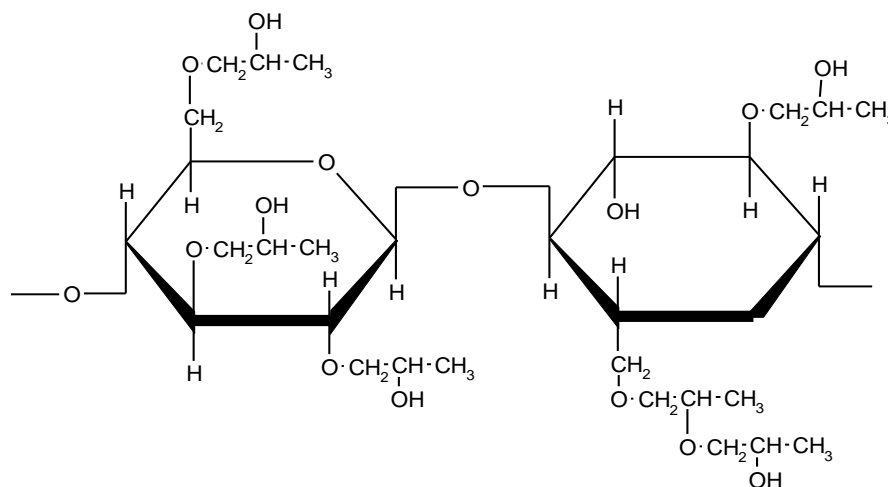


Figure 2.4: Chemical structure of HPC

Similar to hypromellose, the physicochemical properties of HPC are attributable to i) the degree of hydroxypropyl substitution and ii) the molecular weight or degree of polymerisation of the molecule (Hercules 2001). However, unlike hypromellose, HPC is not generally available in a range of different levels of substitution. Only two types of HPC are commercially available; one has a molar substitution of 3.5 to 4.5 of hydroxypropyl groups (approx 60 % substitution), and the other, termed 'low substituted HPC', has a molar substitution of 0.11 to 0.39 of hydroxypropyl groups, and is available from some manufacturers. Low substituted HPC has very different properties to the standard type and is generally used as a disintegrant in solid dosage forms (Kawashima et al 1993).

HPC is available in a range of molecular weights and viscosities, and has various applications based on their characteristics.

Five grades of HPC (Klucel[®]) supplied by Aqualon (a division of Hercules Incorporated, Wilmington, USA) were used in this investigation: MXF Pharm, EXF Pharm, GXF Pharm, JXF Pharm and LF Pharm. The viscosity, molecular weight and particle size of these polymer grades are shown in Table 2.8.

Table 2.8 Klucel grade material properties (Aqualon 2004)

Klucel Grade	Viscosity (cP)/Aqueous Solution (%w/w)	Typical Molecular weight	Particle Size (by weight)
HXF Pharm	1,500 to 3000 1 % w/w	1,150,000	99.9 %<60 Mesh
MXF Pharm	4000 to 6500cP 2 %w/w	850,000	99.9 %<60 Mesh
GXF Pharm	150 to 400cP 2 %w/w	370,000	99.9 %<60 Mesh
JXF Pharm	150 to 400cP 5 %w/w	140,000	99.9 %<60 Mesh
LF Pharm	75 to 150cP 5 %w/w	95,000	99.9 %<20 Mesh
EXF Pharm	300 to 600cP 10 %w/w	80,000	99.9 %<60 Mesh

HPC grades are categorised according to the polymer molecular weight and viscosity is determined varies dependent upon the molecular weight of the polymer. All grades of HPC are available as 'fine grade' (Denoted by an 'X' in the grade name, e.g. EXF) except for the 'L-grade'. The definition of fine grade polymers are based on 99.9 % by mass of the polymer passing through a 60 mesh (equivalent to 250µm). The particle size of LF Pharm is described as 99.9 % by mass of the polymer passing through a 20 mesh (equivalent to 841µm).

2.1.3 Other materials

In addition to the drug substances and polymers considered in this investigation, purified water was also used.

2.1.3.1 Purified water

Purified water meeting USP monograph was sourced from GlaxoSmithKline.

2.2 Analytical Techniques

A range of analytical methods was used throughout the investigation to characterise the spray-dried material, film solutions and films. The analytical methods are summarised here and further details are provided in the relevant Chapters.

2.2.1 Determination of viscosity

The viscosity of the solutions was used in the characterisation of polymers. The viscosity of a polymer solution is a key physical parameter for spray-drying and may affect the characteristics of the spray-dried product produced (Cal and Sollohub 2010; Sollohub and Cal 2010). Viscosity testing was used extensively to characterise the impact of temperature on aqueous solutions of both hypromellose and HPC.

The viscosity of a fluid describes its resistance to flow or movement. It is a measure of the internal friction of a fluid. Therefore, viscosity is often used to describe the flow properties of materials. Friction within a fluid becomes apparent when a layer of fluid is made to move in relation to another. The greater the friction, the greater the amount of force required to cause this movement, which is called shear (Viswanath et al 2007). Viscosity (η) is a function of shear stress (F) and shear rate (S) as shown in Equation 2.1.

$$\eta = F/S \quad \text{(Equation 2.1)}$$

Based on its rheological behaviour, a fluid may be considered 'Newtonian' or Non Newtonian'. Newtonian fluids demonstrate the relationships shown in Figure 2.6 between these three factors.

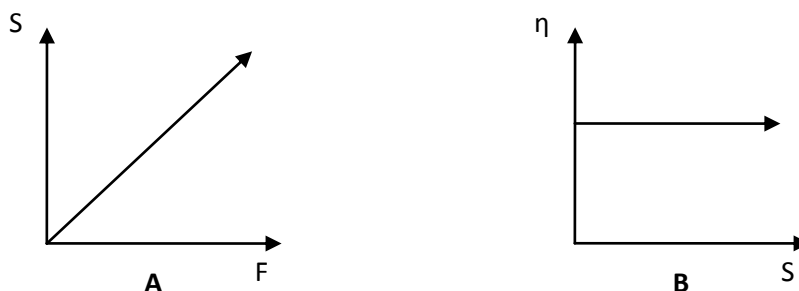


Figure 2.5 The behaviour of Newtonian fluids

An increase in shear stress results in a linear increase in shear rate (as shown in Fig. 2.6A but viscosity remains constant with an increase in shear rate (as shown Fig 2.6B) for Newtonian fluids.

Non-Newtonian fluids do not follow these principles. The relationship between shear stress and shear rate is non-linear and not constant. A change in shear rate will not necessarily result in a similar change in shear stress and consequently the viscosity of a non-Newtonian fluid will change with a change in shear rate.

Depending upon the change to viscosity caused by shear rate or time, there are different types of non-Newtonian fluids (Viswanath et al 2007):

- i) pseudoplastic (decrease in viscosity with an increase in shear rate)
- ii) dilatant (increase in viscosity with an increase in shear rate)
- iii) plastic (behaves as a solid until a specific amount of shear is applied and then shear thins)
- iv) thixotropic (decrease in viscosity at constant shear with increase in time)
- v) rheopectic (increase in viscosity at constant shear with increase in time).

Brookfield viscometers were used to measure polymer viscosity. A RVDV-I viscometer (Brookfield UK) was used to measure polymer solution viscosity (see Chapters 5 and 6) and a LVDV-II viscometer (Brookfield UK) with small sample adaptor was used as described in Chapter 7. More details about the viscometer model and test parameters are found in those Chapters.

2.2.2 Ultraviolet spectrometry

Ultraviolet spectrometry is the measurement and interpretation of ultraviolet radiation absorbed, scattered or emitted by atoms, molecules or other chemical species. Ultraviolet light has a wavelength of 200 nm to 400 nm (Willard et al 1988).

UV transmission was used in this work to characterise the polymer solutions and to investigate the potential formation of liquid crystals in aqueous HPC solutions (Maugey and Navard 2002). UV absorbance was used in this work to measure drug

content and dissolution rate of drug for polymer films produced and characterised in Chapter 8.

UV transmission analysis is a form of UV spectroscopy measuring the amount of light at a particular wavelength that is transmitted through a sample and is the opposite to UV absorption spectroscopy that measures the amount of light absorbed of a particular wavelength by a particular species within a sample (Willard et al 1988).

The radiant power of a beam of radiation is proportional to the number of photons per unit time. Absorbance occurs when a photon collides with a molecule and raises that molecule to its excited state. The number of photon collisions with a molecule will depend upon the wavelength selected. The number of photon collisions will be increased by increasing the path length that the light beam passes through the sample or the concentration of the absorbing species. Increasing the beam power will also increase the number of photon collisions. Absorbance may be defined by the Beer-Lambert law (Equation 2.2).

$$A = \log P_0/P = abc \quad \text{(Equation 2.2)}$$

Where:

A is absorbance

P_0 is radiant power at source

P is radiant power of the transmitted radiation that emerges from absorbing medium (unabsorbed power)

a is proportionality constant (absorptivity)

b is path length

C is concentration of test solution

The absorbance (A) is proportional to the concentration (C) of the solution and the length (b) of the layer of solution through which the light passes. Calculated on the basis that b is 1 cm and c is 1 % w/v solution, the absorbance is called specific absorbance ($A^{1\%}_{1\text{cm}}$)

Per-cent transmission, T , is defined by Equation 2.3

$$\%T = P/P_0 \times 100 \quad (\text{Equation 2.3})$$

Meaning that absorbance is the inverse log of transmission (Equation 2.4).

$$A = \log 1/T = -\log T \quad (\text{Equation 2.4})$$

Application of UV transmission and absorbance is provided in Chapter 4.

2.2.3 Hot stage microscopy

Hot-stage microscopy combines microscopy and thermal analysis to enable the characterization of the physical properties of materials as a function of temperature (Vitez et al 1998). More recently, hot stage microscopes have been integrated with high resolution cameras, data capture software and image manipulation software to enable thermal images to be reliably collected over time as the sample is heated at a pre-determined rate or for a pre-determined period of time. The use of data capture software prevents the need for the analyst to constantly observe the sample for extended periods of time. Sample holders may be programmed to control temperature changes over time so that carefully prepared programmes may be developed to monitor changes to the sample over a predetermined range of temperatures or at a predetermined rate in change of temperature (Vitez et al 1998). Temperature cycling may also be considered if applicable.

A schematic diagram of a typical hot stage microscope sample holder is shown in Figure 2.7. The diagram shows a silver heating block element held between the stage lid and base plate. Both the stage lid and base plate have a window to allow light to pass through the sample. A sample is prepared as normal using a glass cover slip and inserted above the silver heating block element. All other aspects of the microscope are comparable to a conventional light microscope e.g. condenser lens and objective lens.

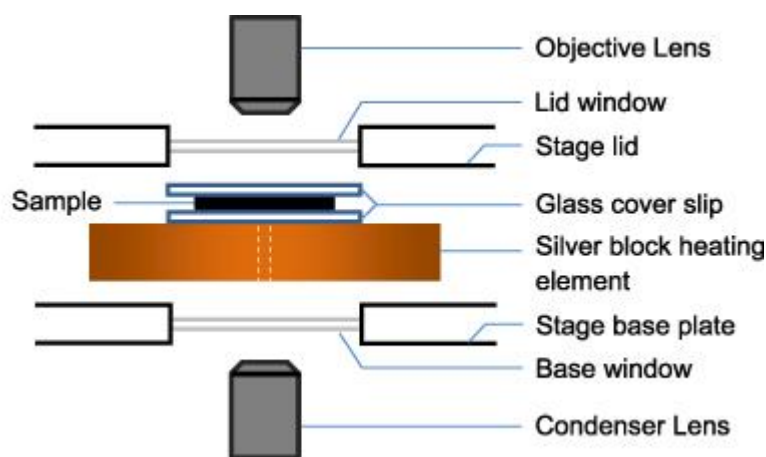


Figure 2.7 Schematic diagram of hot stage microscope sample holder (Mirjalili et al 2012)

Hot-stage microscopy is used in a variety of ways to confirm transitions observed using other techniques. Hot-stage microscopy may be used for the solid-state characterization of bulk drugs, evaluation of crystal forms and hydrates, and other physico-chemical properties (Shur and Price 2012).

Hot stage microscopy was used in this work to complement UV transmission to monitor the potential liquid crystal formation in aqueous polymer solutions. A hot stage microscope integrated with a high-resolution camera, real time video capability and computer software was used to observe changes in aqueous polymer solutions at increasing temperature. (Vitez et al 1998). Details of the hot stage microscopy method used in the work may be found in Chapter 7.

2.2.4 Dissolution testing

Dissolution testing is a commonly applied characterisation technique for oral dosage forms. The principle aim of the technique is to determine the dissolution rate of the active substance from the dosage form. A number of dissolution techniques are described by pharmacopoeia such as the British Pharmacopoeia, the US Pharmacopoeia and the European Pharmacopoeia. These pharmacopoeias specify the apparatus requirements including dimensions of each of the techniques (British Pharmacopoeia 2013; United States Pharmacopoeia 35/National Formulary 30; and European Pharmacopoeia 7th edition). The US Pharmacopoeia for example describes four types of dissolution apparatus i) baskets (USP I); paddles (USP II); reciprocating

cylinder (USPIII) and flow-through cell (USPIV) (United States Pharmacopeia 34/National Formulary Chapter 711, General Dissolution).

Dissolution using paddles is the most commonly used technique for immediate release dosage forms. Dissolution using USP II (paddles) with UV absorbance is used (see Chapter 9) in this investigation to measure paracetamol release from the polymer films.

Selection of the dissolution media is critical to determining the *in-vivo* relevance of the dissolution data obtained. For example, most immediate release solid oral dosage forms will be presented intact to the stomach following administration so a dissolution medium representative of the stomach contents provides greater insight to the impact of the stomach contents on the dissolution of the dosage form (Juenemann et al 2011, Wagner et al 2012). For this investigation purified water was selected as the dissolution media. Further details of the dissolution technique applied to characterise the polymer films is provided in Chapter 8.

2.2.5 Disintegration testing

Disintegration testing is a commonly applied characterisation technique for oral dosage forms. The principle aim of the technique is to determine the time taken for the dosage form to disintegrate. Pharmacopoeia such as the British Pharmacopoeia, the US Pharmacopeia and the European Pharmacopoeia, describe disintegration methods and apparatus applicable to the testing of tablets and capsules but they do not describe a method or apparatus specific for oral films (British Pharmacopoeia 2013; United States Pharmacopeia 35/National Formulary 30; and European Pharmacopoeia 7th edition).

A disintegration technique described by Chen 2006 was used in this investigation and details are provided in Chapter 8.

Dissolution testing and disintegration testing techniques are often used together to predict *in-vivo* behaviour of the dosage form. Disintegration testing indicates how quickly the dosage form will be reduced to component particles *in-vivo* thus enabling the drug substances to be dissolved in the dissolution media (gastro intestinal fluid). In this investigation, the disintegration technique employed is

designed to mimic disintegration of the polymer film on the tongue in the mouth cavity. The dissolution technique is designed to predict how quickly the drug would dissolve in the mouth following disintegration of the film.

2.2.6 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy is an alternative microscopic technique to light microscopy. Scanning Electron Microscopy offers a much greater depth of field compared with light microscopy and therefore is able to generate three-dimensional images. Scanning Electron Microscopy is also able to measure smaller particles compared with light microscopy (Egerton 2005)

Scanning Electron Microscopy uses a focused beam of high-energy electrons to generate a variety of signals at the surface of solid specimens. The signals that derive from electron sample interactions reveal information about the sample including particle shape and topography. Sizes ranging from approximately 5 microns to 1 cm in width can be imaged using conventional SEM techniques. Magnifications from 20x to 30,000x with spatial resolution of 50 to 100 μm are possible (McMullan 1995).

The principle of SEM is that a significant amount of the kinetic energy carried by the accelerated electrons is dissipated as a variety of signals produced by electron-sample interactions when the incident electrons are decelerated in the solid sample. These signals include secondary electrons that produce SEM images but may also include backscattered electrons, diffracted back scattered electrons, photons, visible light and heat. Secondary electrons and backscattered electrons are commonly used for imaging samples; secondary electrons showing morphology and topography and back scattered electrons for illustrating contrast in composition in multiphase sample (Egerton 2005). SEM analysis is typically 'non destructive' so it is possible to analyse the same materials repeatedly (Wells and Joy 2006).

Scanning Electron Microscopy is routinely used to generate high resolution images of shapes of objects; to show spatial variations in chemical composition; and to identify phases based on qualitative chemical analysis and crystalline structure (Clarke and Eberhardt 2002).

Though SEM has vast application in the study of solid materials, the technique does have limitations. For example, the samples must be solid and fit into the microscope chamber. Typically the maximum size is 10cm x 0.4cm and the sample must be stable under vacuum (Egerton 2005).

Details of the scanning electron microscope used in these investigations may be found in Chapter 4.

2.2.7 Differential Scanning Calorimetry (DSC)

DSC measures the amount of energy required to keep a sample at the same temperature as a reference. It measures the enthalpy of transition. When there is no physical or chemical change within the sample there is no change in temperature of the sample nor need to input energy to maintain an isotherm. When a phase change occurs latent heat suppresses the temperature increase or decrease and the change in temperature or isothermal energy required is determined (Wendlandt 1986). DSC can be used to measure a variety of physical changes including, changes in crystalline state and determining melting point or glass transition temperature (Griffin and Laye 1992)

DSC was used in this investigation to determine if polymer films have a glass transition temperature. Details of the DSC method employed may be found in Chapter 4.

2.2.8 Thermal Gravimetric Analysis (TGA)

TGA can be used to measure loss in weight as a function of time and under isothermal conditions where transitions involve dehydration or decomposition (Honda 1911). The rate of such thermally induced changes is a function of molecular structure. Changes in weight result from physical and chemical bonds forming and breaking at elevated temperatures. TGA data can be used to characterise materials as well as investigating the thermodynamics and kinetics of the reactions and transitions that result from the application of heat to the sample (Dollimore 1992).

TGA may be used in isolation or with differential thermal analysis as all weight change processes absorb or release energy (so are measurable by DSC) but not all

energy change processes are accompanied by changes in weight (Charsley and Warrington 1992).

TGA was used in this investigation to complement the DSC analysis (2.2.7) and to gain an insight into the stability of the polymer films produced. Details of the TGA method and apparatus used may be found in Chapter 8.

3 PREPARATION OF POLYMER SOLUTIONS FOR CHARACTERISATION, SPRAY-DRYING AND FILM FORMATION

Polymer solution preparation is fundamental to this investigation as it is required for all aspects of this thesis. Spray drying of polymer solutions is considered in Chapter 4 to investigate the potential to co-process hypromellose with drug substance; the impact of temperature on polymer solution characteristics is considered in Chapters 5, 6 and 7; and film formation from a polymer solution is investigated in Chapter 9 to prepare an age appropriate oral dosage form.

This Chapter provides preparation details for aqueous solutions of hypromellose or HPC; with or without paracetamol or ranitidine.

3.1 Preparation of Polymer Solutions

Aqueous polymer solutions were used throughout this investigation. Aqueous solutions containing i) hypromellose E5, E15 and E50LV were considered for spray-drying; ii) HPC grades EXF, GXF, JXF, LXF and MXF were considered to understand the impact of temperature on the polymer solution and iii) HPC EXF was considered for film formation and characterisation. The method of preparation of aqueous polymer solutions using hypromellose and HPC is described below.

3.1.1 Preparation of hypromellose solutions

Formulation details for each aqueous hypromellose solution prepared may be found in Chapters 4 and 5.

Aqueous solutions of hypromellose were prepared by slowly heating the required quantity of purified water to 75°C to 85°C in a tared glass beaker using a hot plate (IKA magnetic stirrer and hotplate, Germany) with calibrated temperature probe thermostat (IKA, Germany) whilst gently stirring using a magnetic bar (Fisher, UK). Once within the required temperature range the required quantity of hypromellose was dispensed and slowly added to the water whilst continually stirring. It was

important not to add the hypromellose too quickly as the polymer tended to hydrate and swell, becoming difficult to dissolve. After dispersing the hypromellose powder at 75°C to 85 °C, the dispersion was allowed to cool to ambient temperature with constant stirring using the magnetic stirrer. The hypromellose hydrated and dissolved as the solution cooled. The dispersion was mixed at room temperature until all hypromellose had fully dissolved. Where necessary, the hypromellose solution was made to weight with purified water. Each aqueous hypromellose solution was transferred to a clear glass bottle ready for use or stored at ambient temperature.

3.1.2 Preparation of HPC solutions

Formulation details for each aqueous HPC solution prepared may be found in Chapters 6, 7 and 8.

HPC solutions were prepared using a similar method to that used for hypromellose however, it was not necessary to heat the purified water prior to dispersion of the HPC. The required quantity of the appropriate grade of HPC was dispensed and slowly added to the required quantity of purified water in a tared glass beaker at ambient temperature whilst continually stirring using a magnetic stirrer without heating (IKA magnetic stirrer and hotplate, Germany). The HPC dispersion was mixed until the HPC was completely dissolved and a clear solution achieved. Larger molecular weight grades of HPC took longer to dissolve and in some cases it was necessary to leave the solution mixing overnight to fully solubilise the HPC. Where necessary, the HPC solution was made to weight with purified water. Each aqueous HPC solution was transferred to a clear glass bottle ready for use or stored at ambient temperature.

3.2 Preparation of Drug Polymer Solutions/Dispersions

Drug polymer solutions or dispersions were prepared using hypromellose or HPC and ranitidine or paracetamol. Drug polymer solutions or dispersions are used throughout this investigation. Formulation details may be found in the relevant Chapters.

3.2.1 Preparation of hypromellose drug solutions/dispersions

Drug polymer solutions or dispersions using hypromellose were prepared using a similar method to that described in Section 3.1.1. The hypromellose was dissolved in half of the required quantity of water. After dispersing the hypromellose at 75°C to 85°C and solubilising whilst cooling to ambient temperature as previously described, the drug solution/dispersion was prepared. To the other half of the required quantity of water, the paracetamol or ranitidine powder was slowly added at ambient temperature and dispersed using the magnetic stirrer (IKA, Germany). After dispersing the paracetamol or ranitidine, the dispersion was added to the hypromellose solution and mixed using a high shear Silverson L4RT mixer (Silverson, UK) with homogeniser head fitted at 1800rpm (1600 to 2000rpm). Care was taken to avoid excessive entrapment of air during homogenisation. The dispersion was homogenised until a clear solution or a smooth, lump-free homogeneous dispersion (for higher concentrations of paracetamol) formed. A stainless steel spatula was used to examine the dispersion for lumps and consistency. The drug polymer dispersion or solution was made to weight with purified water. The aqueous drug polymer hypromellose solution/dispersion was transferred to a clear glass bottle ready for use or stored at ambient temperature.

3.2.2 Preparation of HPC drug solutions/dispersions

Drug polymer solutions or dispersions using hypromellose were prepared using a similar method to that described in Section 3.1.2 above. The HPC was dissolved in half of the required quantity of water. After solubilising the HPC in half of the required quantity of purified water the paracetamol or ranitidine powder was added (at ambient temperature) to the remaining quantity required of purified water and dispersed or dissolved using the magnetic stirrer (IKA, Germany). After

dispersing the paracetamol or ranitidine, the dispersion or solution was added to the HPC solution and mixed using a high shear Silverson mixer L4RT (Silverson, UK) at 1800 rpm (1600 to 2000 rpm) with homogeniser head fitted. Care was taken to avoid excessive entrapment of air during homogenisation. The dispersion was homogenised until a clear solution or a smooth, lump-free homogeneous dispersion (for higher concentrations of paracetamol) formed. A stainless steel spatula was used to examine the dispersion for lumps and consistency. The drug polymer solution/dispersion was made to weight with purified water. The aqueous drug polymer HPC solution/dispersion was transferred to a clear glass bottle ready for use or stored at ambient temperature.

4 FEASIBILITY OF SPRAY-DRYING AQUEOUS HYPROMELLOSE SOLUTIONS

4.1 Introduction

As discussed in Chapter 1, the use of excipients, particularly in paediatric patients should be minimised. The draft EMA guideline 'Guideline on pharmaceutical development of medicines for paediatric use' (EMA 2013) requires the use of excipients in pediatric patients to be justified and minimized to avoid safety concerns that may be associated with the excipient. Reducing the level of excipients will also help minimize the size of the dosage form which is particularly important for oral solid dosage forms.

Chapter 5 of this investigation considers the potential to co-process an drug substance (paracetamol), with a hydrophilic polymer (hypromellose) by spray-drying to investigate if the co-processed material offers advantages over a binary mix of the two materials. This Chapter considers the feasibility of spray-drying aqueous solutions of hypromellose before considering the addition of the drug substance as discussed in Chapter 5.

As described by Paudel et al (2012), hypromellose is commonly used to stabilise suspensions for spray-drying but very little work has been conducted to investigate the aqueous spray-drying of hypromellose to produce spray-dried hypromellose powder. Alanazi et al (2006) described a solvent spray-drying technique using indomethacin and hypromellose. The applicability of the processing parameters determined will be considered here, for an aqueous based system.

Within this Chapter the preparation of polymer solutions; the influence of temperature on polymer solution viscosity, the development of a suitable spray-drying process and the comparison of spray-dried and non spray-dried materials are considered.

4.2 Materials and Methods

The following hypromellose, Methocel® grades were used for this investigation:

- E5LV Premium
- E15LV Premium
- E50LV Premium

Details associated with these polymer grades may be found in Chapter 1. In this investigation a range of aqueous polymer concentrations (5 %w/w to 30 %w/w) were considered. Table 4.1 shows the polymer solutions considered in this Chapter and the respective formula of each solution based on polymer concentration is provided in Table 4.2.

Table 4.1 Aqueous hypromellose solutions considered

Polymer Grade	Polymer Concentration (%w/w)
Methocel® E5LV	5
	20
	30
Methocel® E15LV	5
	30
Methocel® E50LV	5
	30

Table 4.2 Quantitative composition of aqueous hypromellose solutions (per 500g of solution)

	Polymer Concentration							
	5 %w/w		10 %w/w		20 %w/w		30 %w/w	
Excipient	Content (% w/w)	Quantity (g)	Content (% w/w)	Quantity (g)	Content (% w/w)	Quantity (g)	Content (% w/w)	Quantity (g)
Polymer	5.0	25.0	10.0	50.0	20.0	100.0	30.0	150.0
Purified Water	95.0	475.0	90.0	450.0	80.0	400.0	70.0	350.0
Total	100.0	500.0	100.0	500.0	100.0	500.0	100.0	500.0

4.2.1 Preparation of aqueous hypromellose solutions

Details of the method used to prepare the aqueous hypromellose solutions are provided in Section 3.1.1.

4.2.2 Physical appearance of aqueous hypromellose solutions

Once prepared, the solutions were examined to determine their flow properties by gently stirring the sample using a spatula to determine how easily the solution could be agitated. If the solution was difficult to stir using the spatula, i.e. 'gel-like', it was considered to have poor flow and therefore would not be initially considered for spray-drying. High viscosity polymer solutions would only be considered for spray-drying if similar low viscosity solutions could be successfully spray-dried or if an increase in temperature of the polymer solutions reduced polymer solution viscosity.

The flow of the solution determined by stirring using a spatula was described as follows:

- 'Good' – the solution could be easily agitated/stirred using a spatula.
- 'Fair' – the solution could be agitated but the surface of the solution took slightly longer to settle following agitation.
- 'Poor' – it was very difficult to agitate/stir the solution.

4.2.3 Viscosity determination of aqueous hypromellose solutions

The theoretical aspects associated with the measurement of viscosity are described in Section 2.2.1.

The viscosity of a spray-drying solution is critical to the spray-drying process. High viscosity solutions may be difficult to transfer to the atomising nozzle and consequently spray rates may be very slow, ultimately affecting the spray-dried material produced (Maltesen et al 2008).

The viscosities of those solutions shown in Table 4.1 were measured to assess their suitability for spray-drying. Based on visual observations highly viscous solutions were not considered for spray-drying. Solutions which formed a gel were eliminated

from further investigation as these were considered unsuitable for spray-drying. Solutions which did not form a gel were considered for spray-drying. For the purposes of this work a gel is defined as a solution of hypromellose which forms a semi-solid.

The viscosity of each solution selected for spray-drying was determined using a RVDT I Viscometer (Brookfield, UK). Spindle speed and spindle number were selected as appropriate (refer to Table 4.5). 650mL of polymer solution measured using an 800mL measuring cylinder, was used per viscosity determination in a 1L beaker. Viscosity was initially determined at ambient temperature with the viscometer guard leg in place to aid reproducible location of the spindle in the test solution for each test conducted and to ensure that the spindle height was reproducible between samples. The viscosity reading in % torque was recorded every minute for 5 minutes, timed using a calibrated stop watch, and the mean viscosity in centipoises over 5 minutes was calculated after applying the appropriate 'viscosity factor' according to Brookfield literature (Brookfield 2005).

The impact of temperature on viscosity was also determined. A 2L glass beaker was filled with 500 mL of purified water and heated to the target temperature using an IKA magnetic stirrer/hotplate (IKA, Germany). The test temperature was controlled to $\pm 5^{\circ}\text{C}$ during testing using a IKA calibrated thermostat temperature probe (IKA, Germany). The test solution was placed in a 1 L beaker and the beaker suspended in the heated water using a clamp during viscosity testing. This method prevented significant and localised heating of the test solution caused by the hot plate. Viscosity was determined at ambient temperature, 40°C ($\pm 5^{\circ}\text{C}$) and 60°C ($\pm 5^{\circ}\text{C}$). Once the test solution had reached the required temperature the viscosity was determined every minute for five mins. Viscosity of each solution was measured in duplicate and the mean of ten viscosity measurements was determined.

4.2.4 Spray-drying of aqueous hypromellose solutions

Spray-drying was used to investigate the influence of co-processing the cellulosic polymer, hypromellose with the drug substance paracetamol.

4.2.4.1 Process overview

Spray-drying is a processing technique which dates back to the 19th century and is used today in a number of industries including the food and pharmaceutical industry. Typical spray-dried products are dry milk powder, detergents, and dyes. Spray-drying can also be used to preserve food (Masters 1991). Within the pharmaceutical industry, the technique may be used to co-process two or more materials to optimise their combined functionality, to change the physical properties of a powder to improve flow or change the particle size to improve bioavailability (Okuyama et al 2006, Alanazi et al 2006).

The basic principle of the technique is to remove the solvent from a liquid feed e.g. suspension, solution, dispersion or emulsion by spraying the feed into a hot drying medium. The dried product usually takes the form of powder or granules and its properties may be controlled by the processing parameters used (Shabde 2006).

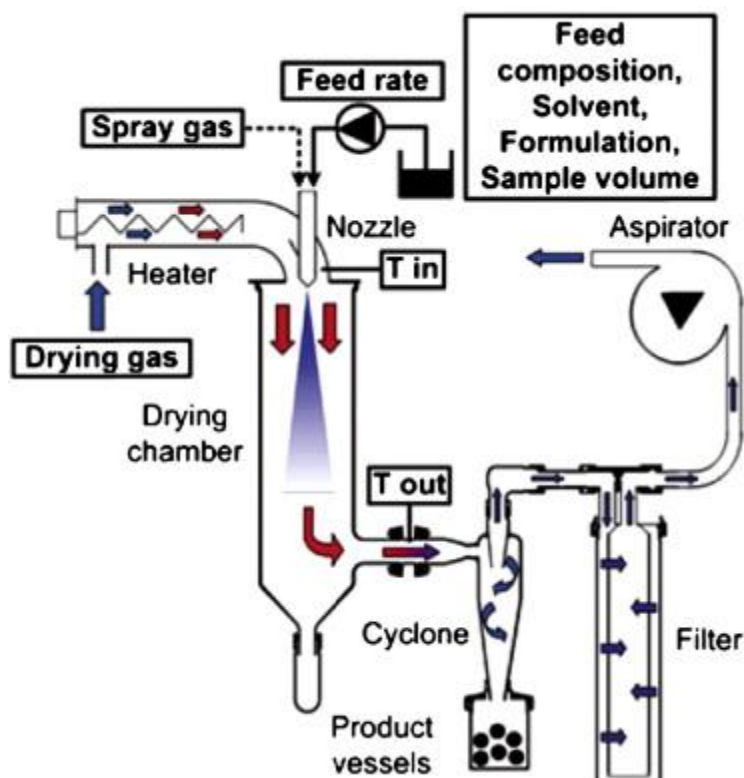


Figure 4.1 Principle components of a spray-drying process (after: Aghbashlo et al 2012).

Spray-drying involves evaporation of moisture from an atomised feed by mixing the spray and the drying medium. Typically, the drying medium is air. Drying continues until the desired moisture content of the particles is reached and they are then separated from the air (Aghbashlo et al 2012).

A spray-drying process typically consists of four sequential processes:

1. Atomisation of the liquid feed,
2. The mixing of the atomised liquid feed with the drying air resulting in heating and subsequent mass transfer,
3. The constant flow of heated air through the system, and
4. The drying of the spray and the separation of the product from the air

A typical fluid bed drier comprises a feed system which is used to transfer the liquid product into the drying chamber via an atomising nozzle (Figure 4.1). A heater heats the intake air and passes it into the drying chamber where the product is dried. A cyclone separates the product from the air flow and the spray-dried material is captured in a container. The air may then be recycled or exhausted depending upon the design of the spray drier. A temperature sensor at the inlet and outlet is used to maintain the drying conditions (Shabde 2006, Maltesen et al 2008).

The critical process parameters associated with spray-drying are a) the solids content of the solution (or liquid feed), b) the feed rate, c) the air volume, d) the atomising air pressure, and e) the inlet temperature. The humidity of the inlet air is also critical but may not be able to be controlled (Tewa-Tagne et al 2007, Vehring 2007).

These process parameters interact to affect the process and/or physical properties of the spray-dried material. For example, an increase in solids content of the spray solution could result in an increase in particle size of the spray-dried material and also increase the rate of production of spray-dried material. Feed rate also influences the rate of production but it also influences particle size; a faster feed rate usually results in smaller particles (Cal and Solluhub 2010). As the feed rate becomes faster, more energy is required to dry the particles and consequently the

outlet temperature decreases and the residual moisture content increases (Maltesen et al 2008).

The inlet temperature is generally regarded as that of the heated drying air (Paudel et al 2013). The moisture gradient between the wet surface of the atomised droplet and the dry air leads to evaporation at temperatures that may be below the boiling point of water (Vehrsing 2007). The outlet temperature is generally regarded as the temperature of the air with the solid particles just prior to the cyclone (Paudel et al 2013). The outlet temperature in most cases is likely to be the maximum product temperature due to the heat, mass transfer and low humidity at this particular stage of the spray-drying process. A minimal temperature difference between inlet and outlet temperature results in a very small quantity of residual moisture in the spray-dried material. An increase in this temperature difference increases the residual moisture content of the spray-dried material (Vehrsing 2007).

The air volume used during spray-drying determines the amount of energy available for vapourisation and as a consequence has a significant effect on the drying process (Cal and Sollohub 2010). A high air volume results in a high degree of separation in the cyclone improving yield, whilst a low air volume results in the spray-dried material having a low residual moisture content which may influence the physical properties of the spray-dried material (Billon et al 2000).

4.2.4.2 Development of a spray-drying process for aqueous solutions of hypromellose

Aqueous solutions of hypromellose E5LV and E50LV were spray-dried using a Labplant SD-05 Spray Drier (Labplant UK) using the process parameters given in Table 4.3, fitted with a 0.5 mm spray nozzle. Similar parameters were previously used by Alanazi et al (2006) who attempted to spray dry hypromellose and were applied to this investigation. Each solution (1000 mL) was spray-dried.

Table 4.3 Spray-drying process parameters used

Process Parameter	Setting
Product temperature	Ambient (°C)
Air Flow Rate	50 m ³ /hrs
Inlet temperature	160 °C
Pump rate	7 mL/min (max)
Exhaust Temperature	90°C to 110 °C
Nozzle	0.5 mm
Atomising air	1 bar

Figure 4.1 demonstrates aspects of the spray-drying process that these parameters refer to. The 'Product Temperature' is the temperature of the hypromellose solution immediately prior to spray-drying; 'Air Flow Rate' is the set point for the drying air volume; 'Inlet temperature' is the temperature of the drying air; 'Pump rate' is the spray rate at which the hypromellose solution is provided to the atomiser; 'Exhaust Temperature' is the temperature range of the air leaving the spraying chamber and is controlled by modifying the inlet temperature or air flow rate; the 'nozzle' is the diameter of the spray nozzle used; and the 'atomising air' is the pressure used to generate atomisation of the hypromellose solution.

Spray-dried hypromellose was obtained from the collection vessel and characterised as described in section 4.2.4.

4.2.5 Characterisation of spray-dried hypromellose

Spray-dried hypromellose was characterised using SEM and compared with non spray-dried hypromellose. The viscosity of polymer solutions prepared using spray-dried and non spray-dried hypromellose was also compared to determine if the functional attributes of the hypromellose had been affected by the spray-drying process.

4.2.5.1 Physical appearance by Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) at x50, x100, x500, x1000 and x2000 magnification using a Philips XL30 SEM (Philips, Netherlands) was used to compare the physical appearance of spray-dried hypromellose and non spray-dried

hypromellose. Samples of non spray-dried and spray-dried hypromellose powder were applied by brush to an adhesive carbon disk on a specimen stub. Excess powder was removed by a compressed air jet. The samples were sputter-coated with platinum for 45s (Agar Scientific Coater US), then imaged.

The particle size and shape of spray-dried and non spray-dried material were compared at each magnification.

4.2.5.2 Viscosity testing

Aqueous polymer solutions of spray-dried and non spray-dried hypromellose were prepared as described in Section 3.2.1. Aqueous solutions of polymer concentrations of 0.5 %w/w and 5 %w/w concentrations were prepared. The viscosities of these solutions were measured as described in Section 3.2.3 and compared to determine if there was any change in functionality between spray-dried and non spray-dried polymer. The effect of temperature on viscosity was also considered by measuring viscosity at ambient, 40°C (± 5 °C) and 60°C (± 5 °C).

4.3 Results and Discussion

4.3.1 Preparation and physical appearance of aqueous hypromellose solutions

Table 4.4 shows a description of flow for each hypromellose solution. These polymer solutions were deselected based on the potential for the feed rate during spray-drying to be restricted by the viscosity of the solution and hence the appearance of the spray-dried material produced to be directly associated with the polymer solution viscosity.

Table 4.4 Assessment of spray-drying solution suitability based on polymer grades and polymer concentrations

Polymer Grade	Polymer Concentration (%w/w)	Observations
Methocel® E5LV	5	Solution has good flow so was considered for spray-drying.
	20	Very viscous but solution has fair flow so was considered for spray-drying.
	30	Very viscous. Solution has poor flow so was not considered for spray-drying.
Methocel® E15LV	5	Solution has fair flow and was considered for spray-drying.
	30	Very viscous. Solution has poor flow so was not considered for spray-drying.
Methocel® E50LV	5	Solution has fair flow and was considered for spray-drying.
	30	Very viscous. Solution has poor flow so was not considered for spray-drying.
Methocel® K100LV	10	Very viscous. Solution has poor flow so was not considered for spray-drying.

Note

Shading indicates which of the polymers were considered unsuitable for spray-drying in this investigation.

Aqueous solutions containing polymer concentrations of 30 %w/w hypromellose were very viscous for all polymer grades selected. These solutions could only be

considered for spray-drying if their viscosity could be reduced by increasing the temperature of the solution.

This initial visual assessment to determine flow, indicated that polymer loading was critical to the feasibility of spray-drying hypromellose solutions. Furthermore, it also indicated that only low molecular weight grades of hypromellose could be considered for spray-drying at an appropriate concentration (>5 %w/w).

4.3.2 Viscosity determination of aqueous hypromellose solutions

Viscosity data were obtained for those formulations considered suitable for spray-drying

Table 4.5 – Viscosity method parameters and mean viscosity data

Polymer Grade and Concentration	Product Temperature		
	25 °C	40 °C	60 °C
5 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	66.0	49.6	75.0
Standard Deviation (±)	0.0	0.5	2.1
Sample B			
Mean Viscosity (cP)	67.0	50.0	75.0
Standard Deviation (±)	0.0	0.0	0.0
Method Details			
Spindle Number	1	1	1
Speed	100rpm	100rpm	100rpm
20 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	187.1	135.0	1297.0
Standard Deviation (±)	1.4	4.3	120.3
Sample B			
Mean Viscosity (cP)	188.3	136.6	1204.4
Standard Deviation (±)	1.0	1.2	56.8
Method Details			
Spindle Number	2	2	2
Speed	10rpm	100rpm	2.5rpm
5 % HPMC E15LV			
Sample A			
Mean Viscosity (cP)	221.2	118.6	263.4
Standard Deviation (±)	6.4	1.0	8.0
Sample B			
Mean Viscosity (cP)	224.0	117.6	257.2
Standard Deviation (±)	3.6	1.5	1.6
Method Details			
Spindle Number	1	1	1
Speed	20rpm	20rpm	20rpm
5 % HPMC E50LV			
Sample A			
Mean Viscosity (cP)	892.8	433.6	679.2
Standard Deviation (±)	1.6	6.1	22.6
Sample B			
Mean Viscosity (cP)	888.8	435.2	680.4
Standard Deviation (±)	1.6	2.0	17.5
Method Details			
Spindle Number	1	1	1
Speed	5rpm	5rpm	5rpm

Note:

Mean values are determined from 5 viscosity readings for each test condition.

As described in Section 4.2.2, viscosity of polymer solution was determined at ambient temperature, 40°C and 60 °C. If temperature could be used as a potential means to reduce the viscosity of the hypromellose solutions, spray-drying solutions could be held at an appropriate temperature during spray-drying using a water bath or jacketed vessel with thermostat control to enable the spray-drying of solutions either having higher polymer concentration or containing higher molecular weight polymer.

The viscosity data and viscosity method parameters used are shown in Table 4.5. The viscosity data are illustrated in Figures 4.2a, 4.2b, 4.2c and 4.2d.

It was noted during the viscosity testing that at 60°C all hypromellose solutions tested became cloudy. This is due to the cloudpoint of the hypromellose being reached as described by Sarker (1979). Sarker described the cloudpoint as the temperature at which the hypromellose polymer molecules precipitate out of solution. Cloud point is the temperature at which the light transmission of a gel is reduced by 50 % of the initial value. Cloudpoint is often referred to as the lowest temperature at which turbidity of solution first occurs (Klug 1971, Fagan et al 1989).

Figures 4.2a, 4.2b, 4.2c and 4.2d show the mean viscosity measurements (n=5) determined for solutions containing 5 % w/w E5, E15 or E50LV and 20 %w/w E5LV at ambient, 40°C and 60°C (Data for ‘Solution A’ is plotted. Data for ‘Solution B’ follows similar trends as shown in table 4.5).

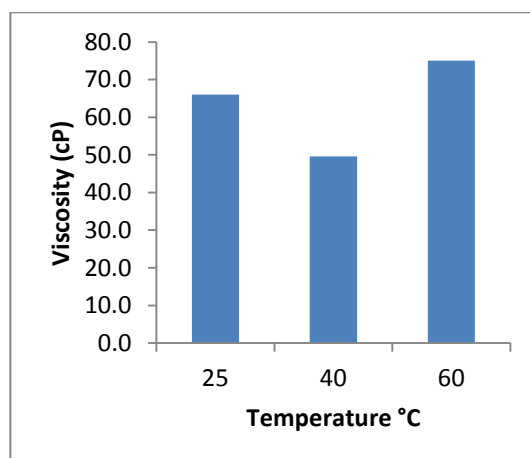


Figure 4.2a The effect of temperature on the viscosity of 5 %w/w hypromellose E5LV solutions

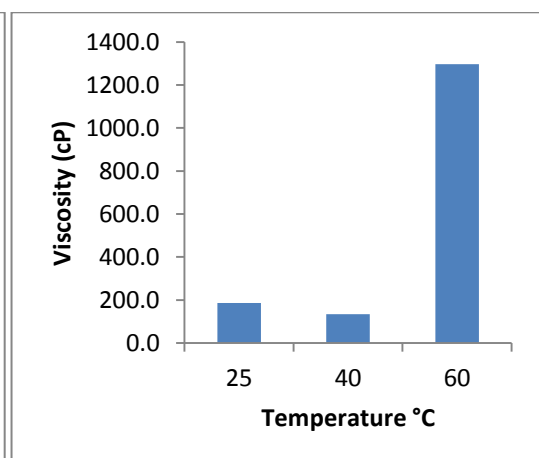


Figure 4.2b The effect of temperature on the viscosity of 20 %w/w hypromellose E5LV solutions

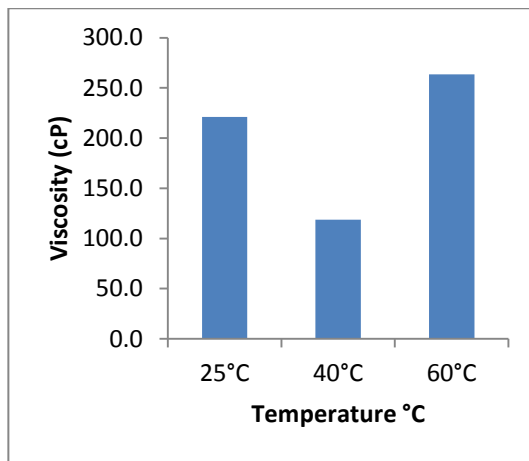


Figure 4.2c The effect of temperature on the viscosity of 5 %w/w hypromellose E15LV

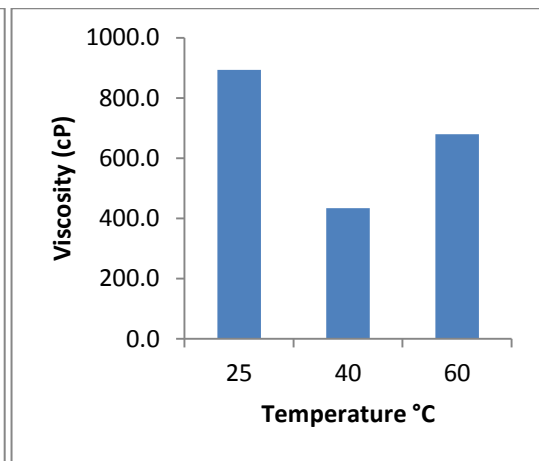


Figure 4.2d The effect of temperature on the viscosity of 5 %w/w hypromellose E50LV

The viscosity data show that hypromellose solution viscosity reduced at 40°C but increased at 60 °C. For both the E5 and E15 hypromellose the viscosity at 60°C was greater than that at 25 °C. This effect was most pronounced for 20 % w/w E5 LV solutions. At 60°C this solution was observed to completely gel during viscosity testing. The viscosity of 5 %w/w E50LV at 60°C did not exceed the viscosity of the same solution at ambient temperature. This temperature effect on viscosity is associated with the gelation temperature (Sarker 1979) and the concentration of E grade hypromellose polymers. As the temperature begins to increase the polymer molecules are dehydrated thus reducing viscosity before, at higher temperatures (the gelation temperature), continued dehydration enables greater polymer-polymer interaction to take place, thus increasing viscosity (Sarker 1979). This effect is more significant at higher polymer concentrations due to the potential for greater polymer-polymer interaction. The relatively high molecular weight of the E50LV polymer probably prevented similar entanglement as observed for E5 and E15 polymer solutions at 60°C and therefore the viscosity at this temperature did not exceed the viscosity measured at ambient temperature.

4.3.3 Spray-drying of aqueous hypromellose solutions

4.3.3.1 Development of a spray-drying process for aqueous solutions of hypromellose

A solution of 5 % w/w hypromellose E5LV solution was spray-dried according to the conditions described in Section 4.2.4. 200mL of the hypromellose solution was spray-dried in 30 min and 7.68 g of spray-dried hypromellose was yielded from the spray-drying process. This equated to a yield of 76.8 %.

Alanazi et al (2006) described a spray-drying process for hypromellose with indomethacin. The hypromellose was solubilised in purified water as described here but the indomethacin was solubilised in ethanol. The ethanolic solution of indomethacin was added to the aqueous hypromellose solution prior to spray-drying. Alanazi et al (2006) was able to achieve a flow rate of 16 mL/min. In this investigation a maximum flow rate of 7 mL/min could be achieved. Based on observations in this study the spray rate was limited due to the viscosity of the hypromellose solution. The ethanolic solution used by Alanazi et al (2006) may have been less viscous due to the hydration of the hypromellose being retarded by the use of ethanol (Roberts et al 2007) upon mixing the ethanolic solution of indomethacin with the aqueous solution of hypromellose. The presence of ethanol may have caused dehydration of the hypromellose in aqueous solution reducing the solution viscosity.

However, the spray rate used in this investigation achieved a similar target exhaust temperature to that achieved by Alanazi of 90 to 110°C but also an excellent process yield of 76.8 %. Billon et al (2000) achieved an optimised spray-drying yield of approximately 80 %w/w using paracetamol following experimental design indicating that a yield of 76.8 % is acceptable.

Spray solution viscosity is critical to the spray-drying process. If the spray solution viscosity is too high, the spray rate will be impacted and ultimately the spray-drying process will be rate limited by the solution viscosity. Consequently, as polymer concentration and polymer molecular weight both directly impact solution viscosity only low concentrations of low molecular weight polymers may be considered for aqueous spray-drying.

The viscosity of aqueous hypromellose solutions limits the solids content of spray-drying solutions and also restricts the molecular weight of the hypromellose that may be selected for spray-drying. Only low molecular weight hypromellose grades at concentrations of 5 %w/w are feasible due to the viscosity of the aqueous solutions formed. This constraint will limit the applicability of spray-drying hypromellose.

It may be possible to use temperature to reduce the viscosity of hypromellose solutions. However, due to the non-linear impact of temperature on viscosity; very careful temperature control would be required to avoid excessively dehydrating the polymer and consequently significantly increasing viscosity of the polymer solution. A greater understanding of polymer viscosity at temperatures close to the polymer cloud point is required to determine the optimum temperature for spray-drying by reducing the polymer viscosity to enable transfer from a source to the spray nozzle by transfer tubing. This approach may also enable higher molecular weight polymers or higher polymer concentrations to be considered but would require significant modifications to standard spray dryer units. For example, the entire transfer tube from a heated source to the spray nozzle prior to atomisation, would require insulation and precise temperature control. This may be feasible using temperature control based on re-circulating hot and cold water.

An alternative method to incorporate a drug substance in the polymer solution is to use a solvent such as ethanol as used by Alanazi et al (2006). The use of a solvent system, however, may pose challenges for commercial manufacturability over aqueous spray-drying due to the need to dispose or clean the solvent waste.

4.3.3.2 Characterisation of spray-dried hypromellose

4.3.3.2.1 Physical appearance by Scanning Electron Microscopy

The SEM images associated with the spray-dried material showed a significant change in physical appearance of the spray-dried hypromellose compared with non spray-dried hypromellose (Figures 4.4 to 4.12). Based on the SEM images, the mean particle size of the spray-dried material was estimated as 20 µm whilst the mean particle size of the non spray-dried material was estimated as 200 µm. In addition, as can be seen in Figure 4.8, the spray-dried material was uniform in shape and size

and spherical whilst Figure 4.4 shows the non spray-dried material was long and thin. Figures 4.3 and 4.4 show the non spray-dried material to be non uniform in terms of shape and size whilst Figures 4.8 and 4.9 show the spray-dried material to be far more uniform. Figures 4.13, 4.14 and 4.15 show that some of the spherical spray-dried particles appear to have collapsed. This is likely to be due to the vacuum applied during SEM analysis. This indicates that the particles may be hollow.

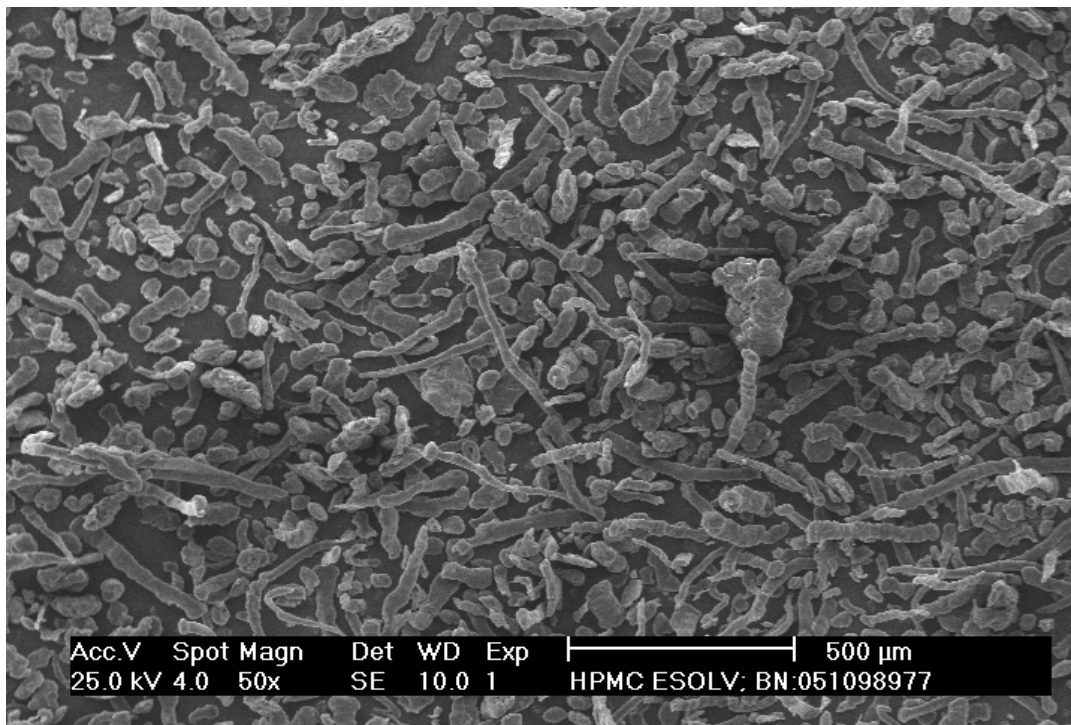


Figure 4.3 SEM of E5LV Non Spray-dried Hypromellose Powder (Scale bar indicates 500μm)

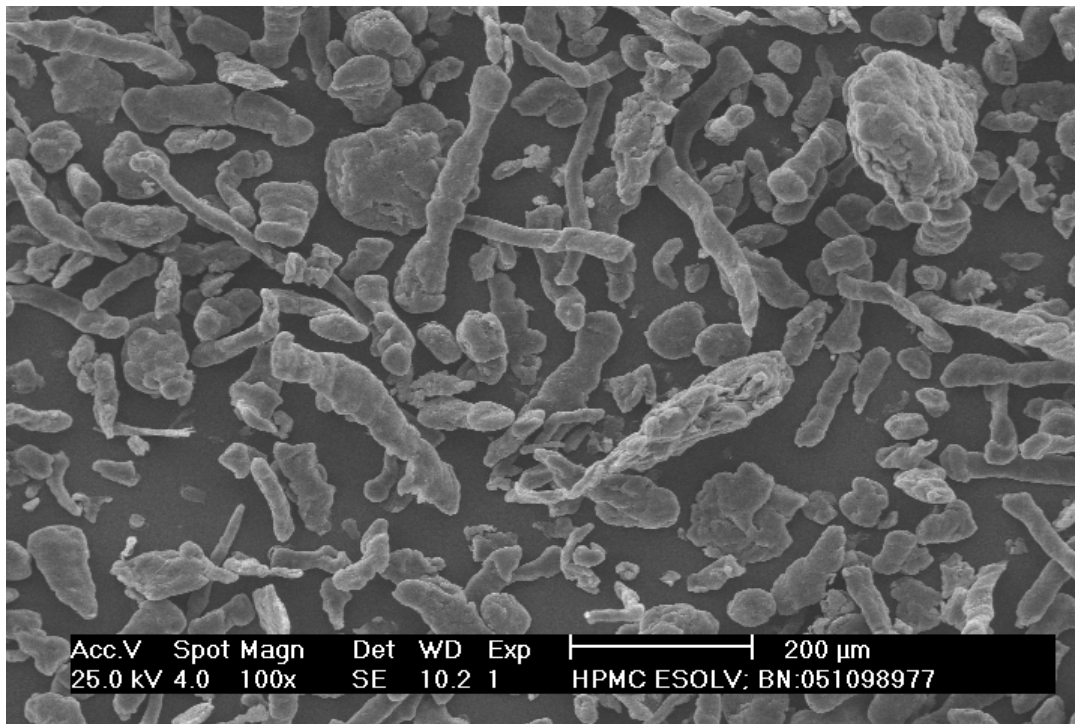


Figure 4.4 SEM of E5LV Non Spray-dried Hypromellose Powder (Scale bar indicates 200μm)

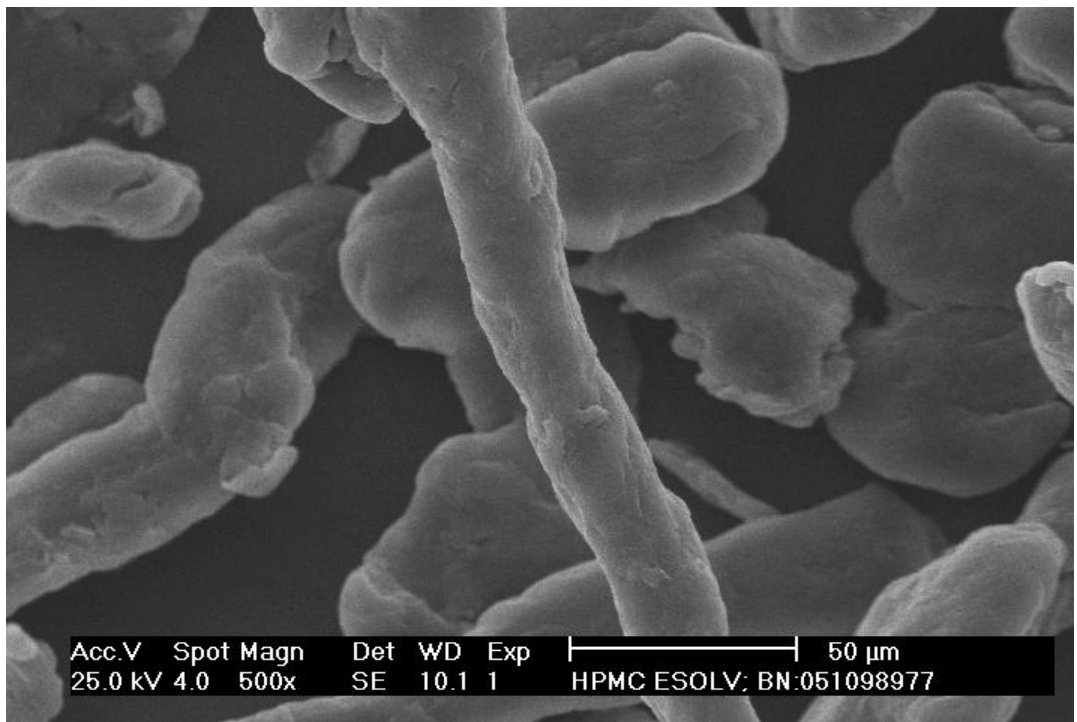


Figure 4.5 SEM of E5LV Non Spray-dried Hypromellose Powder (Scale bar indicates 50μm)

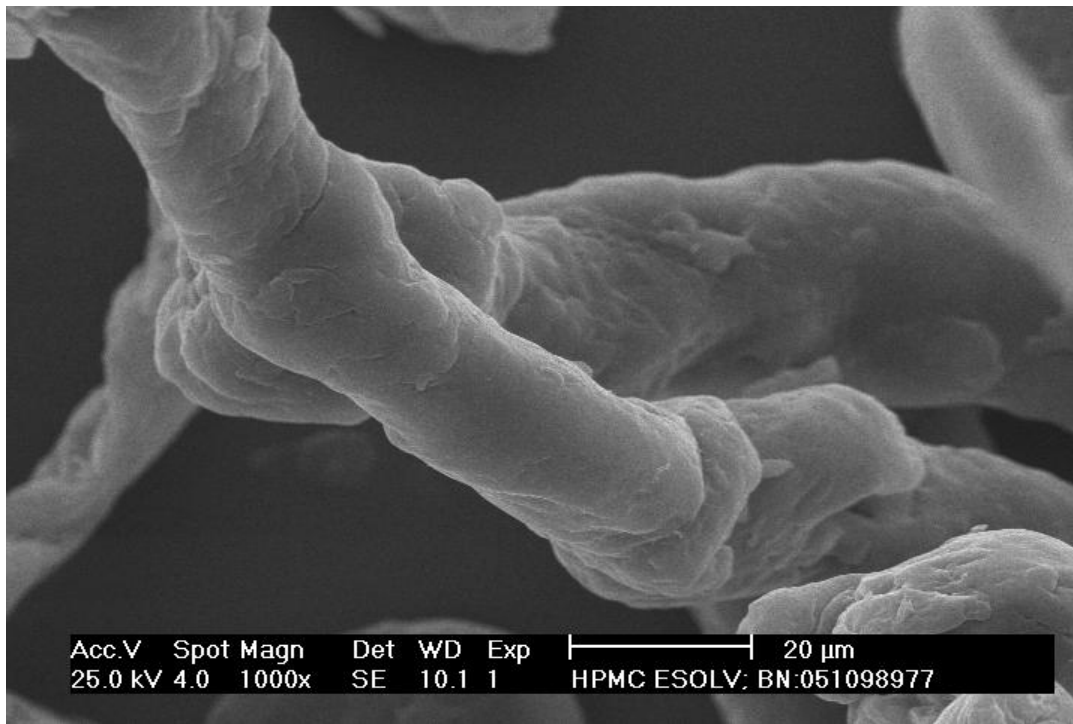


Figure 4.6 SEM of E5LV Non Spray-dried Hypromellose Powder (Scale bar indicates 20μm)

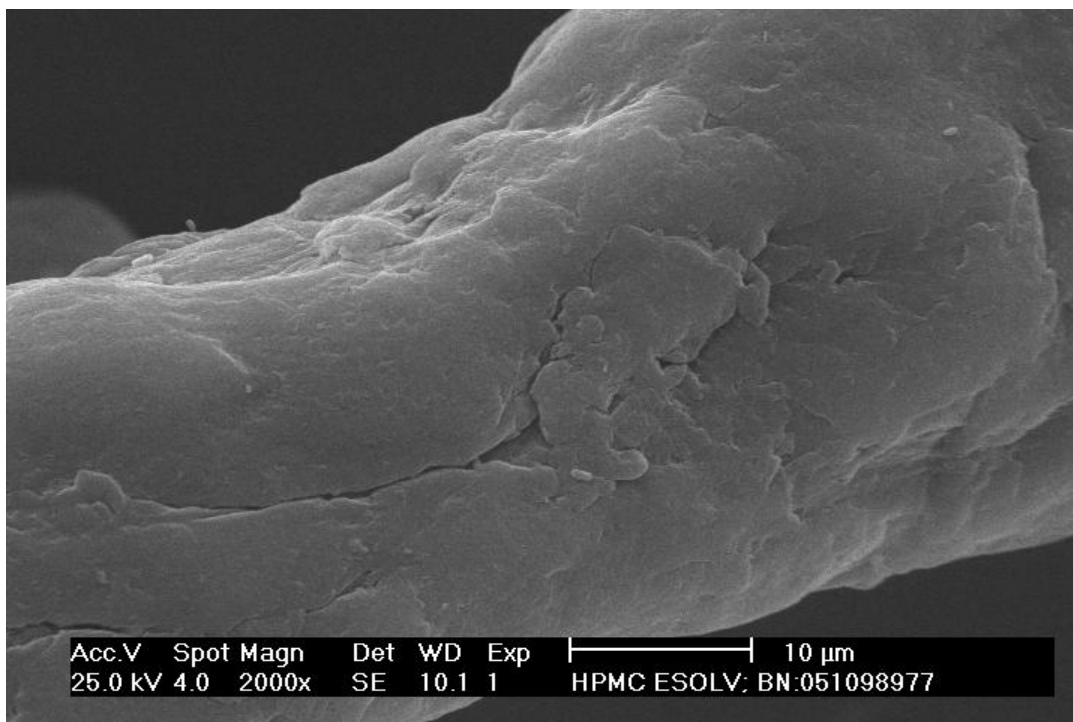


Figure 4.7 SEM of E5LV Non Spray-dried Hypromellose Powder (Scale bar indicates 10μm)

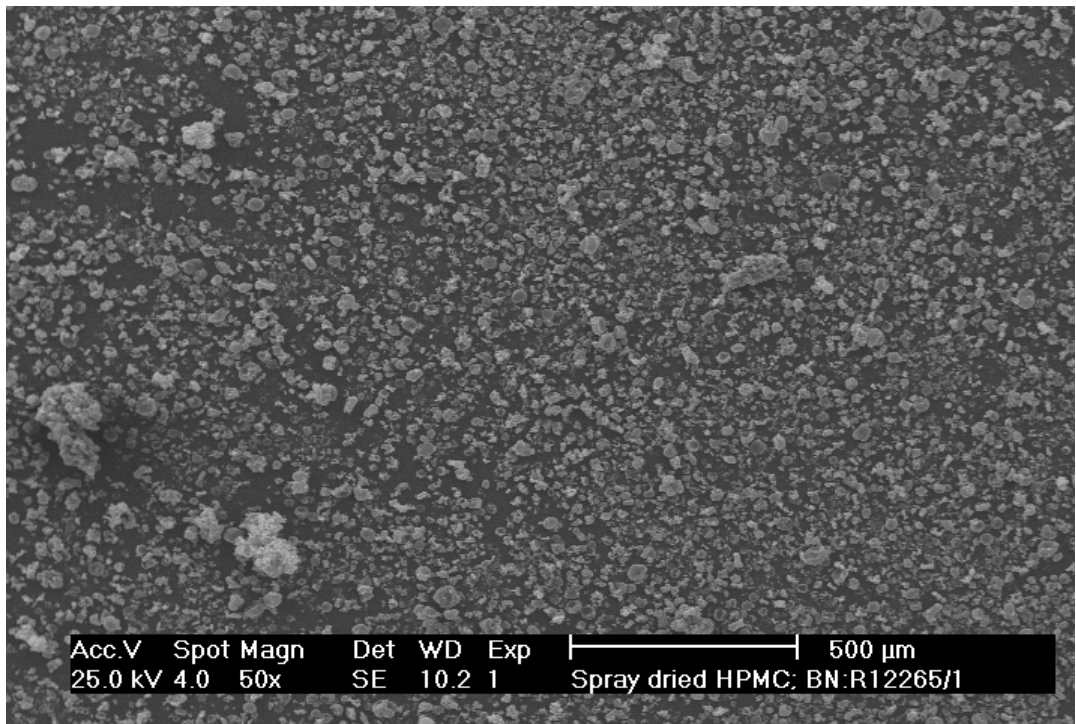


Figure 4.8 SEM of E5LV Spray-dried Hypromellose Powder (Scale bar indicates 500μm)

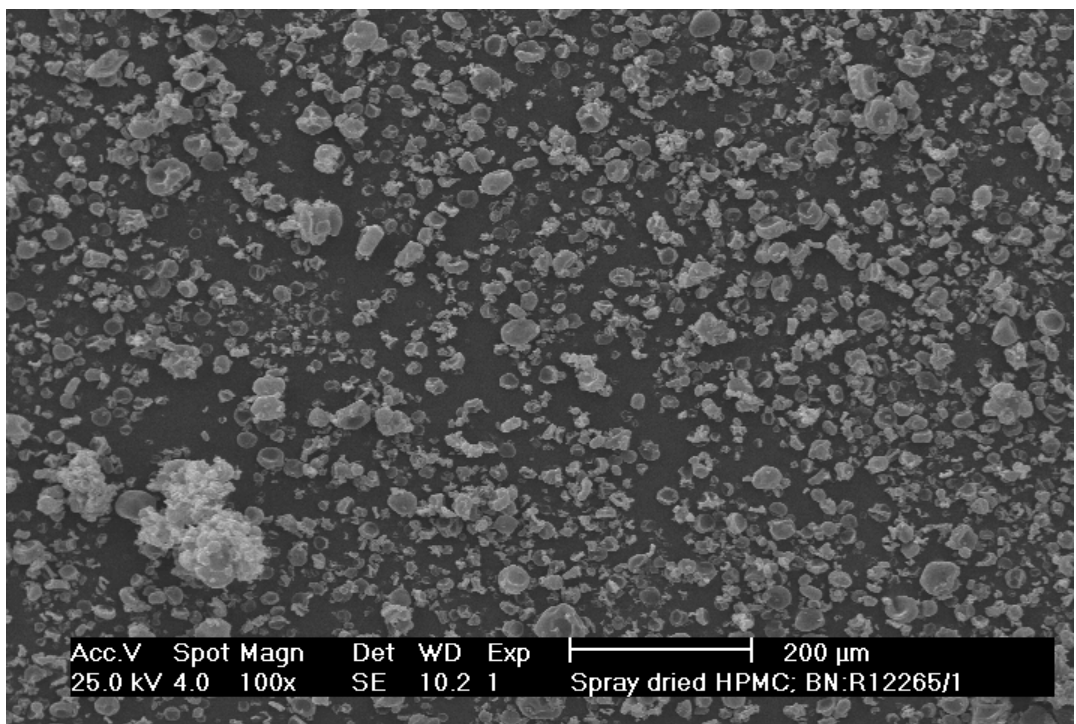


Figure 4.9 SEM of E5LV Spray-dried Hypromellose Powder (Scale bar indicates 200μm)

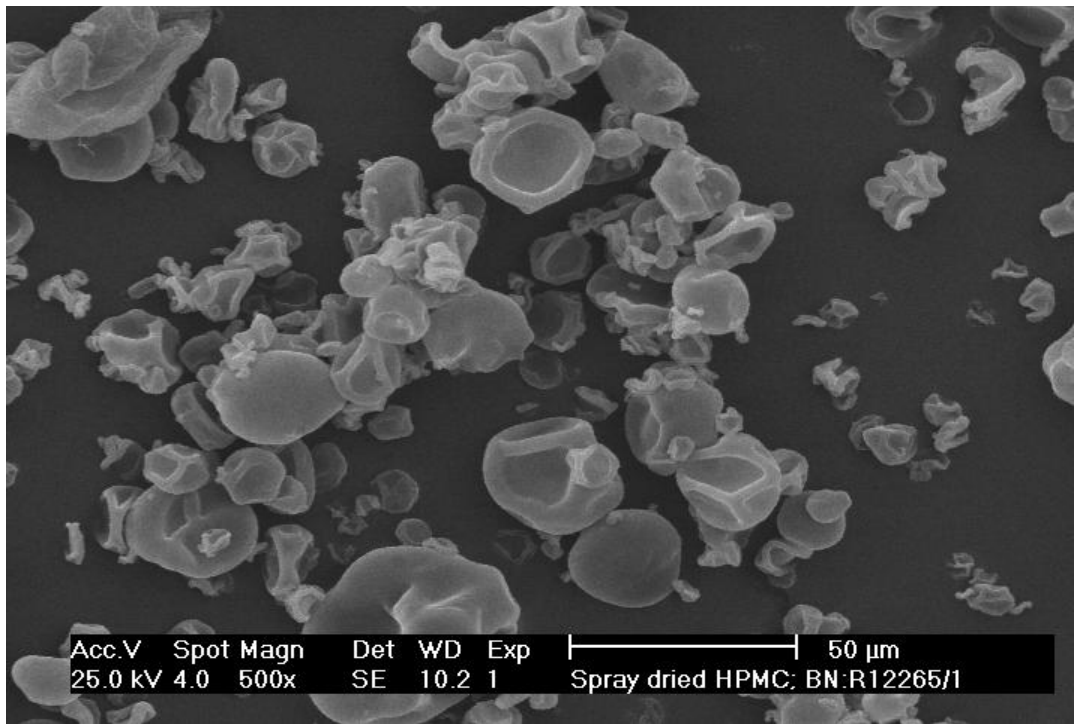


Figure 4.10 SEM of E5LV Spray-dried Hypromellose Powder (Scale bar indicates 50μm)

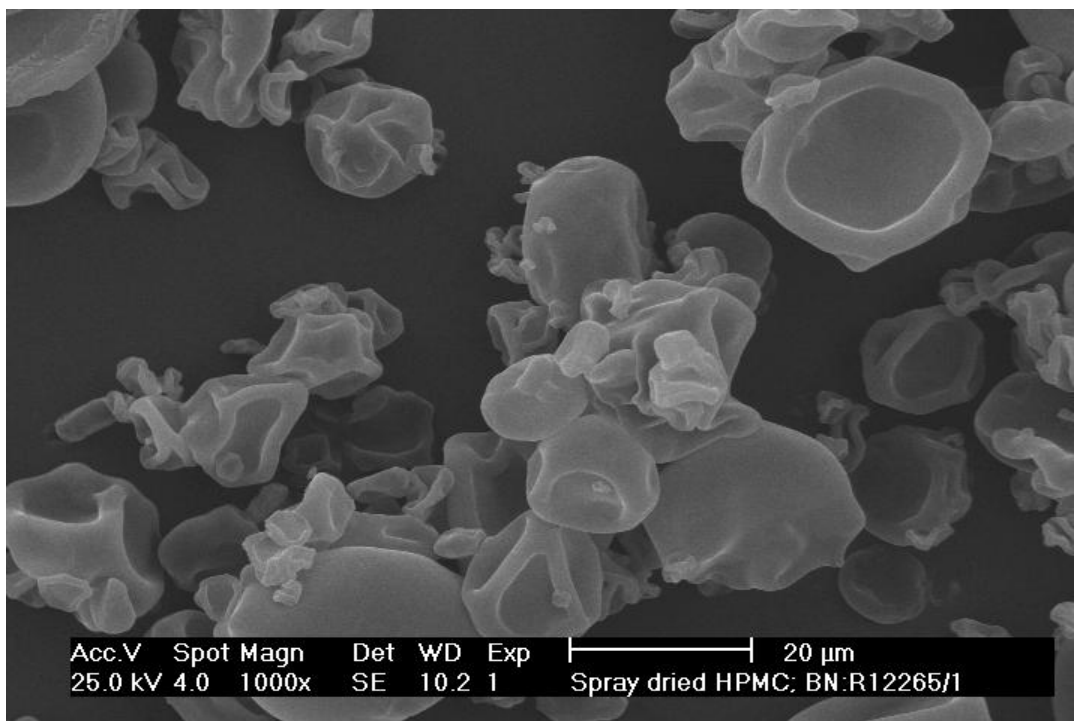


Figure 4.11 SEM of E5LV Spray-dried Hypromellose Powder (Scale bar indicates 20μm)

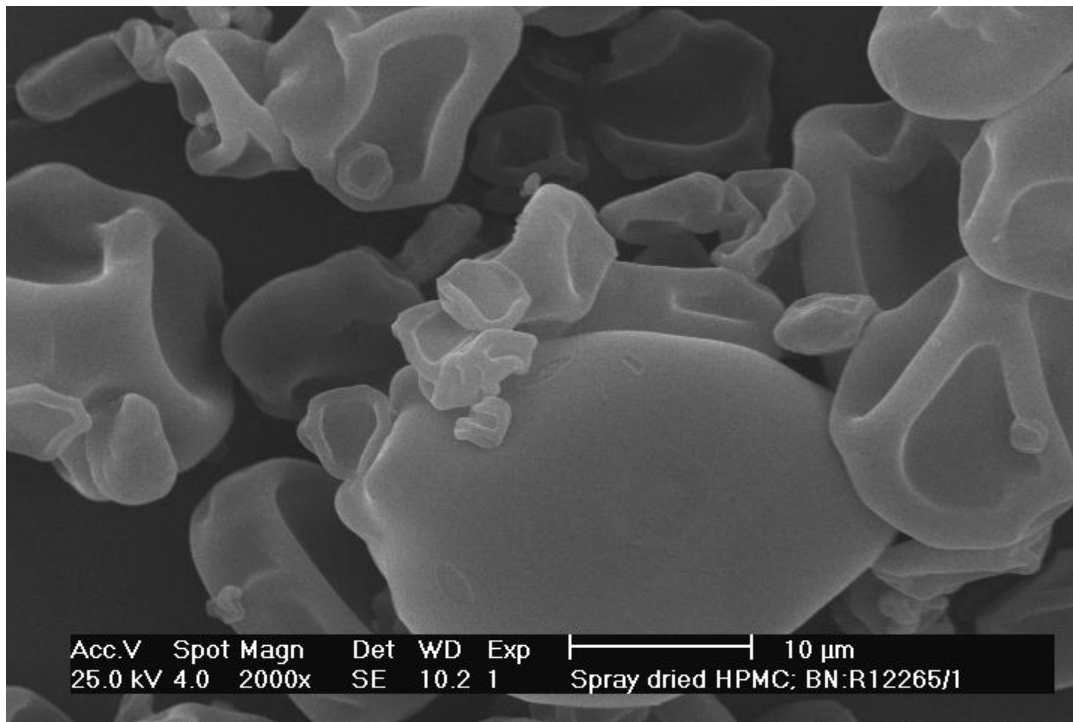


Figure 4.12 SEM of E5LV Spray-dried Hypromellose Powder (Scale bar indicates 10μm)

4.3.3.2.2 Viscosity testing

Spray-dried and non-spray-dried hypromellose E5LV was used to prepare 0.5 % and 5 % w/w solutions and their viscosities determined. Upon preparing the solution, the spray-dried material was very difficult to 'wet' and had increased cohesion properties compared with non spray-dried hypromellose. The fine particle size of the spray-dried hypromellose was highly cohesive and difficult to disperse in the purified water. However, once dispersed using a Silverson mixer, the spray-dried material performed similar to the non spray-dried material. Table 4.6 shows the viscosity data and viscosity method parameters used.

Table 4.6 Viscosity method parameters and mean viscosity data of polymer solutions prepared using non spray-dried and non spray-dried hypromellose

Polymer Grade and Concentration	Product Temperature		
	25 °C	40 °C	60 °C
5 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	66.0	49.6	75.0
Standard Deviation (±)	0.0	0.5	2.1
Sample B			
Mean Viscosity (cP)	67.0	50.0	75.0
Standard Deviation (±)	0.0	0.0	0.0
Method Details			
Spindle Number	1	1	1
Speed	100rpm	100rpm	100rpm
Spray Dried 5 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	66.0	50.8	73.4
Standard Deviation (±)	0.0	1.6	0.9
Sample B			
Mean Viscosity (cP)	66.0	50.8	72.8
Standard Deviation (±)	0.0	1.1	0.8
Method Details			
Spindle Number	1	1	1
Speed	100rpm	100rpm	100rpm
0.5 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	14.8	13.5	12.0
Standard Deviation (±)	0.2	0.7	0.0
Sample B			
Mean Viscosity (cP)	15.5	14.3	12.0
Standard Deviation (±)	0.4	0.4	0.0
Method Details			
Spindle Number	1	1	1
Speed	100rpm	100rpm	100rpm
Spray Dried 0.5 % HPMC E5LV			
Sample A			
Mean Viscosity (cP)	14.8	11.9	11.8
Standard Deviation (±)	0.2	0.2	0.2
Sample B			
Mean Viscosity (cP)	14.8	11.8	11.7
Standard Deviation (±)	0.2	0.2	0.1
Method Details			
Spindle Number	1	1	1
Speed	100rpm	100rpm	100rpm

Note:

Mean values are determined from 5 viscosity readings for each test condition.

Table 4.6 shows that spray-dried and non spray-dried E5 LV hypromellose solutions have similar viscosities at 0.5 % w/w and 5 % w/w polymer concentration demonstrating the functionality of polymer is not impacted by the spray-drying process. However, the viscosity data also show that the 0.5 % w/w polymer solution behaves differently to the 5 % w/w polymer solution at increased temperature. The data demonstrate that 0.5 % w/w polymer solution does not exhibit a gelation temperature. This may be due to minimal polymer-polymer interaction at this concentration and the sensitivity of the viscosity method employed being insufficient to determine any change in viscosity caused by polymer dehydration and polymer-polymer interaction as previously described in Section 4.3.1.

Spray-drying hypromellose significantly changed the physical shape of the hypromellose but did not alter its functionality. The viscosities of solutions containing similar concentrations of spray-dried and non spray-dried materials were similar.

Based on the viscosity data obtained for spray-dried and non spray-dried hypromellose, spray-drying does not appear to improve the overall function of the polymer. By drastically changing the physical appearance of the polymer powder however, the reduced particle size and spherical shape associated with the spray-dried material may offer some advantages. For example, a reduced particle size is likely to increase the rate of hydration of the polymer which may offer advantages to modified release matrices by improving the formation of the controlling gel layer.

The spherical shape of the spray-dried hypromellose is likely to have an increased surface area than the non-spray-dried material. This may offer advantages for modified release matrix tablets as more uniform gel layers may be possible to form. In addition the spherical particles are likely to hydrate more quickly than the non spray-dried material due to the increased surface area. The spherical particles may also offer improved tableting properties in terms of compression and flow. The physical appearance of the spray-dried hypromellose is distinctly different to that of non spray-dried hypromellose and the potential benefits of spray-dried hypromellose could be further explored.

4.4 Conclusion

Only low molecular weight hypromellose grades at concentrations of 5 %w/w are feasible due to the viscosity of the aqueous solutions formed. This constraint limits the applicability of spray-drying aqueous solutions of hypromellose.

It may be possible to use temperature to reduce the viscosity of hypromellose solutions. A greater understanding of polymer viscosity at temperatures close to the polymer cloud point is required to determine the optimum temperature for spray-drying by reducing the polymer viscosity to enable transfer from a source to the spray nozzle by transfer tubing.

Spray-drying significantly changed the physical structure of hypromellose powder. The physical appearance of the spray-dried hypromellose is distinctly different to that of non spray-dried hypromellose and the potential benefits of spray-dried hypromellose could be further explored.

A suitable spray-drying process for an aqueous solution of 5 % hypromellose E5LV has been developed. The potential to spray-dry an aqueous solution of hypromellose to optimise the physical properties of the material without compromising its ability to hydrate and swell, could offer significant advantages in the manufacture pharmaceutical products.

Spray-drying will be used to investigate the potential to co-process paracetamol with hypromellose E5LV by spray-drying in Chapter 5, to determine if the functionality of the hypromellose may be enhanced by preparing a polymer:drug particle.

5 PREPARATION AND VISCOSITY DETERMINATION OF AQUEOUS HYPROMELLOSE DISPERSIONS CONTAINING PARACETAMOL

5.1 Introduction

It was determined in Chapter 4 that it is possible to spray dry aqueous solutions of hypromellose but that polymer solution viscosity restricts the grade and concentration of polymer that may be spray-dried. As previously discussed in Chapter 1 the potential to co-process polymer and drug substance may present significant advantages for dosage form design.

Based on the findings in Chapter 4, prior to assessing the feasibility of spray-drying aqueous hypromellose solutions containing paracetamol, the impact of paracetamol on the viscosity of hypromellose solutions was investigated. Within this Chapter the preparation of polymer solutions containing paracetamol and the influence of temperature on polymer solution viscosity are considered.

A 5 % w/w hypromellose E5LV solution was successfully spray-dried (see Chapter 4) and for process efficiency, a target minimum solid concentration of 20 %w/w is desired (Billon 2000). A spray-drying dispersion containing 5 % w/w hypromellose E5LV and 15 % w/w paracetamol was therefore considered for this investigation.

5.2 Materials and Methods

5.2.1 Preparation of aqueous hypromellose dispersions containing paracetamol

A dispersion containing 5 %w/w hypromellose E5LV and 15 %w/w paracetamol (to be known as 'drug-polymer dispersion' from here on in this chapter) was prepared as described in Section 3.2.1. Table 5.1 shows the formulation that was prepared.

Table 5.1 Quantitative composition of drug-polymer dispersion (per 500g of dispersion)

Excipient	Formulation	
	Content (% w/w)	Quantity (g) per 500g Solution
Hypromellose E5LV	5.0	25.0
Paracetamol	15.0	75.0
Purified Water	80.0	400.0
Total	100.0 %	500.0g

5.2.2 Physical appearance of aqueous hypromellose dispersions containing paracetamol

Once prepared, the drug-polymer dispersion was examined to determine its flow properties by gently stirring the sample using a spatula to determine how easy the solution could be agitated as described in Section 4.2.1. The appearance of the dispersion was recorded.

5.2.3 Viscosity determination of aqueous hypromellose dispersions containing paracetamol

The viscosity of the drug polymer dispersion was determined at ambient temperature and at 40°C and 60°C according to the viscosity method described in Section 4.2.2.

5.3 Results and Discussion

5.3.1 Preparation and physical appearance of aqueous hypromellose dispersions containing paracetamol

A smooth, white paracetamol dispersion which was free of lumps was produced and combined with a clear hypromellose solution. After adding the paracetamol dispersion to the hypromellose solution and subsequent mixing, a smooth white dispersion was produced.

5.3.2 Viscosity determination of aqueous hypromellose dispersions containing paracetamol

Table 5.2 shows viscosity data obtained for the dispersion containing 5 % hypromellose E5LV and 15 %w/w paracetamol.

Table 5.2 Viscosity method parameters and mean viscosity data for 5 %w/w HPMC E5LV containing 15 %w/w paracetamol at 25°C and 40 °C.

Polymer Grade and Concentration	Product Temperature	
	25 °C	40 °C
5 % HPMC E5LV		
Sample A		
Mean Viscosity (cP)	103.0	166.2
Standard Deviation (±)	0.0	19.8
Sample B		
Mean Viscosity (cP)	105.0	167.1
Standard Deviation (±)	0.0	24.9
Method Details		
Spindle Number	1	1
Speed	20rpm	20rpm

The drug-polymer dispersion has a greater viscosity at ambient temperature than the 5 % hypromellose E5LV solution prepared in Chapter 4 (103 cP versus 66 cP respectively, refer to Tables 5.2 and 4.4). During viscosity testing it was noted that at 40°C the dispersion began to flocculate and sediment resulting in the viscosity readings obtained over 5 mins showing a decrease in viscosity. Large standard deviations are calculated for these samples. At 60 °C, the dispersion flocculated and

then caked. The cake could not be resuspended by agitation. The viscosity at 60°C was consequently not determined as the dispersion was not uniform.

The inclusion of 15 %w/w paracetamol in the 5 %w/w hypromellose E5LV solution increased the viscosity at ambient temperature. The increase in viscosity is likely to be due to the presence of dispersed undissolved paracetamol forming physical bridges with each other and the hydrated hypromellose molecules.

The viscosity of the drug-polymer dispersion was higher at 40°C than at 25°C prior to the dispersion eventually flocculating. The viscosity data obtained show that at 40°C the dispersion was non-homogeneous as the viscosity decreased over the 5 minutes testing period. As the paracetamol flocculated, the dispersion became non-homogeneous, and consequently, the composition of the dispersion in the micro environment around the viscometer spindle is continually changing and hence reducing viscosity data recorded. As described in Chapter 4, the viscosity of the 5 %w/w hypromellose E5LV solution without paracetamol decreased at 40°C and the solution remained clear (refer to Table 5.4). As the temperature was increased to 60°C the viscosity increased, indicating that the gelation temperature was reached between 40°C and 60 °C. The viscosity of 5 %w/w hypromellose E5LV solutions containing paracetamol increased between 25°C and 40°C suggesting that the gelation temperature was reached at a temperature <40 °C. This may be due to the dispersed paracetamol providing opportunity for polymer-paracetamol interaction in addition to typical polymer-polymer interaction as dehydration occurs at increasing temperature (Mitchel et al 1990). The gelation temperature of a dispersion containing 5 %w/w E5LV hypromellose and 15 %w/w paracetamol is between ambient temperature and 40 °C. The gelation temperature of an aqueous solution containing 5 %w/w E5LV hypromellose is between 40°C and 60 °C.

It was not possible to assess the effect of paracetamol on the cloudpoint of the hypromellose in the drug-polymer dispersion by visual assessment, as the drug-dispersion was white in appearance. As discussed in Chapter 4, the cloudpoint may be described as the temperature at which the hypromellose polymer molecules precipitate out of solution (Sarker 1979). Paracetamol may also reduce the cloudpoint of the hypromellose solution and hence the precipitation of the

hypromellose molecules may have caused flocculation of the dispersed paracetamol as observed at 40 °C.

Hypromellose solutions containing dispersed drug particles have a reduced cloudpoint and gelation temperature (Mitchell et al 1990). This results in flocculation of the drug particles and physical instability of the drug-polymer dispersion when heated above 40 °C. In Chapter 4, it was demonstrated that heating to 40°C could be used to reduce polymer solution viscosity. It was not possible to use heat to reduce the viscosity of a drug-polymer dispersion without affecting the physical stability of the dispersion.

5.4 Conclusion

The presence of paracetamol at 15 %w/w in a 5 % w/w hypromellose E5LV solution affects the gelation temperature and cloudpoint of hypromellose.

These data indicate that preparing a dispersion containing hypromellose and paracetamol is possible but that heating to reduce viscosity, as previously considered for aqueous hypromellose solutions without paracetamol in Chapter 4, has a detrimental impact on the physical stability of the dispersion. It may therefore not be possible for this drug-polymer dispersion to be spray-dried as the viscosity may be too high to enable appropriate feed rate.

The drug-polymer dispersion has a gelation temperature lower than that observed for an aqueous hypromellose solution using the same polymer at the same concentration. Based on the increase in viscosity observed between 25°C and 40°C in the presence of paracetamol, the gelation temperature of a dispersion containing 5 %w/w E5LV hypromellose and 15 %w/w paracetamol is between ambient temperature and 40 °C. The gelation temperature of an aqueous solution containing 5 %w/w E5LV hypromellose is between 40°C and 60 °C.

The drug-polymer dispersion has a cloudpoint temperature lower than that observed for an aqueous hypromellose solution using the same polymer. The cloudpoint of a dispersion containing 5 %w/w E5LV hypromellose and 15 %w/w paracetamol is between ambient temperature and 40 °C. The cloudpoint of an aqueous solution containing 5 %w/w E5LV hypromellose is between 40°C and 60 °C.

Spray drying of hypromellose solutions containing paracetamol was not performed due to the flocculation of the dispersion obtain at temperatures >25°C. Further work associated to optimise the physical stability of the 5 % hypromellose E5LV solution containing paracetamol will not be conducted at this stage. The use of HPC as an alternative aqueous soluble polymer will be considered in Chapter 6.

6 INVESTIGATING THE INFLUENCE OF TEMPERATURE ON PHYSICAL PROPERTIES OF AQUEOUS SOLUTIONS OF HPC

6.1 Introduction

Chapters 4 and 5 demonstrated the influence of temperature and the presence of paracetamol on the viscosity of hypromellose solutions and the associated implications for spray-drying aqueous hypromellose solutions. This Chapter investigates if aqueous solutions of HPC are influenced by temperature in a similar way to hypromellose. Aqueous solutions of HPC are known to undergo phase transformations at elevated temperatures (Vshivkov and Rusinova 2007). In this investigation a range of Klucel® HPC polymer grades (molecular weights 80,000 to 370,000 Daltons), at a range of concentrations were considered.

Aqueous solutions were prepared and changes in physical structure at increasing temperature determined using viscosity and UV transmission testing. Based on these properties, an application using HPC to develop a paediatric dosage form is proposed.

6.2 Materials and Methods

The following Klucel® HPC grades were used for this investigation:

- i. EXF Pharm
- ii. LF PHarm
- iii. JXF Pharm
- iv. GXF PHarm
- v. MXF Pharm
- vi. HXF Pharm

Details associated with these polymer grades may be found in Section 2.1.2.2 of this thesis. In this Chapter a range of aqueous polymer concentrations (5 %w/w 10 %w/w and 20 %w/w) was considered.

Table 6.1 shows the polymer solutions considered and the respective composition of each solution based on polymer concentration.

Table 6.1 Quantitative composition of aqueous HPC solutions (per 500g of solution)

	Polymer Concentration					
	5 %w/w		10 %w/w		20 %w/w	
Excipient	Content (% w/w)	Quantity (g)	Content (% w/w)	Quantity (g)	Content (% w/w)	Quantity (g)
Polymer	5.0	25.0	10.0	50.0	20.0	100.0
Purified Water	95.0	475.0	90.0	450.0	80.0	400.0
Total	100.0 %	500.0g	100.0 %	500.0g	100.0 %	500.0g

6.2.1 Preparation of aqueous HPC solutions

Aqueous solutions of HPC were prepared as described in Section 3.1.2.

6.2.2 UV transmission measurement of aqueous HPC solutions

The theory of UV spectroscopy is described in Section 2.2.2 of this investigation. UV transmission is used here to determine how HPC solutions physically change with an increase in temperature. The per-cent UV transmission decreased as the test samples became more cloudy.

UV transmission was measured using a spectrophotometer (Hewlett Packard Model 8453, UK) with jacketed cuvette holder (Agilent, US). A water bath (Thermo Scientific, UK) set at 65°C was used to circulate warm water around the jacketed cuvette holder (Agilent US) and a temperature probe (RS Components UK) was used to measure the temperature of the test sample within the cuvette. The temperature probe was held using a clamp inside the top of the cuvette to monitor the temperature of the test solution during UV transmission measurement. Purified water was used as a blank to generate a UV transmission baseline at 540 nm. Per-cent UV transmission at 540 nm was measured across the sample at ambient temperature and at 1 to 2°C sample temperature intervals up to 50°C or until a constant transmittance reading was reached. Software (UV Vis Chemstation, Agilent Technologies, US) was used to analyse the data obtained by the

spectrophotometer. The per-cent UV transmission reading was plotted against temperature. A change in physical appearance of the test solution was indicated by a change in per-cent UV transmittance.

6.2.3 Viscosity determination of aqueous HPC solutions

The viscosities of the aqueous HPC solutions were measured using a different method to that used previously in Chapter 4. To acquire more data points to investigate the effect of temperature on viscosity of aqueous HPC solutions an alternative method to enable greater control of sample temperature increase was implemented. This method enabled viscosity to be determined at 5°C temperature intervals from ambient temperature to 60°C

6.2.3.1 Viscosity determination using small sample adaptor

The viscosity of each solution was determined using a Brookfield LVDV III viscometer and jacketed small sample adaptor (Brookfield, UK) with integrated sample temperature measurement. The viscosity of each solution was measured from ambient temperature to 60°C at 5°C intervals. A water bath (Thermo Scientific, UK) was used to control the temperature of the small sample adaptor and is set at 65 °C. The parameters shown in Table 6.2 were used to determine solution viscosity at increasing temperature.

Table 6.2 Viscometer spindle type and speed Used for viscosity testing

Viscosity (cP)	≤50	50 to 120	120 to 400	400 to 1500	1500 to 7000
Spindle	SC4-18	SC4-18	SC4-18	SC4-18	SC4-34
Spindle Speed (rpm)	30	12	6	1.5	6

Note:

Sample size used 8mL

The test sample volume (8 mL) was extracted from the stock polymer solution and transferred to the small sample adaptor using a 10 mL polypropylene syringe (BD Plastipak, US). Having connected the small sample adaptor to the viscometer the water bath pump was started and the sample was heated. Viscosity measurement commenced and viscometer torque; viscosity in centipoises and sample temperature were recorded. The viscosity of each HPC solution in centipoises was determined as a function of temperature for each sample.

6.3 Results and Discussion

6.3.1 Preparation of aqueous HPC solutions

Upon addition to purified water the HPC particles hydrate and swell prior to solubilisation. Consequently the higher molecular weight grades of HPC took longer to solubilise as the gel layer which formed at the surfaces of the HPC particles was very viscous and caused the HPC particles to be difficult to solubilise. In association with this observation, it was not possible to form HPC solutions using MXF and HXF Pharm grades at 5 %w/w concentration as a viscous gel formed quickly after HPC addition preventing agitation by the magnetic stirrer and solubilisation of the HPC particles (shown shaded in Table 6.3). This was also the case for EXF, LXF, JXF and GXF grades at concentrations of 20 %w/w and at GXF at a concentration of 10 %w/w as shown in Table 6.3. Table 6.3 also shows the molecular weight and nominal viscosity associated with each HPC polymer grade considered.

The difficulty to solubilise high molecular weight HPC grades (>370,000 Daltons) and high polymer concentrations restricted the grades of and the maximum concentration of HPC that could be used to form a true HPC solution. The maximum viscosity of HPC solution considered for this work was 6900 cP as determined for 5 %w/w GXF.

Preparation of the HPC aqueous solutions demonstrated that HPC powder is best dispersed and dissolved at room temperature whilst hypromellose is best dispersed at high temperature prior to solubilising at reduced temperature. The need to heat purified water prior to dispersion of hypromellose is a manufacturability disadvantage of hypromellose compared to HPC, due to the energy and time required to reach 70°C to 85 °C.

Table 6.3 HPC polymer grades, concentrations considered and occurrence of gelling

HPC Polymer Grade	Molecular Weight (Daltons)	Nominal Viscosity (cP)	Polymer Concentration (%w/w)		
			5 %	10 %	20 %
EXF Pharm	80,000	300 to 600 (10 % w/w)	5 %	10 %	20 %
			✓	✓	✗
LF Pharm	95,000	75 to 150 (5 % w/w)	5 %	10 %	20 %
			✓	✓	✗
JXF Pharm	140,000	150 to 400 (5 % w/w)	5 %	10 %	20 %
			✓	✓	✗
GXF Pharm	370,000	150 to 400 (2 % w/w)	5 %	10 %	20 %
			✓	✗	✗
MXF Pharm	850,000	4,000 to 6,500 (2 % w/w)	5 %	10 %	20 %
			✗	✗	✗
HXF Pharm	1,150,000	1,500 to 3000 (1 % w/w)	5 %	10 %	20 %
			✗	✗	✗

Note

The '✓' indicates those polymer solutions which were successfully prepared and further characterised. The '✗' indicate those polymer solutions that were successfully prepared but formed a gel and were not considered for further characterisation.

As illustrated in Table 6.3, based on viscosity, only low molecular weight HPC grade ($\leq 370,000$ Daltons) was suitable for spray-drying. High molecular weight polymer grades ($> 370,000$ Daltons) formed a gel at solutions of $\geq 5\%$ w/w which would restrict flow rate to the atomising nozzle of the spray drier. Concentrations of $>10\%$ w/w were also unsuitable for low molecular weight HPC grade polymers due to the formation of a gel. The viscosity of aqueous HPC solutions limits the solids content of spray-drying solutions and also restricts the molecular weight of the HPC that may be selected for spray-drying. This limitation was also observed for hypromellose as described in Chapter 4.

6.3.2 UV Transmission data for aqueous HPC solutions

UV transmission was successfully applied to identify physical changes in the visual appearance of the solution caused by temperature increase. In all cases the HPC solution changed from clear to cloudy upon heating. Being controlled at 65 °C, the

water bath could not control the lower temperatures of the samples (below 30 °C). The lower temperature was determined by ambient temperature within the laboratory. The method could have been improved by conditioning the samples and holding them at a defined temperature prior to testing, for example 20°C using a second water bath. This limitation is not considered to have compromised the data collected for this part of the investigation.

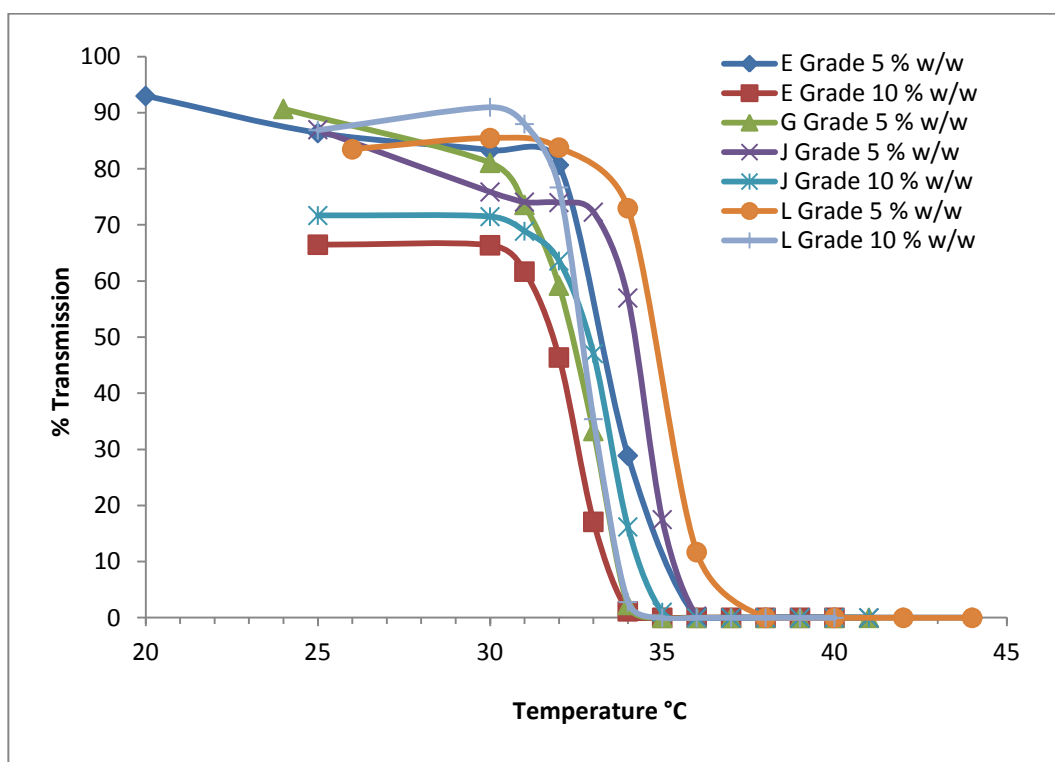


Figure 6.1 The effect of temperature on % transmission for aqueous solutions of HPC.

Per-cent UV transmission data were collected for those HPC solutions prepared as detailed in Table 6.3. Figure 6.1 shows the influence of temperature on the per-cent UV transmission of HPC solutions of various HPC polymer grades at various polymer concentrations. In all cases as the sample temperature increased the percent UV transmission of the HPC solution decreased. The onset of this change occurred slowly initially up to 30°C but changed significantly between 30°C and 35°C before rapidly reaching the minimum percent UV transmission at 35°C to 38 °C.

Solutions containing 10 % polymer reached their minimum per-cent UV transmission at a slightly lower temperature than solutions containing 5 % polymer.

The molecular weight of HPC appeared to have little impact on the trends observed in percent UV transmission.

HPC solutions containing 10 %w/w EXF and JXF HPC gave the lowest percent UV transmission at 25 °C. This may be due to the onset of change in physical appearance occurring at a temperature below 25°C and although these solutions appeared clear and particulate free to the naked eye, prior to testing, there were some changes already occurring that the percent UV transmission method was able to detect.

An increase in HPC concentration results in a more significant effect of temperature on per-cent UV transmission. These physical changes are the result of either HPC dehydration and precipitation or the formation of liquid crystals within the solution.

6.3.3 Viscosity data for aqueous HPC solutions

Viscosity testing was successfully performed as described in Section 6.2.2.

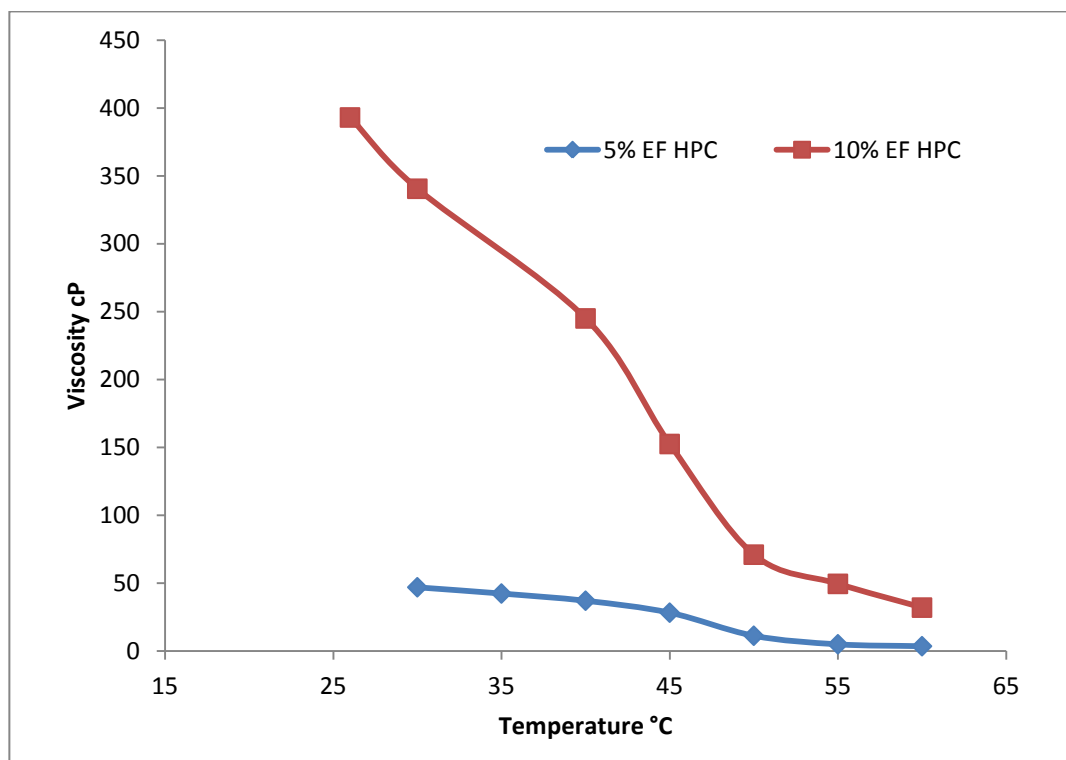


Figure 6.2 The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC EXF

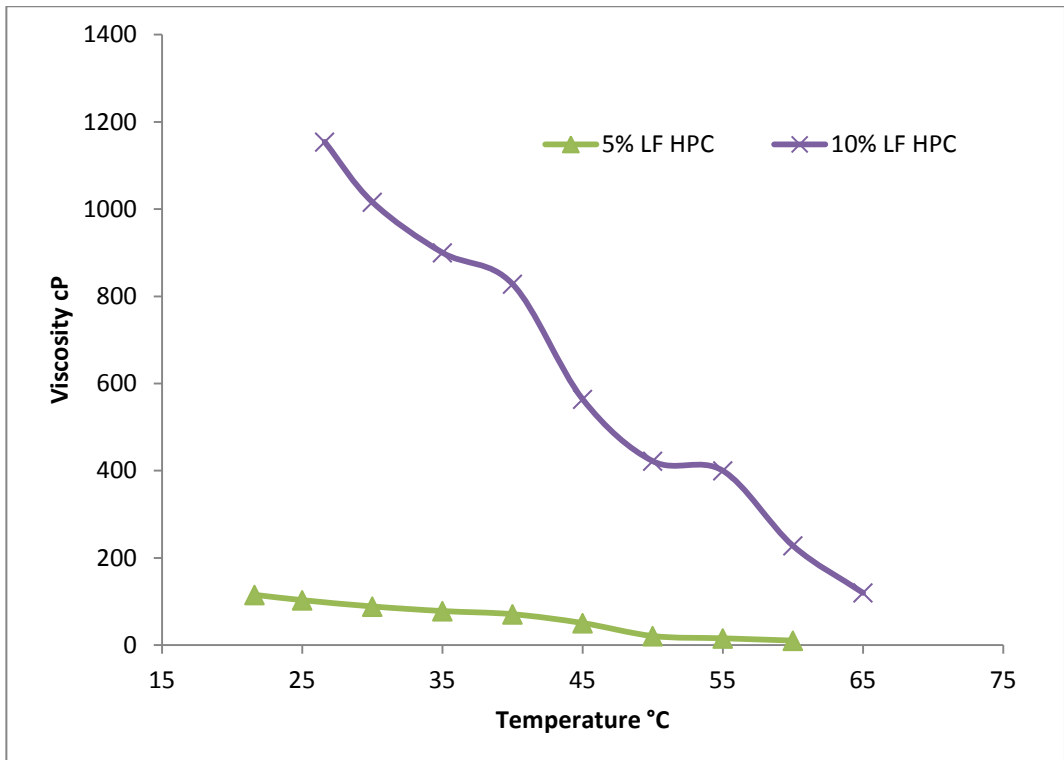


Figure 6.3 The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC LXF

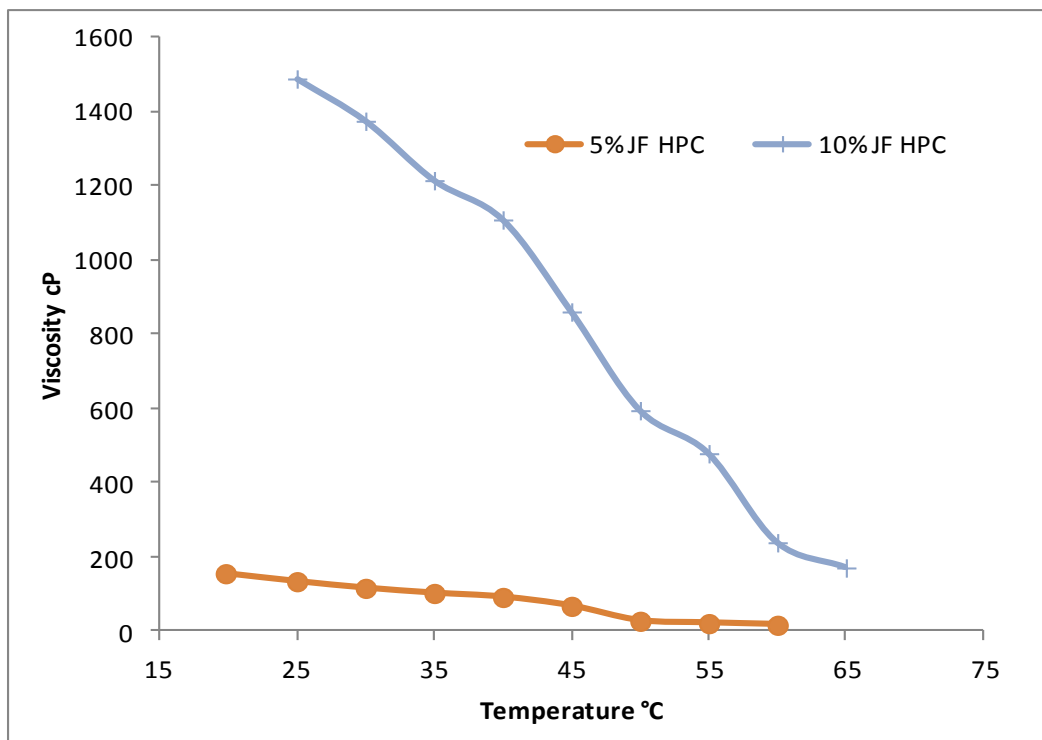


Figure 6.4 The effect of temperature on viscosity of solutions containing 5 %w/w or 10 %w/w HPC JXF

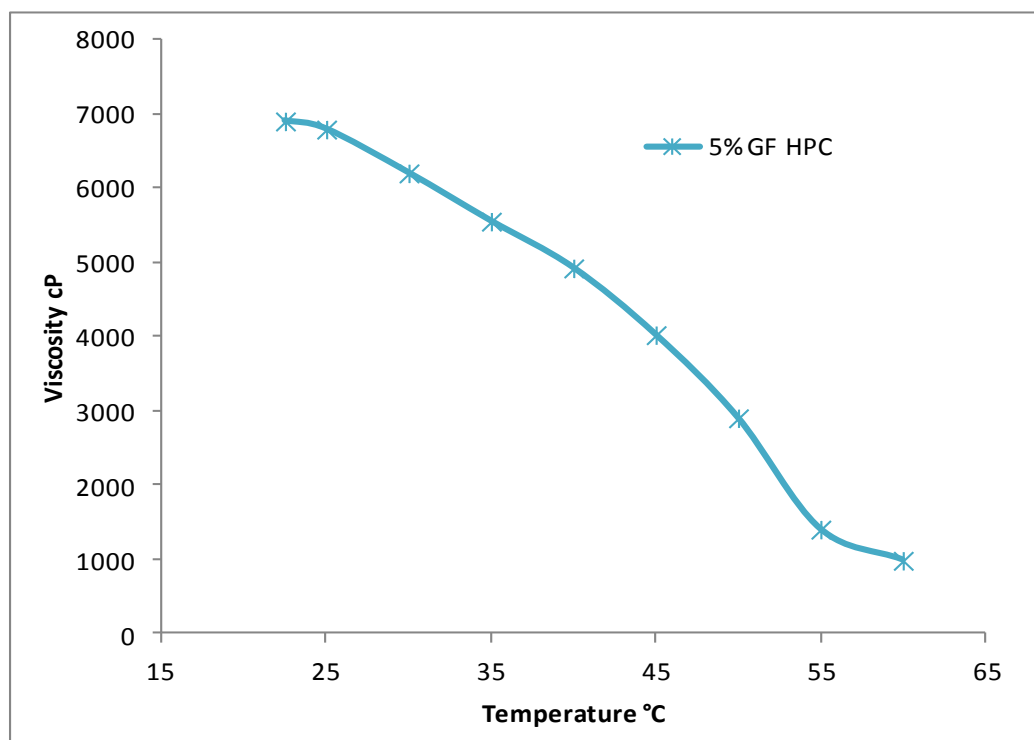


Figure 6.5 The effect of temperature on viscosity of solutions containing 5 %w/w HPC GXF

Viscosity determination was successfully performed using the Brookfield LVDV III viscometer with small sample adaptor and appropriate spindle and spindle speed. Being controlled at 65 °C, the water bath could not control the lower temperatures of the samples (below 30 °C). These were controlled only by ambient temperature within the laboratory. Similar to the per-cent UV transmission data reported previously, the method could have been improved by conditioning the samples and holding them at a defined temperature prior to testing, for example 20°C using a second water bath. This limitation is not considered to have compromised the data collected for this part of the investigation.

Figure 6.5 shows that at 30°C the viscosity of solutions containing 10 % w/w EXF was approximately 7 times that of solutions containing 5 % w/w EXF. The viscosity of 10 % w/w LXF is approximately 11 times that of 5 %w/w LXF and the viscosity of 10 % w/w JXF was approximately 12 times that of 5 % w/w JXF demonstrating that the effect of polymer concentration on solution viscosity was different for each polymer grade. The larger molecular weight polymers exhibited the highest viscosity. However, the impact of molecular weight on solution viscosity was also

non linear. EXF and LXF were more similar in molecular weight (80,000 compared to 90,000) than LXF and JXF (90,000 compared to 140,000) yet the difference in viscosity at 5 % and 10 %w/w was greater between EXF and LXF than LXF and JXF.

All HPC solutions investigated showed a reduction in viscosity with an increase in temperature. In all cases a near sigmoidal shape was evident for viscosity versus temperature plots. The change in viscosity appeared to occur in 3 phases; i) initially a linear reduction in viscosity ii) at 40°C the rate of change in viscosity was more significant and at phase iii) at 50°C the rate of change reached a minimum and minimum viscosity was reached. These phase changes occur at similar temperatures to the phase changes also observed in Section 6.3.2.

HPC polymer solutions did not exhibit the same viscosity behaviour as hypromellose solutions. HPC polymer solutions did not exhibit a gelation temperature like hypromellose solutions and consequently an increase in temperature resulted in a decrease in viscosity.

HPC solutions containing 10 %w/w HPC exhibited the greatest change in viscosity with increasing temperature. Solutions containing high concentrations of HPC exhibited the greatest change in viscosity. For all grades of HPC, the viscosity of 10 % w/w solutions at 60°C approached the viscosity of 5 % w/w solutions at 30 °C. The higher molecular grades of HPC also demonstrated the greatest change in viscosity.

Plots of percent UV transmission versus temperature and viscosity versus temperature exhibited a similar sigmoidal shape and indicated that change with temperature occurred in distinct phases. The effect of increase in temperature on HPC solution viscosity and per-cent UV transmission indicated that the HPC solutions investigated undergo phase transition changes (Guido 1995). All grades of HPC and concentrations considered demonstrated similar phase changes in viscosity and approached a minimal viscosity at approximately 60 °C indicating that the solutions were being changed to a similar 'end point' or 'completion stage' with increasing temperature. These data also indicate that aqueous solutions of HPC did not exhibit a gelation temperature as observed for aqueous solutions of hypromellose in Chapter 4.

The temperature at which these phase changes occur were similar for per-cent UV transmission and viscosity (see Figure 6.1 and Figure 6.6). These data suggest that the effect of temperature on percent UV transmission and the effect of temperature on viscosity are directly linked. The physical change which resulted in a change per-cent UV transmission is also attributable to the change in viscosity.

These physical changes could be associated with the formation of liquid crystals at elevated temperatures. Liquid crystal defines a physical state at which the material exhibits both liquid and solid crystal properties. Liquids crystals are capable of flowing like liquids but are optically anisotropic. Such a state may also be termed mesomorphic state. There are three distinct categories of mesomorphic state; smectic, nematic and cholesteric (Gray 1962). For the purposes of this work, the terms 'liquid crystal' is used to describe material exhibiting both liquid and solid crystal properties.

This HPC is a semi-rigid macromolecule capable of exhibiting liquid crystallinity both at elevated temperatures and in a variety of organic solvents as well as in water. Similar observations to those presented here were first reported by Werbowyj and Gray (1980), who showed that HPC is soluble in cold water but when aqueous solutions of HPC are warmed to about 40 °C, a phase separation occurs with a sharp increase in turbidity and a decrease in viscosity. The temperature at which this phase separation occurs may be known as the cloud point or lower critical solution temperature (LCST) (Nishio et al 2002). Nishio's work suggested that the scattering of light was due to the separation of a polymer rich phase which with further heating coagulated to form a white gel. Nishio et al (2002) defined cloud-point as the temperature at which the light scattered at a 90° angle to the incident beam (Nishio 2002). Nishio measured the cloudpoint upon heating at 0.2 °C/min as 44°C for HPC grades E, L, and G and as 41°C for J grade HPC for solutions containing ≤40 % w/w HPC. An anisotropic phase, which shows birefringence under crossed polars, was also observed in concentrated HPC solutions (>40 %w/w) and the appearance of cholesteric colours was observed in HPC solutions containing >60 %w/w HPC (Nishio et al 2002). The liquid crystalline structure of these concentrated aqueous HPC solutions has been characterised by Werbowyj and Gray (1976; 1980).

A phase diagram may be used to describe these phase changes i) isotropic ii) anisotropic and iii) biphasic (Werbowyj and Gray 1980 ; Guido and Grizzuti 1995, Vshivkov and Rusinova 2006) for HPC concentration versus temperature.

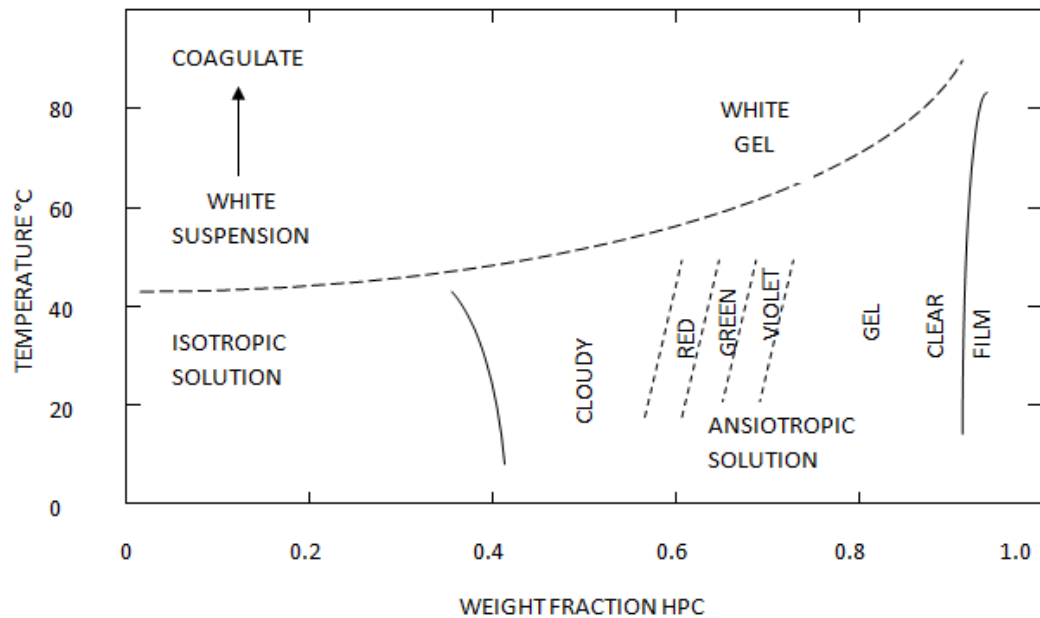


Figure 6.7 Phase diagram for HPC solutions proposed by Werbowyj and Gray 1980.

Fortin and Charlet (1989) explored this phase diagram further using carefully fractionated samples of HPC with different degrees of substitution and concluded that the reduced aqueous solubility of HPC at high temperature originates from the melting of the enhanced water structure built around the hydrophobic regions of the polymer molecule. This could also be considered as the dehydration of the polymer at high temperatures.

Aqueous solutions of HPC at concentrations of 20 %w/w are considered isotropic at room temperature but form precipitating spherical droplets at 40°C turning white and turbid. Under the microscope these droplets look anisotropic with the presence of maltese crosses. The precipitation of these droplets coincides with a sharp increase in turbidity (Guido and Grizzuti 1995).

The reduction in viscosity may be explained due to the dehydration of the HPC molecules and the resulting chain flexibility. Chain rigidity is associated with strong hydrogen bonding; between HPC molecules and with water molecules (Guido and

Grizzuti 1995). As these hydrogen bonds are broken by temperature increase the HPC molecules become more flexible and able to form spherical droplets which eventually precipitate.

This investigation considered HPC concentrations lower than those considered in previous work Werbowyj and Gray (1980), Guido and Grizzuti (1995) and Nishio et al (2002) considered HPC concentrations of ≥ 10 % w/w). However, the impact of polymer concentration on cloudpoint is consistent with observations previously reported. An increase in polymer concentration reduces the cloudpoint temperature for isotropic HPC solutions due to the formation of liquid crystals or HPC spheres which form with an increase in temperature. HPC molecules are dehydrated with heating and the hydrogen bonds between the HPC molecules and water molecule are broken resulting precipitation of the liquid crystals and consequently a reduction in viscosity.

The phases of change observed here are similar to those described by Werbowyj and Gray (1980) and Guido and Grizzuti (1995). In phase i) the HPC solutions are isotropic; in phase ii) the solutions reach cloudpoint and transition to the completed biphasic phase (phase iii). At the concentrations considered here it is not possible for the HPC solutions to reach the anisotropic phase typically observed for HPC concentrations >40 % w/w with an appropriate increase in temperature. The data reported here may be used to further expand the phase diagrams proposed for <20 % w/w HPC concentrations.

Based on these observations HPC polymer solutions may be suitable for spray-drying at an increased temperature, as previously described for hypromellose. Temperature control may not be as critical as a gelation temperature is not present. However, the liquid crystal phenomenon observed could impact both the spray-drying process and characteristics of the spray-dried material produced.

The physical changes observed which occur at temperatures close to 37°C are likely to have significant application for drug development due to the association with body temperature. An application of these physical changes will be discussed further in Chapter 8.

6.4 Conclusion

These data presented in this chapter illustrated that an increase in temperature causes reduction in solubility of HPC in water resulting in precipitation of HPC and consequently a reduction in solution viscosity. Precipitation of the HPC also caused the aqueous HPC solutions to appear cloudy at increased temperature. This temperature is referred to as the 'cloud-point' temperature. Changes in viscosity may occur at temperatures below the cloud-point temperature and at the cloudpoint temperature the viscosity of the HPC solution is significantly decreased. Aqueous HPC solutions do not exhibit a gelation temperature as aqueous hypromellose solutions do.

Due to the precipitation of HPC in aqueous HPC solutions at an increased temperature, these solutions will not be considered for spray drying. The impact of temperature on HPC hydration shown here will be further explored in the presence of paracetamol and ranitidine.

7 INVESTIGATING THE INFLUENCE OF TEMPERATURE AND DRUG SUBSTANCE ON AQUEOUS SOLUTIONS OF HPC

7.1 Introduction

The data in Chapter 6 demonstrated the changes in physical structure of aqueous HPC solutions at increasing temperature determined using viscosity and UV transmission testing. Based on these properties, applications using HPC to develop a paediatric dosage form were examined. Prior to evaluating these applications the impact of drug substances paracetamol and ranitidine on the effects previously observed in Chapter 6 will be considered in this Chapter.

The effects of concentration of these two commonly prescribed paediatric drugs which have different solubilities were considered by solubilising them in various aqueous concentrations of HPC Klucel®EXF Grade solutions and comparing the effect of temperature on viscosity and UV transmission of these solutions with data obtained in Chapter 6 for HPC solutions without drug substance.

7.2 Materials and Methods

Klucel® HPC EXF Pharm was used for this investigation. Details associated with this polymer may be found in Chapters 1 and 2. An aqueous polymer concentration of 5 %w/w was used. A low concentration of the lowest viscosity polymer was considered for this investigation to avoid potential limitations and challenges that may be associated with the high viscosity of solutions prepared using higher molecular weight polymer grades. Data obtained may be transferable to other grades of HPC.

Details of paracetamol and ranitidine may be found in Chapter 1 and 2. In this Chapter a range of concentrations of drug substances were considered.

Table 7.1 shows the concentrations of the drug substances used and the respective composition of each solution are shown in Tables 7.2 and 7.3.

Table 7.1 Active polymer solutions considered

Polymer Grade	Polymer Concentration (mg/g)	Drug	Drug Concentration (mg/g)	Drug:Polymer Ratio
EXF	50	Paracetamol	5	1:10
			10	1:5
			15	3:10 (1:3.3333)
			20*	1:2.5
			25*	1:2
		Ranitidine	2.5	1:20
			5	1:10
			50	1:1
			100	2:1

Note

* A clear solution could not be achieved so a maximum paracetamol concentration of 15 mg/g was considered for this investigation.

Ranitidine hydrochloride is significantly more soluble than paracetamol (>10x) so a higher concentration range could be considered for ranitidine. A maximum concentration of 15 mg/g was achieved for paracetamol and a highest concentration of 100 mg/g was considered for ranitidine. Consequently, a drug:polymer ratio range of 1:10 to 3:10 (1:3.333) was considered for paracetamol and 1:20 to 2:1 for ranitidine.

Table 7.2 Quantitative composition of paracetamol aqueous HPC solutions (per 500g of solution)

	Drug substance Concentration (mg/g)*									
	5		10		15		20		25	
Excipient	% w/w	g	% w/w	G	% w/w	g	% w/w	g	% w/w	g
Paracetamol	0.5	2.5	1.0	5.0	1.5	7.5	2.0	10.0	2.5	12.5
Polymer	5.0	25.0	5.0	25.0	5.0	25.0	5.0	25.0	5.0	25.0
Purified Water	qs	qs	qs	Qs	qs	qs	qs	qs	qs	qs
Total	100.0	500.0	100.0	500.0g	100.0	500.0	100.0	500.0	100.0	500.0

Note

* Concentrations are expressed as mg/g of solution.

Table 7.3 Quantitative composition of ranitidine aqueous HPC solutions (per 500g of solution)

	Drug substance Concentration (mg/g*)							
	2.5		5		50		100	
Excipient	% w/w	g	% w/w	g	% w/w	g	% w/w	g
Ranitidine**	0.25	1.25	0.5	2.5	5.0	25.0	10.0	50.0
Polymer	5.0	25.0	5.0	25.0	5.0	25.0	5.0	25.0
Purified Water	qs	qs	qs	qs	qs	qs	qs	qs
Total	100.0	500.0	100.0	500.0g	100.0	500.0	100.0	500.0

Note

* Concentrations are expressed as mg/g of solution.

** Weighing factor for ranitidine hydrochloride (refer to Table 2.6).

7.2.1 Preparation of aqueous HPC solutions

Aqueous solutions of HPC were prepared as described in Section 3.2.2.

7.2.2 UV transmission measurement

The theory of UV spectroscopy is described in Section 2.2.2 of this investigation. UV transmission was used here to determine how HPC solutions physically change with an increase in temperature. As the test sample becomes more cloudy, the per-cent UV transmission decreases. UV transmission measurements were performed as described in Section 6.2.3.

The per-cent UV transmission was plotted as a function of temperature. A change in physical appearance of the test solution was indicated by a change in per-cent UV transmittance.

7.2.3 Viscosity determination of aqueous HPC solutions

The viscosity of the aqueous HPC solutions was measured using the same method described in Section 6.2.2.

7.2.4 Hot stage microscopy

HPC solutions were characterised using hot stage microscopy. Hot stage microscopy is described in Section 2.2.3. HPC solutions were heated using a Mettler hot stage plate (Mettler FTP82HT, UK) and images were captured using an Olympus Camera and Microscope (BH2 Optical Microscope, UK). A sample of 5 % w/w EXF HPC solution containing 15 mg/g of paracetamol was heated from room temperature to 45°C at a rate of 2 °C/min and then held at 45°C for 2 minutes before cooling back to room temperature. Changes in the physical appearance were observed at 100x magnification using cross polarised light.

7.3 Results and Discussion

7.3.1 Preparation of aqueous HPC solutions containing drug substance

Ranitidine formed a yellow solution when dissolved in purified water. 5 % w/w EXF HPC solutions containing ranitidine at a concentration of 100 mg/g were distinctly more intense in colour than those containing a 2.5 mg/g of ranitidine. Paracetamol formed a colourless solution at concentrations up to 15 mg/g. As UV transmission was used to investigate the impact of temperature on the physical changes within the solution and the potential formation of liquid crystals, it was important that clear solutions were used for this investigation. Therefore, only drug concentrations that produced a clear solution were considered. Ranitidine has a higher solubility than paracetamol so a higher concentration of ranitidine could be used. Paracetamol concentrations of 5 mg/g, 10 mg/g and 15 mg/g and ranitidine concentrations of 2.5 mg/g, 5 mg/g, 50 mg/g and 100 mg/g were investigated.

7.3.2 UV transmission data for HPC solutions containing drug substance

The effect of temperature on percent UV transmission for HPC solutions containing paracetamol and ranitidine at various concentrations was successfully determined. Similar problems were incurred with consistently controlling the temperature of samples at ambient temperatures (<30 °C) as reported in Section 6.3.2.

UV transmission was successfully used to identify physical changes in the visual appearance of the solutions caused by temperature increase. In all cases HPC solutions containing paracetamol and ranitidine changed from clear to cloudy upon heating.

Per-cent UV transmission data were collected for 5 %EXF HPC solutions prepared containing paracetamol and ranitidine as detailed in Table 7.1. The per-cent UV transmission data for these HPC solutions against temperature are shown in Figure 7.1 and 7.2.

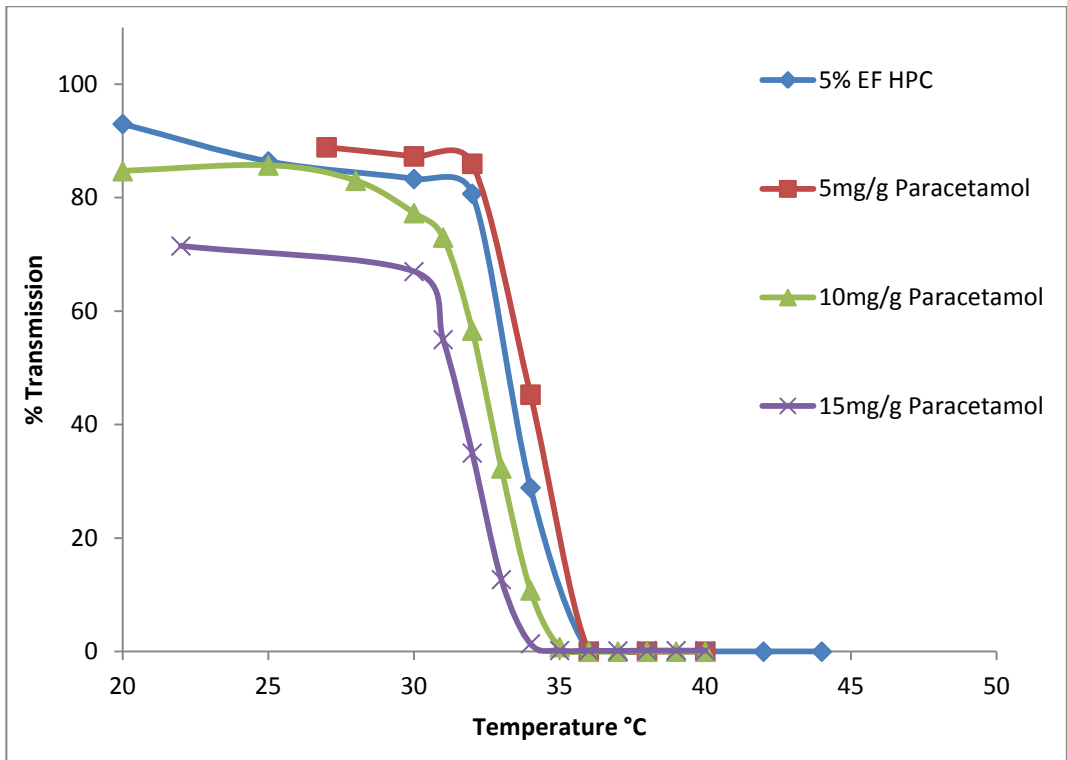


Figure 7.1 Effect of temperature on the % transmission for 5 %EXF HPC solution containing different concentrations of paracetamol

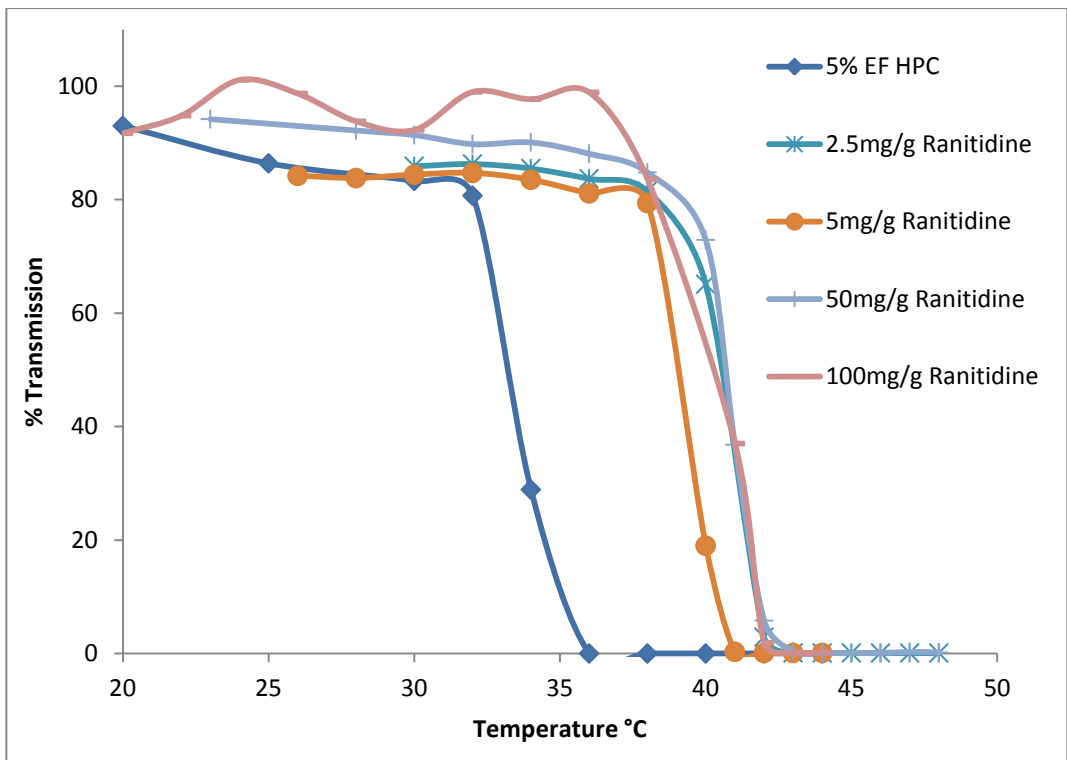


Figure 7.2 Effect of temperature on the % transmission for 5 %EXF HPC solution containing different concentrations of ranitidine

These data demonstrate that minimum per cent UV transmission is achieved at 34°C to 36°C for 5 % w/w EXF HPC solutions containing paracetamol at concentrations up to 15 mg/g and 42°C to 44°C for 5 % w/w EXF HPC solutions containing ranitidine at concentrations up to 100 mg/g.

Each HPC solution containing paracetamol reached a minimum per cent UV transmission at a lower temperature than HPC solutions containing no drug. HPC solutions containing paracetamol exhibited a slow onset of physical change initially as indicated by per-cent UV transmission measurement, followed by a significant change between 30°C and 35°C before rapidly reaching minimum per-cent UV transmission at 35°C to 38°C, as previously observed for HPC solutions without drug (Section 6.3.2). The concentration of paracetamol appeared to influence the temperature at which the onset of change occurred. HPC solutions containing 15 mg/g paracetamol begin to change at a slightly lower temperature than HPC solutions containing 10 mg/g paracetamol solutions which change at a lower temperature than HPC solutions containing 5 mg/g paracetamol solutions or HPC solutions containing no drug. Thus the onset temperature decreased with increasing paracetamol concentrations.

HPC solutions containing 15 mg/g paracetamol exhibit a lower percent UV transmission at ambient temperature (22°C) than HPC solutions containing no paracetamol or those containing 5 mg/g and 10 mg/g of paracetamol. This may be due to the onset of physical change occurring at a temperature below 22°C or be due to the maximum aqueous solubility of the paracetamol being exceeded at 15 mg/g and the undissolved paracetamol impacting the per cent UV transmission.

HPC solutions containing ranitidine reached a minimum per cent UV transmission at a higher temperature than HPC solutions not containing drug substance or those HPC solutions containing paracetamol. The concentration of ranitidine did not influence the onset temperature or the temperature at which minimum per cent UV transmission occurred.

The HPC solution containing 100 mg/g ranitidine exhibited more variability in per cent UV transmission against temperature between 20°C and 38°C than all other samples tested. This may be due to the physical changes at this concentration

occurring non-homogeneously within the sample. The process of physical changes or phases of transformation occurring within all samples tested may be being exaggerated at the 100mg/g concentration due to the higher concentration of drug and associated high drug:polymer ratio of 1:5.

These data indicate that drug concentration (influenced by drug solubility) influence the phase transformation exhibited by HPC. Similar effects have also been observed by Prevys et al (1997) and Nishio et al (2002).

7.3.3 Viscosity data for HPC solutions containing drug substance

Viscosity testing was performed as described in Section 7.2.2.

Figure 7.3 illustrates the effect of temperature on the viscosity of HPC solutions containing ranitidine.

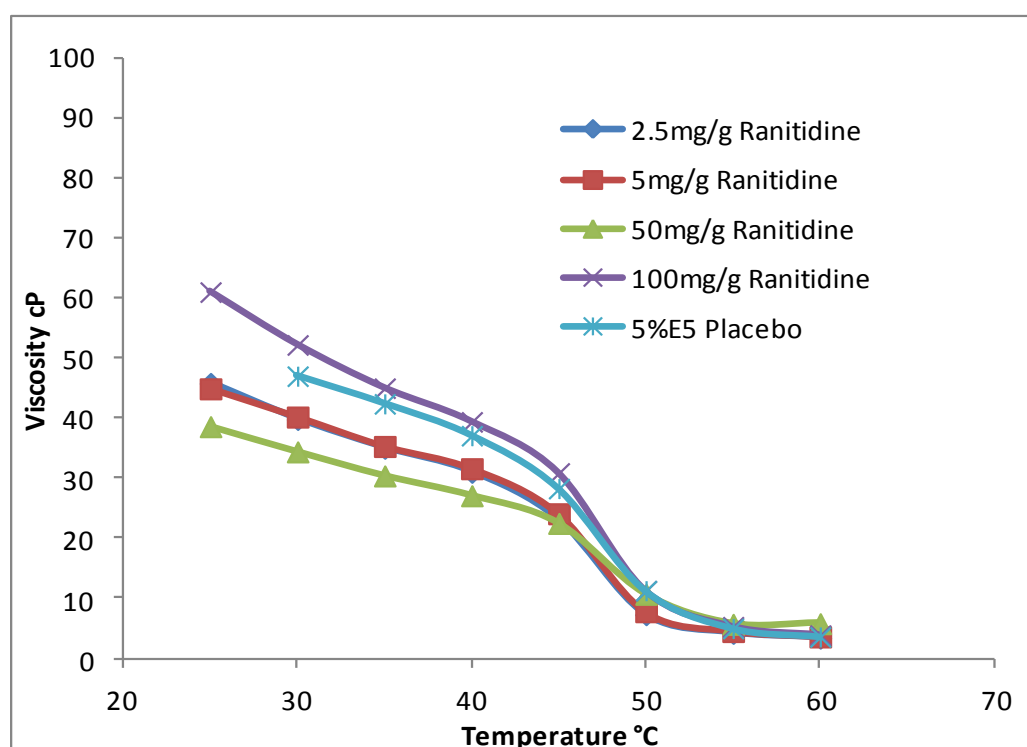


Figure 7.3 Effect of temperature on viscosity of 5 %EXF HPC solutions containing different concentrations of ranitidine

Each HPC solution containing ranitidine showed a decrease in viscosity with an increase in temperature. Fig 7.3 shows similar sigmoidal shapes to that previously

observed for HPC solutions not containing drug substance. As previously observed and described in Chapter 6, the change in viscosity appeared to occur in 3 phases; i) 1 linear reduction in viscosity ii) at 45°C the rate of change in viscosity is more significant and at phase iii) 50°C the rate of change reaches a minimum and minimum viscosity is reached. HPC solutions containing ranitidine reached the second phase at a slightly higher temperature than HPC solutions not containing a drug substance.

The HPC solution containing 100 mg/g ranitidine had the highest viscosity; slightly higher than the HPC solution not containing drug at 30 °C. HPC solutions containing 2.5, 5 and 50 mg/g ranitidine have a slightly lower viscosity than the HPC solution not containing drug. The impact of ranitidine concentration had minimal impact on the viscosity of the solutions and had the least impact at 60°C where all solutions had similar viscosities.

HPC solutions containing 5 %EXF HPC and various concentrations of ranitidine exhibited similar change in viscosity with increasing temperature to 5 % EXF HPC solutions not containing drug substance. Ranitidine had minimal impact on viscosity of the HPC solution.

Figure 7.4 illustrates the effect of temperature on the viscosity of HPC solutions containing paracetamol.

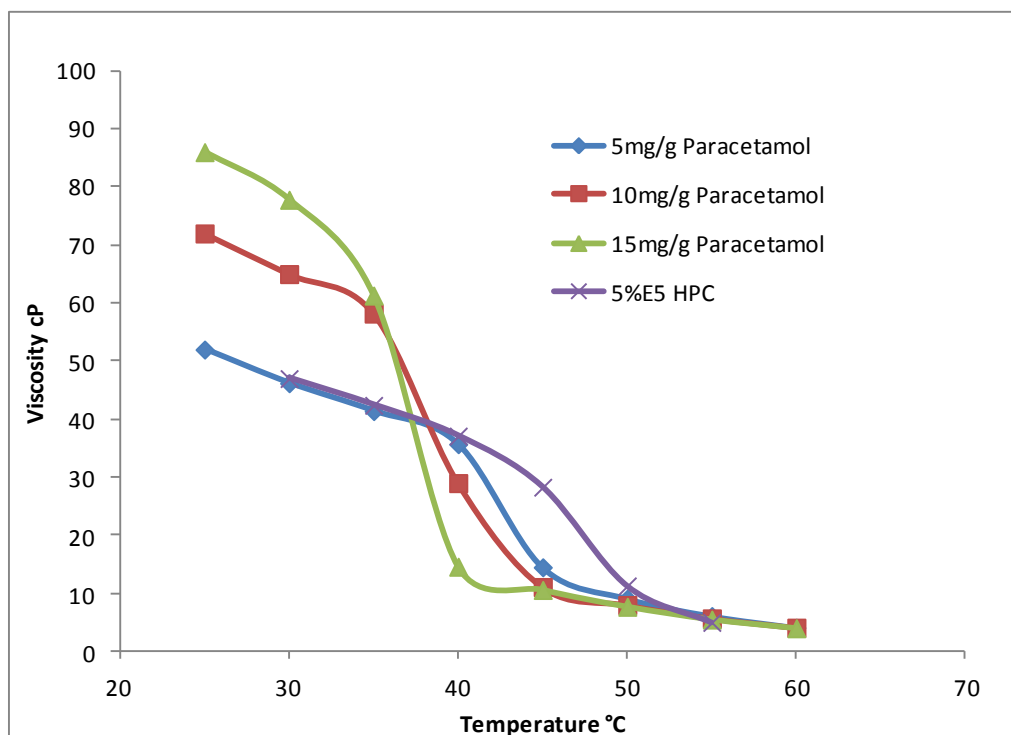


Figure 7.4 Effect of temperature on viscosity of 5 %EXF HPC solutions containing different concentrations of paracetamol

Each HPC solution containing paracetamol showed a decrease in viscosity with an increase in temperature. The plot shown in Fig 7.4 shows a similar sigmoidal shape plot to that previously observed for HPC solutions not containing drug substance (Section 6.3.3) and those containing ranitidine. At 35°C the viscosity of HPC solutions containing 10 mg/g and 15 mg/g paracetamol decreased significantly. Viscosity of HPC solutions containing 5 mg/g paracetamol decreases at 40 °C. Minimum viscosities were reached at 40°C for 15 mg/g and at 45°C for 5 mg/g and 10 mg/g paracetamol HPC solutions. HPC solutions containing 10 mg/g and 15 mg/g paracetamol exhibited a decrease in viscosity at a slightly lower temperature than HPC solutions not containing drug substance, those containing 5 mg/g HPC solutions containing paracetamol reached minimum viscosity at a temperature slightly lower than HPC solutions not containing drug substance. HPC solutions containing a higher concentration of paracetamol exhibit the greatest and fastest change in viscosity.

HPC solutions containing 5 %EXF HPC and various concentrations of paracetamol exhibited a similar pattern in change in viscosity with increasing temperature to 5 % EXF HPC solutions not containing drug substance. The inclusion of paracetamol

increased the viscosity of HPC solutions and reduced the temperature at which phase changes occurred in viscosity.

7.3.4 Hot stage microscopy

Hot stage microscopy was used to investigate the physical change which occurred to HPC polymer solutions upon heating.

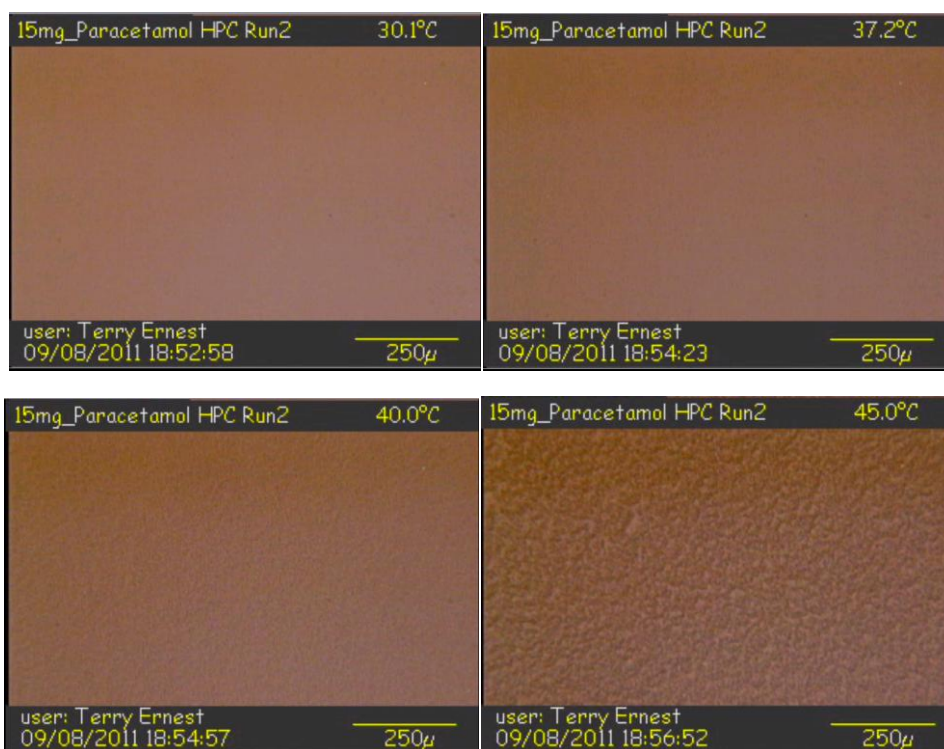


Figure 7.5 Still images obtained from the Hot Stage Microscope of HPC polymer solution containing 15 mg/g paracetamol heated at various temperatures.

The images shown in Figure 7.5, are still shots obtained during video data capture. Changes in physical appearance were observed at 100x magnification using cross polar light.

These hot stage microscopy images shows how the liquid solution dehydrates and precipitated at increasing temperature. With increasing temperature, greater 'texture' may be observed within the sample. These images are consistent with physical changes discriminated using UV transmission and viscosity determination.

Plots of percent UV transmission versus temperature and viscosity versus temperature for HPC solutions containing drug substance exhibited a similar sigmoidal shape and indicate that change with temperature occurred in distinct phases as observed in Chapter 6.

The influence of paracetamol and ranitidine on these changes was also similar for both percent UV transmission and viscosity. Ranitidine increases the temperature at which these phase changes occurred and paracetamol decreased the temperature of change.

The low solubility of the paracetamol reduces the cloud point of the HPC solutions resulting in precipitation of the HPC molecules occurring at a lower temperature and hence giving a reduced cloud-point temperature. This is also supported by the change in viscosity observed for high concentration paracetamol solutions.

The effect of ranitidine on HPC solutions may be described by the salting in behaviour associated with the hydrochloride salt (Drummond et al 1992, Carlsson 1990, Prevysh et al 1996, Bonnet-Gonnet et al 2001 and Nishio et al 2002). As the hydrochloride salt dissociates upon solubilisation of the ranitidine hydrochloride the hydrogen ions are available to repair the hydrogen bonds which break during dehydration of the HPC molecules. This results in an increased LCST for solutions containing ranitidine and a consequential change to the cloud point temperature for these solutions. This effect is not directly associated with the concentration of ranitidine as eventually the effect of temperature overcomes the ability for the hydrogen bonds to be replaced.

The effect of ranitidine on HPC solution viscosity did not appear to be related to the effect on percent UV transmission. This may be due to the viscosity effects observed occurring in the isotropic phase and being independently of the phase transition associated with temperature. The viscosity changes observed for HPC solutions containing ranitidine occurred at temperatures below the cloudpoint and are similar to the viscosity changes which occur for HPC solutions not containing drug substance. If the cloudpoint can be increased by the addition of drug substance the viscosity of the solution will not be impacted and will perform similarly to HPC solutions not containing drug substance. Changes in viscosity which occur at

temperatures below the cloudpoint are not associated with the phase transition and precipitation of the HPC. This is likely to be due to the realignment of the HPC molecules at increasing temperature just prior to liquid crystal formation (see Section 6.3). The realignment results in a reduction in viscosity but not a change in per cent UV transmission as the HPC does not need to precipitate for a change in viscosity to be observed.

7.4 Conclusion

HPC solutions containing paracetamol and ranitidine were influenced by temperature in a similar way to HPC solutions without drug, as discussed in Chapter 6. Ranitidine increased the temperature at which these phase changes occur and paracetamol decreases the temperature. The 'sparingly soluble' drug paracetamol (<15 mg/ml) decreased the temperature of dehydration and precipitation onset and the 'freely soluble' drug ranitidine (>100 mg/ml) increased the temperature of dehydration and precipitation. The 'freely soluble' drug ranitidine (>100 mg/ml) did not influence the viscosity of the HPC solution. Aqueous solutions containing HPC do not exhibit a gelation temperature as aqueous solutions containing hypromellose do.

8 HPC Film Preparation and Characterisation

8.1 Introduction

Following the observations made in Chapters 5, 6 and 7 application of these findings to develop a paediatric dosage form using HPC are considered in this Chapter. This Chapter considered the development of an aqueous based HPC film designed to dissolve/melt within the mouth following administration. The dosage form design considered dose flexibility, dose accuracy and potential swallowing difficulties experienced by this age group. Manufacturability of the dosage form was also considered.

Findings in previous Chapters indicated that that the viscosity of a HPC aqueous solution reduced at 35°C to 38 °C; approximately body temperature. This unique characteristic was used as the basis to develop the dosage form.

Based on the data obtained for active HPC solutions in Chapter 7, 5 % Klucel Pharm EXF polymer solutions were used. Films were prepared without drug and with various concentrations of paracetamol and ranitidine. The effect of drying conditions during film manufacture and the inclusion of drug substance on the film characteristics were also investigated.

This Chapter describes the manufacture and characterisation of HPC based films manufactured using an aqueous system.

8.1 Materials and Methods

Klucel® HPC EXF Pharm was used for this investigation. Details associated with this polymer may be found in Chapter 1 and Chapter 2. An aqueous polymer concentration of 5 %w/w was used. A low concentration of the lowest viscosity polymer was considered for this investigation to avoid potential limitations and challenges that may be associated with the high viscosity of solutions prepared using higher molecular weight polymer grades (see Sections 4.3.1 and 4.3.2). Data obtained may be transferable to other grades of HPC.

Paracetamol and ranitidine were used as model drugs. Details of paracetamol and ranitidine may be found in Chapter 1 and 2. In this Chapter, a range of drug substance concentrations were considered (Table 8.1).

Table 8.1 Polymer and drug solution concentrations used to produce films

Polymer Grade	Polymer Concentration (mg/g)	Drug	Drug Concentration (mg/g)	Drug:Polymer Ratio
EXF	50	None	None	Polymer only
		Paracetamol	5	1:10
			15	3:10 (1:3.3333)
		Ranitidine	2.5	1:20
			5	1:10
			15	3:10 (1:3.3333)
			50	1:1
			100	1:2

8.2.1 Manufacture of HPC Films

HPC films were prepared from aqueous HPC solution. HPC solutions listed in Table 8.1 were prepared as described in Section 3.2.2.

One mL of each solution per film was transferred using a calibrated positive displacement pipette (Gilson Microman, US) to a PTFE coated ampoule cap used as a casting plate (Fig. 8.1 (Part Number FB67567 Fisherbrand, FisherScientific, UK)).



Figure 8.1 PTFE coated ampoule cap used as a casting plate

The HPC solution was slowly transferred from the pipette to the casting plate avoiding entrapment of air. A number of casting plates were prepared for each solution and dried in a Gallenkamp vacuum oven. After drying to a constant weight, the films were removed from the casting plate using a scalpel to remove the films from the aluminium outer wall and then peeling the film from the saran-faced surface. The films were then characterised using a variety of techniques.

8.2.1.1 Development of drying process

The required drying time and temperature were determined by drying to a constant weight at 40 °C, 60°C and 80°C in the Gallenkamp vacuum oven using a vacuum of 400 mbar. Having determined the required drying time at each oven temperature at a vacuum of 400mbar, the same drying time for each drying temperature was used to prepare subsequent films; thus avoiding the need to weigh each subsequent film to ensure drying was complete. A 5 % EXF HPC solution containing 15 mg/g paracetamol was used to determine the required drying time.

The tare weights of 9 numbered casting plates were determined and each filled with 1mL of 5 % EXF HPC solution containing 15 mg/g paracetamol. The weight of the casting plates plus the 1mL solution was determined and recorded. Three of the plates were dried at 40 °C, 3 at 60°C and 3 at 80 °C. In all cases the vacuum applied was set at 400 mBar. The weights of the samples were recorded at 30 min intervals. The films were dried until a constant weight was achieved. These respective drying times, 6 hrs at 40 °C, 3 hrs at 60°C and 2 hrs at 80°C were used throughout this investigation and films produced at these conditions were characterised and compared.

In addition the impact of vacuum applied during drying was also assessed. Vacuums of 400 mBar and 600 mBar were used to dry films and the impact on the physical appearance of the films produced was determined.

8.2.2 Characterisation of films

Three films of the placebo solution and three films of each concentration of paracetamol and ranitidine solutions were cast. Films were cast by drying the

solutions at various drying temperatures and times. When dried, the films were carefully removed from the casting plates using a scalpel.

After their preparation, the films were characterised using a variety of techniques. The influence of the three pre-determined drying conditions, drug substance solubility and drug substance concentration on film characteristics was determined. The film manufacturing process and *in-vivo* application of the films produced was assessed following characterisation.

8.2.2.1 Film weight

Films cast were weighed using an analytical balance (Mettler AT400, UK). The weight of each film and the associated mean weights of each of the three films were determined.

8.2.2.2 Film thickness

The individual thicknesses of films cast were measured using a calibrated micrometer (Mitutoyo, Japan). The thickness of each film and the associated mean thicknesses of each of the three films were determined.

8.2.2.3 Disintegration of films

Disintegration testing of films cast was performed according to the methods of Chen (2006) using a 50mL beaker and purified water. Twenty five mL of purified water was placed into the beaker and the beaker placed into a water bath heated at 37 °C. Once the contents of the 50 mL reach 37°C a film is placed into the beaker and the contents of the beaker swirled every ten seconds. The disintegration time was determined when the film began to break or disintegrate. The time taken for the film to fully dissolve was also recorded.

8.2.2.4 SEM analysis of films

SEM images of placebo and films containing paracetamol and ranitidine were obtained as detailed in Section 2.3.1. SEM images of dried films were obtained using a Hitachi S-4700 at 50k magnification.

8.2.2.5 Dissolution and Assay of Films

Different types of dissolution methodology were introduced in Section 2.2.4.

The process of dissolution is described by the Noyes-Whitney equation (Eq 8.1):

$$\frac{\delta w}{\delta t} = k(c_s - c) \quad \text{(Equation 8.1)}$$

Noyes-Whitney describes dissolution as the rate of increase of material in solution

dissolving from a solid $\left(\frac{\delta w}{\delta t}\right)$ (where w is bulk concentration and t is time) being equal to the product of rate constant of dissolution (k) and the difference in concentration between the saturation solubility of the dissolving material and the concentration of that material in the bulk media ($c_s - c$). The rate constant of dissolution (k) per unit time is determined as (Eq 8.2):

$$k = \frac{DA}{\delta} \quad \text{(Equation 8.2)}$$

Where D is the diffusion coefficient of the dissolved solute, A is the area of the solvate particles exposed to the solvent and δ is the thickness of the diffusion layer.

The dissolution rate of films cast from 5 % HPC EXF solutions containing paracetamol at 5 mg/g 10 mg/g and 15 mg/g concentration were determined using USP II paddle apparatus (ref.USP<711>) on a Distek 2100C Dissolution Bath. Nine hundred mL of purified water was used as a media and a paddle speed of 50rpm used. Films were placed in the dissolution vessel whilst still within the casting plates. The casting plate was dropped into the heated media prior to starting the paddles. Care was taken to ensure that the casting plates were orientated with the film uppermost and in the centre of the vessel prior to starting the paddles. The casting plates acted as sinkers to prevent the films from floating.

Water was selected to investigate dissolution performance of the films cast.

Samples were obtained using an automated software program (IDISis v3.01.00B2, UK) and a pump (Icalis Data Systems PCP490, UK), at 5 10 15, 30, 45 and 60 minute intervals. The samples were filtered in-line using a 10 μ m cartridge filter

(Pharmatest, Germany) and the concentration of paracetamol dissolved in the samples obtained was determined using UV absorbance.

UV spectrometry and absorbance is described in Section 2.2.2 of this investigation. A UV absorbance of 243 nm was used to measure the quantity of paracetamol released at each time point. Summaries of the dissolution method and UV method are provided in Tables 8.2 and 8.3.

For UV spectroscopy a specific absorbance ($A^{1\%}_{1\text{cm}}$) value of 712 is recommended in the British Pharmacopeia for assay of paracetamol tablets in 0.1M NaOH. As water was used as the dissolution media, the suitability of this $A^{1\%}_{1\text{cm}}$ was checked by measuring the UV absorbance of 15 mg of Paracetamol in 100mL NaOH and 15 mg of Paracetamol in 100mL of purified water. Using an $A^{1\%}_{1\text{cm}}$ of 712, an assay value of 100.1 % was obtained for the NaOH Paracetamol Solution and an assay value of 93.6 % was obtained for the aqueous paracetamol solution. Based on this data an $A^{1\%}_{1\text{cm}}$ of 712 was considered appropriate for the online analysis associated with the dissolution testing of the films and solid state paracetamol.

Table 8.2 Summary of dissolution method parameters

Dissolution Parameters	Value
Apparatus	USP <711> Apparatus 2 (paddles)
Dissolution Media	Purified Water
Dissolution Medium Volume	900ml (\pm 9ml)
Dissolution Temperature	37.0°C (\pm 0.5 °C)
Rotation Speed	50rpm (\pm 2rpm)
Sampling Time	0, 5 10 15, 30, 45 and 60 mins
Filter	10 μ m, polypropylene
Pump Speed	75rpm

Table 8.3 Summary of on-line UV analysis

UV Analysis Parameters	Value
Wavelength	243 nm
Cell Pathlength	2mm
$A^{1\%}_{1\text{cm}}$	712

Film dissolution data were compared to the dissolution of solid state paracetamol. 15 mg of paracetamol powder was dispensed into 3 weighing boats. Using the

dissolution parameters shown in Table 8.2 and UV analysis parameters shown in Table 8.3, the contents of the weighing boats were transferred to three dissolution vessels whilst the paddles were rotating. Dissolution data were obtained as previously described for the films.

The same UV analysis was used to assay paracetamol content of films cast. Five films of each drying condition weighed using an analytical balance and each individual weight recorded. The films were then placed into 250mL volumetric flasks and dissolved using sodium hydroxide according to British Pharmacopeia (BP 2013). The solutions were measured using UV absorbance at 257 nm using 715 as the A1:1 value as provided in BP2013. The quantity of paracetamol present in each film was determined as mg of paracetamol per mg of film.

8.2.2.6 DSC analysis of films

As described in Section 2.3.5 DSC was used in this investigation to determine if there was a glass transition temperature associated with the HPC films or other thermal events. Placebo films and films containing paracetamol and ranitidine were tested. Testing was performed using a DSC Instrument (DSC Q2000 V24.4 Build 116, Country). Samples of each film were prepared by weighing 1 mg (+/- 0.5 mg) of film using a scalpel to cut the film. The test film weight for each sample was recorded. Each sample was scanned at a heating rate of 10 °C/min up to 250 °C.

8.2.2.7 TGA analysis of films

As described in Section 2.3.6, to supplement the DSC testing, TGA was also used. Placebo films and films containing paracetamol and ranitidine were also tested. Testing was performed using a TGA instrument (TGA Q500 V6.7 Build 203, US). Samples of each film were prepared by weighing 1 mg (+/- 0.5 mg) of film using a scalpel to cut the film. The test film weight for each sample was recorded. Each sample was scanned at a heating rate of 10 °C/min up to 250 °C.

8.3 Results and Discussion

8.3.1 Manufacture of Films

A 5 % EXF HPC solution containing 15 mg/g paracetamol was used to determine the most appropriate film drying conditions. 1mL of 15 mg/g solution was dried to constant weight at 40 °C, 60°C and 80°C using a vacuum of 400mBar. Figure 8.2 shows the weight loss over time during drying.

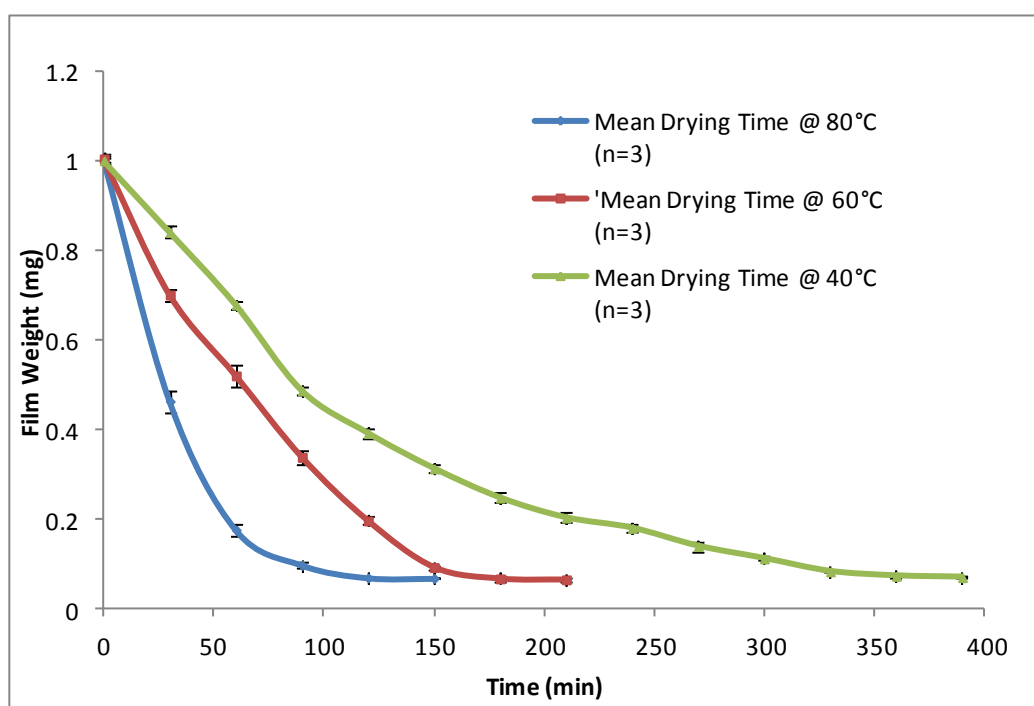


Figure 8.2 Effect of drying time on 15 mg/g paracetamol film samples dried at 40°C, 60°C and 80°C.

These data demonstrate that when drying the films at oven temperatures of 40 °C, 60°C or 80 °C, a constant weight was achieved after 6, 4 or 2 hrs respectively. The constant weight to which the films were dried was approximately consistent with the polymer content and paracetamol content mass present in each film. For example, a 1g 5 %w/w HPC film containing 15 mg/g of paracetamol contained 50 mg of HPC EXF Polymer and 15 mg of Paracetamol, corresponding to 65 mg of dry material. The remaining quantity of purified water per 1g film (935 mg) was removed during drying. Drying endpoint was confirmed when films were dried to a consistent film weight and may also be verified by comparing this dry weight to the theoretical dry film weight calculated based on polymer and drug mass per film.

Therefore, these data demonstrate that the drying process employed i.e. either 2 hrs at 80 °C, 4 hrs at 60°C or 6 hrs at 40°C were effective at removing all purified water from the sample enabling a film to be formed.

During this drying investigation the vacuum applied was also considered and 400mBar was found to be the most appropriate. In the absence of vacuum a significant quantity of condensation formed within the oven and this is likely to impact the drying of the films due to the potential for secondary 'wetting' of the films. A high vacuum of 600mBar resulted in the presence of significant air bubbles within the film surface and consequently poor quality films were produced. A vacuum of 400mBar was determined as the greatest vacuum possible to decrease the drying time without compromising film quality.

From a commercialisation perspective the fastest drying time achievable without compromising film quality would be utilised.

The effect of drying time and temperatures implemented here and shown in Table 8.4, on film characteristics will be investigated in this Chapter.

Table 8.4 Drying conditions employed for HPC film manufacture.

Drying Temperature °C	Drying Time (Hrs)	Vacuum (mBar)
40	6	400
60	3	400
80	2	400

The HPC solutions shown in Table 8.1 were produced and dried according to the conditions shown in Table 8.4. Table 8.5 below summarises the potential to form films for each polymer solution.

Table 8.5 Physical appearance films produced from solutions prepared in Table 8.1

Polymer Grade	Polymer Concentration (mg/g)	Drug	Drug Concentration (mg/g)	Drug:Polymer Ratio	Appearance of films produced
EXF	50	None	None	Polymer only	Intact, clear film with no cracks
		Paracetamol	5	1:10	Intact, clear film with no cracks
			15	3:10 (1:3.3333)	Intact, clear film with no cracks
		Ranitidine	2.5	1:20	Intact, clear, slightly yellow film with no cracks
			5	1:10	Intact, opaque, pale yellow film with no cracks
			15	3:10 (1:3.3333)	Intact, opaque, pale yellow film with no cracks
			50	1:1	White to slightly brown film with a number of severe cracks around the edges. A poor brittle film.
			100	1:2	A brown film with a number of severe cracks around the edges. A poor brittle film.

Note

Shaded area indicates solutions for which films could not be successfully prepared.

Table 8.5 shows that HPC solutions containing ranitidine at higher concentrations formed very poor films. The films produced from solutions containing 50 mg/g and 100 mg/g ranitidine were severely cracked and brown in colour. The films had a

large hole in the centre and severe cracks around the edges that resembled channels. Films produced from solutions containing a lower concentration of ranitidine (2.5 mg/g, 5 mg/g and 15 mg/g) were much better but were opaque with a slightly uneven distribution of colour and opaqueness. The films were intact without any signs of cracking. It was possible to form HPC films from solutions containing ranitidine at concentrations up to 15 mg/g. It was not possible to form HPC films from solutions containing ranitidine at concentrations of 50 mg/g or greater.

Films prepared from HPC solutions not containing drug substance and solutions containing paracetamol at concentrations up to 15 mg/g were clear and fully intact with no signs of cracking or fracture. Good quality films may be produced from HPC solutions containing no drug substance and those containing paracetamol up to 15 mg/g. These films were fully characterised using a range of characterisation techniques.

Based on the aqueous solubility of ranitidine it was possible to prepare solutions at concentrations up to 100 mg. Paracetamol however, has a much lower aqueous solubility and therefore the maximum solution concentration that could be prepared using paracetamol was 15 mg/g. The visual observations made (Table 8.5) suggest that the maximum drug:polymer ratio that enabled good intact films to be produced is 3:10, meaning a minimum polymer level of 3 times that of the level of drug was required to form good quality films.

Drug:polymer ratio is critical to determining the visual quality of films produced. This requirement is likely to limit the drug loading permissible for this HPC polymer film system as high polymer content is likely to have a detrimental impact on other film characteristics such as disintegration time and dissolution rate.

8.3.2 Film Characterisation

8.3.2.1 Film weight and film thickness

Upon removing the dried films from the casting plates the films were weighed and the film thickness determined for placebo films and those containing 5 mg/g and 15

mg/g paracetamol. The impact of drying conditions on film weight and film thickness was determined. The data obtained is shown in Table 8.6.

The weights obtained show that some material was lost to the walls of the casting plates for all films and for all drying conditions. Placebo films dried for 2 hrs at 80°C had a slightly lower weight and were slightly thinner than all other films prepared.

Table 8.6 The impact of drying conditions on film weight and film thickness

Formulation	Drying Conditions	Film Weight (mg)	Film Thickness (µm)
5% EF HPC Placebo Solution	6 hours @ 40°C	28.35	60
		20.62	57
		24.18	61
	3 hours @ 60°C	26.30	60
		28.50	59
		27.50	61
	2 hours @ 80°C	17.00	38
		22.50	38
		20.00	37
5% EF HPC Solution containing 5mg/g Paracetamol	6 hours @ 40°C	24.40	64
		22.40	57
		17.40	67
	3 hours @ 60°C	22.60	68
		31.20	63
		19.00	63
	2 hours @ 80°C	23.90	51
		33.03	70
		25.40	51
5% EF HPC Solution containing 15mg/g Paracetamol	6 hours @ 40°C	31.83	62
		27.37	79
		29.80	65
	3 hours @ 60°C	38.40	86
		36.30	88
		37.70	84
	2 hours @ 80°C	28.94	80
		31.81	69
		36.60	81

8.3.2.2 Disintegration of films

Figure 8.3 shows disintegration and complete dissolution times (by visual observation) for polymer films prepared without drug substance and polymer films containing 5 mg/g and 15 mg/g paracetamol.

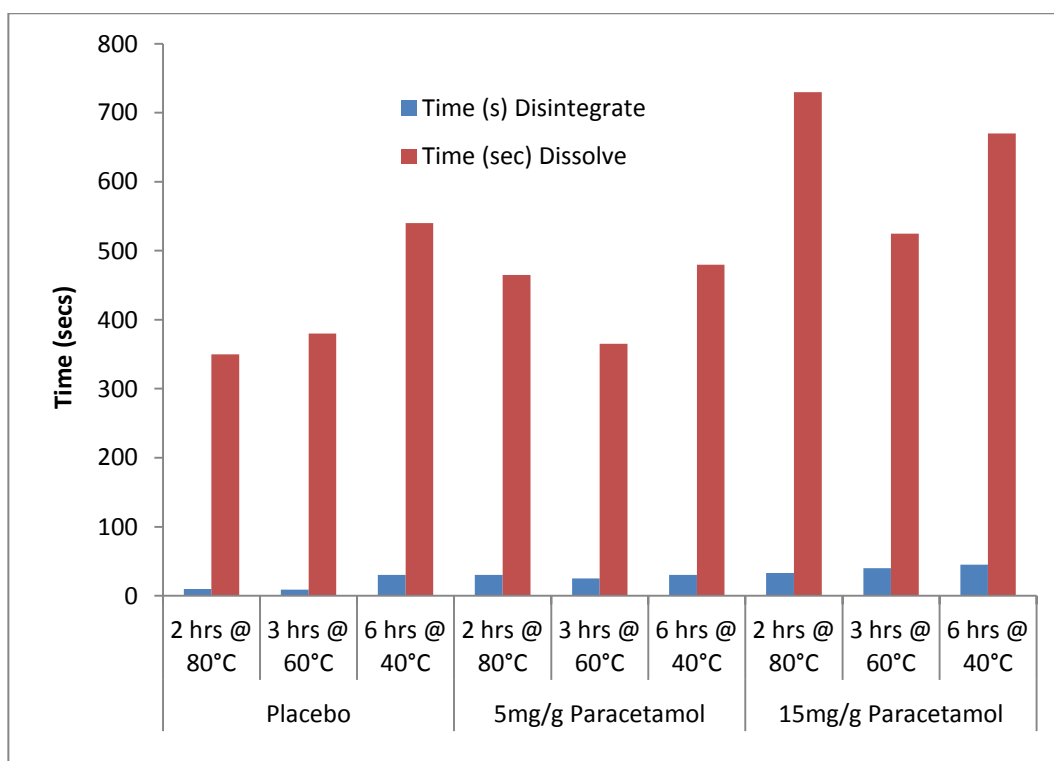


Figure 8.3 Film disintegration time and time to dissolve for HPC films without drug substance and HPC films containing 5 mg/g and 15 mg/g paracetamol

The disintegration data for HPC films containing paracetamol exhibited slightly slower times than films containing no drug substance ('placebo'). However, placebo films dried for an extended period at a lower temperature (6 hrs at 40 °C) disintegrated more slowly compared with similar films dried for a shorter period at a higher temperature. The disintegration time for placebo films dried for 6 hrs at 40°C is similar to the disintegration times for films containing paracetamol. The drying conditions did not affect the disintegration times for films containing paracetamol. An increase in paracetamol concentration increased the disintegration times of the films produced.

Times to completely dissolve showed that all films completely dissolved in 5 to 12 minutes (300 to 720 s). Films containing 5 mg/g paracetamol took longer to dissolve than placebo films; and films containing 15 mg/g paracetamol took longer to dissolve than films containing 5 mg/g paracetamol. Thus an increase in drug content increased the time taken for the film to fully dissolve.

Drying conditions appeared to influence the time taken for the entire film to dissolve. For placebo films, those dried for 6 hrs at 40°C took the longest to dissolve whereas for films containing 5 mg/g and 15 mg/g paracetamol, films dried for 3 hrs at 60°C dissolved the quickest.

The method used to determine disintegration was previously used by Chen (2006) to compare various marketed films and films prepared using different polymers but was very subjective. Disintegration time is determined by the time taken for the film to initially break or disintegrate. The sample is manually agitated during testing by moving the beaker every 10 seconds. The degree of agitation is therefore not controlled and may contribute to differences observed in disintegration times between films. A pharmacopeial test for film disintegration does not currently exist. Standard pharmacopeial tablet disintegration apparatus was considered (BP2013) but the films adhered to the walls of the chambers during reciprocation. An improved disintegration method is required to provide more qualitative assessment of film disintegration.

Placebo films dried for 6 hrs at 40°C exhibited a longer disintegration time than placebo films dried for 2 hrs at 80°C or 3 hrs at 60 °C. Data shown in Figure 6.2 in Section 6.3.3 shows the impact of temperature on HPC solution viscosity. The data indicate that above the cloud point temperature (60°C and 80°C) the viscosity of the polymer solution is likely to be very low due to significant dehydration and disentanglement of the HPC molecules during drying. Due to the dehydration and disentanglement of the HPC molecules the polymer film may also be more brittle and prone to faster disintegration upon rehydration. This is also likely to result in more brittle films being formed. Conversely, at (or just below) the cloud point (40 °C) the HPC solution exists in an anisotropic phase and the HPC will only be partly dehydrated. Upon introduction to an aqueous media complete rehydration will be slower due to partial hydration and entanglement. Disintegration times associated with films dried at 40°C may therefore be longer than for films dried at 60°C or 80 °C.

Data presented in Chapter 7 indicate that the inclusion of paracetamol in the HPC polymer solution reduced the cloud point temperature of the solution and increased the viscosity of the solution. The difference in drying temperature

therefore had much less of an impact on polymer film disintegration due to each drying temperature used being above the cloud point for HPC solutions containing paracetamol (33 °C) as it does for placebo films. However, due to the presence of paracetamol in the solution, the HPC molecules may be unable to disentangle as readily during drying and consequently are possibly not able to dehydrate to the same extent as HPC molecules in placebo films. Films prepared from HPC solutions containing 5 mg/g and 15 mg/g paracetamol disintegrate and dissolve similarly to placebo films dried for 6 hrs at 40°C due to similarities in the extent of dehydration and disentanglement in these films during drying.

8.3.2.3 SEM analysis of Films

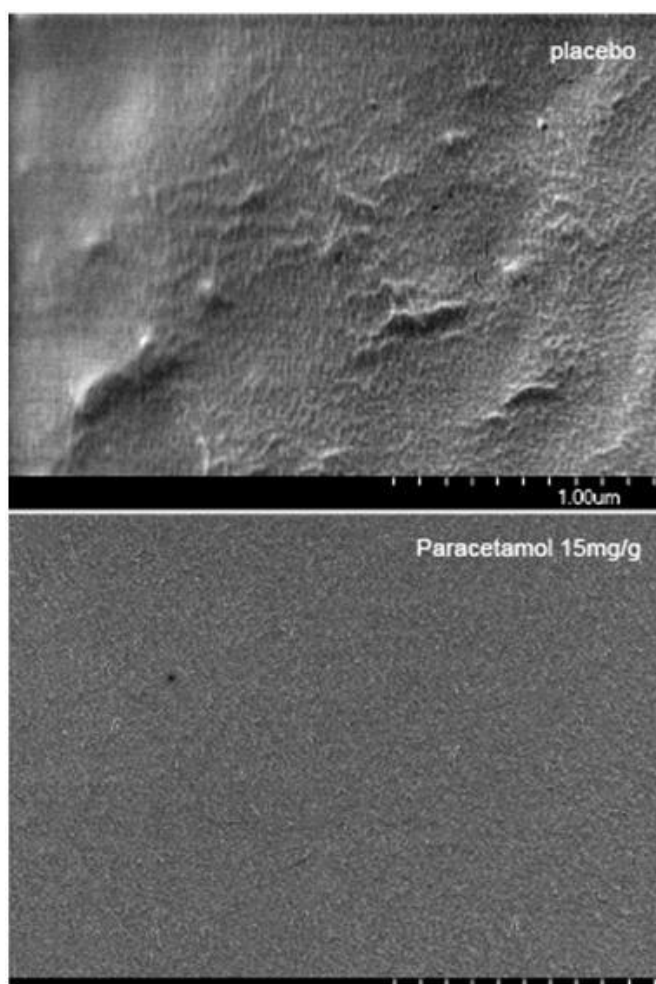


Figure 8.4 SEM images of placebo and 15 mg/g paracetamol film surface

SEM images in Figure 8.4 show a smoother film surface for the film prepared from HPC solution containing 15 mg/g paracetamol than the film prepared from the

placebo sample. This may be due to the influence of paracetamol reducing the viscosity of the film solution and enabling a smoother surface to form during drying.

8.3.2.4 Dissolution of paracetamol from HPC films

Dissolution testing of films containing 5 mg/g and 15 mg/g of paracetamol and dried at 40 °C, 60°C and 80°C was performed according to the method described in 8.2.2.5. Dissolution results are shown in Figures 8.6 and 8.7.

The dissolution profiles obtained for films prepared from HPC solutions containing 5 mg/g and 15 mg/g paracetamol demonstrate that drug release is slower from the films than for drug substance alone. This indicates that the HPC polymer film imparts a delay in the dissolution of the drug substance. The dissolution of the drug substance is likely to be determined by the dissolution of the film i.e. the dissolution of the polymer film is rate limiting. The drug substance is dissolved in the film and therefore as the polymer films dissolves the drug substance will remain dissolved in the dissolution media. The dissolution of the drug substance in the dissolution media is therefore likely to be independent of the solubility of the drug substance as long as it is solubilised within the polymer film. In other words, once dissolved in the HPC aqueous polymer solution the dissolution of the drug substance should be independent of the concentration or absolute solubility in the dissolution media. However, if the absolute solubility of the drug substance is poor in the dissolution media, precipitation of the drug substance may eventually occur.

This is supported by the dissolution profiles obtained for paracetamol drug substance. The time taken to reach 90 % drug release (T90) for 5 mg of paracetamol was 5 mins. The T90 for 15 mg of paracetamol was 10 mins. The T90 for films prepared from HPC solutions containing 5 mg/g and 15 mg/g was the same, 30 mins. The paracetamol drug substance samples follow the Noyes Whitney equation (refer to 5.2.2.1), whereby the particle size, concentration and solubility of the drug substance drive the dissolution rate of the drug substance. As the particle

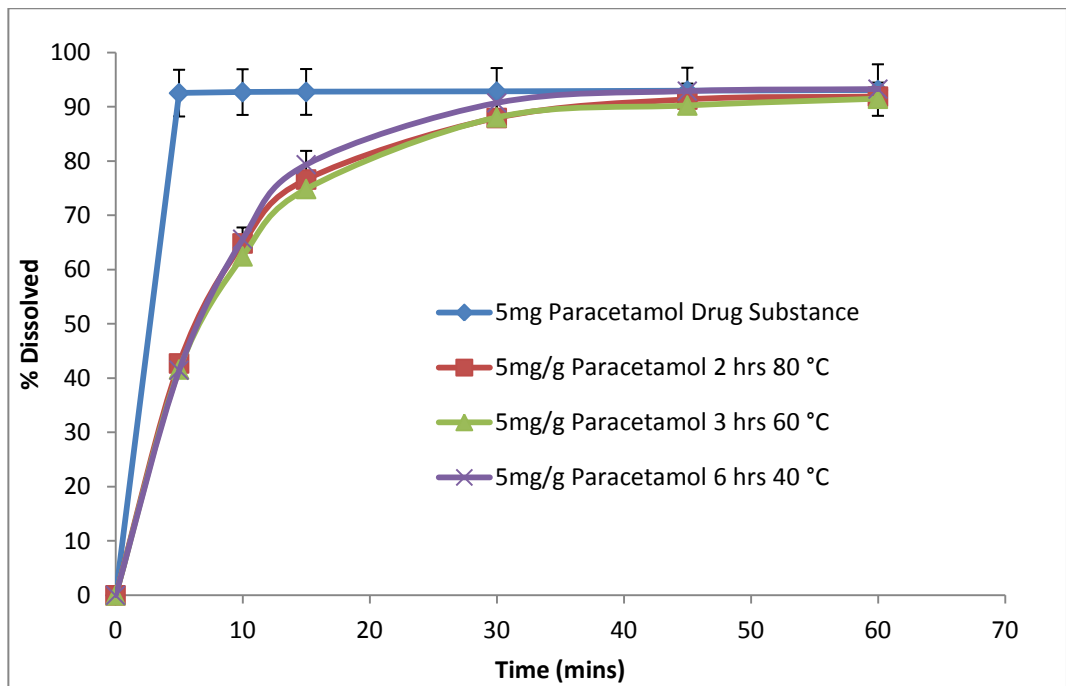


Figure 8.5 Mean (n=3) paracetamol release from 5 mg/g films dried at various conditions and compared to 5 mg paracetamol (Powder) in purified water

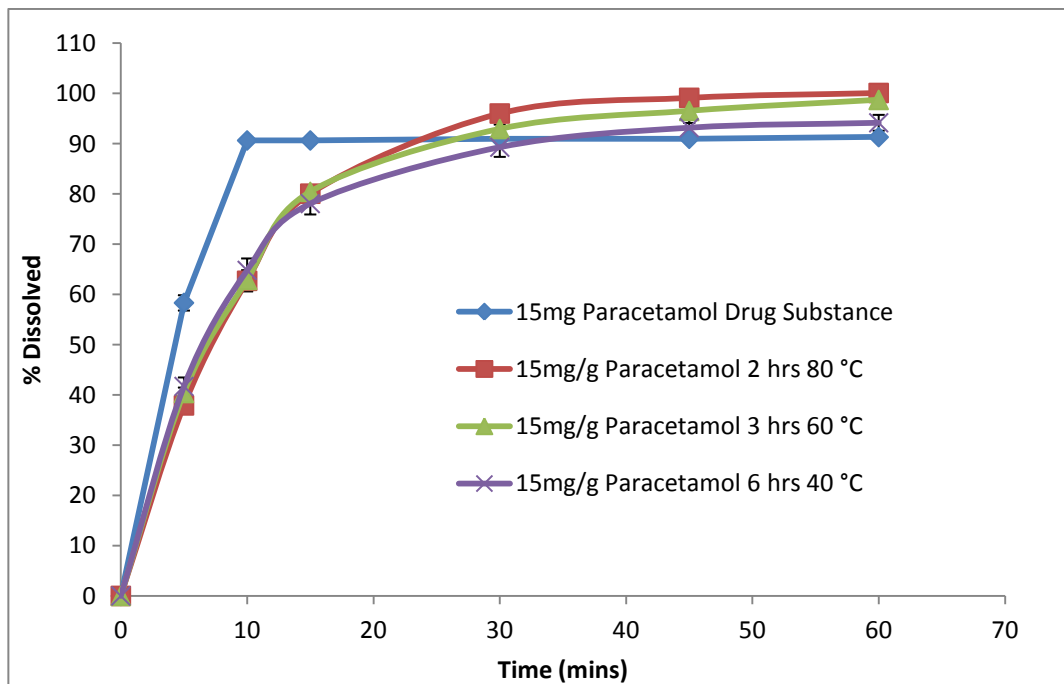


Figure 8.6 Mean (n=3) paracetamol release from 15 mg/g films dried at various conditions and compared to 15 mg paracetamol (powder) in purified water

size and solubility is constant the dissolution will be affected by the concentration of the sample i.e. 5 mg v 15 mg. 15 mg of paracetamol will take slightly longer than 5 mg of paracetamol to reach 90 % release due to the difference in concentration gradient between the two films. In the film samples the paracetamol dissolution is rate limited by the dissolution of the film itself.

Based on these dissolution profiles, the use of HPC polymer films offers significant advantages for oral drug delivery. Drug dissolution from the films is independent of drug substance solubility and concentration if the drug substance is dissolved in the polymer film. The dissolution of the drug in the film is similar to that may occur from an oral solution. This dosage form could therefore help enable linear pharmacokinetics of the drug substance across a range of doses. This has particular advantages for paediatric medicines as this dosage form not only offers dose flexibility based on the size of the dosage unit, but also the potential to predict pharmacokinetics and pharmacodynamics performance when dose titrating by weight or body mass.

Such dissolution performance may also enable HPC films to be used to deliver a combination of drugs with similar dissolution profiles. This would not typically be achievable using other solid oral dosage formulations such as tablets as the dissolution performance of the drug substances would be dependent on the physicochemical properties of the individual active substances which are likely to be different.

Furthermore, the slight delay in drug release imparted by the polymer film may also provide taste masking particularly for highly soluble drug substances with a low concentration taste threshold. For the drug substance to reach the taste concentration threshold sufficient polymer film has to have dissolved and the drug substance concentration threshold be maintained in the mouth cavity (Wise 2013). If the rate of drug release is slower than the rate at which the drug is cleared from the mouth cavity the taste concentration threshold will not be reached.

In addition the drug released from the polymer film is presented to the oral cavity in the solubilised state and therefore there is the potential for drug absorption from the oral cavity.

Buccal absorption avoids first pass metabolism and therefore HPC polymer films may be particularly useful for the oral delivery of drugs requiring avoidance of first pass metabolism.

Drug substance dissolution rate is therefore controlled by the dissolution rate of the polymer film in the dissolution media. Therefore, dissolution rate may be influenced by polymer concentration, film thickness and polymer solubility in the dissolution medium.

The dissolution data shown here also indicate that paracetamol release from films prepared from HPC solution containing 5 mg/g and 15 mg/g paracetamol is independent of the drying conditions used to cast the films. It may therefore be possible to dry the polymer films at a high drying temperature for a short period of time without influencing the dissolution rate of the HPC films produced. Further work may consider the potential application of microwave drying to decrease the drying time. This may offer advantages for scale up and commercialisation. The use of a solvent instead of water would also decrease the drying time but may offer more complications for commercialisation and is not as environmentally friendly as an aqueous based system.

Compared to other films prepared using polymers such as hypromellose (Chen 2006, and Garsuch and Breitkrutz 2010) HPC aqueous films have similar disintegration times. Complete dissolution times recorded here are significantly slower than observed for films produced using other polymer solvent systems but this investigation demonstrates that this has no impact on drug substance dissolution and may positively impact patient adherence. This slow dissolution may help provide taste masking of poorly tasting drug substances. These films are ideally suited for paediatric patients as once administered polymer film hydration occurs rapidly preventing the dosage from being 'ejected' by the patient.

Palatability of the films could be further assessed by performing taste studies in human subjects. If required it may be possible to reduce the time to complete dissolution by reducing the level of polymer used in the film or by adding a surfactant to increase the rate of hydration and subsequent dissolution of the HPC polymer upon administration.

8.3.2.5 Film assay testing

Films prepared at 5 mg/g and 15 mg paracetamol were assayed as detailed in 8.2.2.5.

Table 8.7 Theoretical composition of 5 mg/g and 15 mg/g paracetamol HPC films.

Theoretical Quantity per g of Film Solution (mg)	5 mg/g Paracetamol	15 mg/g Paracetamol
HPC (5 %w/w)	50	50
Paracetamol	5	15
Total Weight	55	65
mg of Paracetamol / mg of film	0.0909	0.2308

The assay data obtained is shown in Table 8.8

Table 8.8 Assay data obtained for films prepared using HPC solutions containing 5 mg/g and 15 mg/g paracetamol

Formulation	Drying Conditions	n =5	Weight (mg)	Assay (mg)	Paracetamol Concentration (mg) / Film (mg)	% Nominal Conc
15 mg/g Paracetamol	6 hrs @ 40 °C	Mean	29.556	6.945	0.234	101.395
		±SD	1.859	0.526	0.005	2.196
		%RSD	6.289	7.572	2.166	2.166
15 mg/g Paracetamol	3 hrs @ 60 °C	Mean	29.940	7.120	0.234	101.574
		±SD	1.560	0.262	0.007	2.866
		%RSD	5.211	3.683	2.821	2.821
15 mg/g Paracetamol	2hrs @ 80 °C	Mean	31.912	7.435	0.230	99.657
		±SD	2.989	0.684	0.017	7.582
		%RSD	9.367	9.195	7.608	7.608
5 mg/g Paracetamol	6 hrs @ 40 °C	Mean	26.520	2.571	0.099	108.506
		±SD	0.971	0.094	0.001	1.281
		%RSD	3.660	3.670	1.181	1.181
5 mg/g Paracetamol	3 hrs @ 60 °C	Mean	26.400	2.538	0.096	105.883
		±SD	1.317	0.077	0.003	3.191
		%RSD	4.989	3.040	3.014	3.014
5 mg/g Paracetamol	2 hrs @ 80 °C	Mean	26.640	2.426	0.097	106.489
		±SD	3.543	0.320	0.001	1.329
		%RSD	13.300	13.195	1.248	1.248

These data are presented as mg of paracetamol per mg of film and as % nominal. % nominal is calculated based on the actual weight of the film removed from the film forming plate. The % nominal mg of paracetamol per mg of film is shown in Table 8.6.

Assay values obtained and \pm SD (Table 8.7) would meet typical values for other solid oral dosage forms (EP 2013). Films dried for 2 hours at 80°C show the greatest variation in film weight and assay however, the drying conditions used do not appear to influence the data obtained for % nominal concentration. The mean % nominal assay data obtained film for the films prepared from HPC solution containing 5 mg/g films are slightly higher than those for the films prepared from the HPC solutions containing 15 mg/g paracetamol but this may be due to some evaporation occurring during the HPC polymer solution manufacture.

The drying conditions used do not appear to influence the assay data obtained enabling a high drying temperature to be used to reduce the drying time for commercial manufacture.

8.3.2.6 Thermal analysis of films

DSC and TGA analysis were performed for placebo HPC films and HPC films containing 5 mg/g and 15 mg/g paracetamol to determine if a glass transition temperature was apparent or if any changes in the physical properties could be observed.

The TGA plot in Fig. 8.7 for the placebo film shows a residual moisture content of 2.402 %. This may be associated with the drying process employed as part of the casting or the equilibrium moisture content of the film after drying. The film may have reached equilibrium moisture content upon storage after manufacture.

This DSC heating programme used in Fig. 8.7 was performed to remove the moisture from sample (step 1 and 2) and to determine if a glass transition temperature T_g was present behind the main moisture peak. No T_g was observed for the placebo film using DSC.

Sample: 5% HPC Placebo EE411574/C
Size: 1.3570 mg
Comment: Performance Check

TGA

File: I:\...TGA Q500\Data\TA0091\TA00913.001
Operator: MKN
Run Date: 22-Nov-10 11:57
Instrument: TGA Q500 V6.7 Build 203

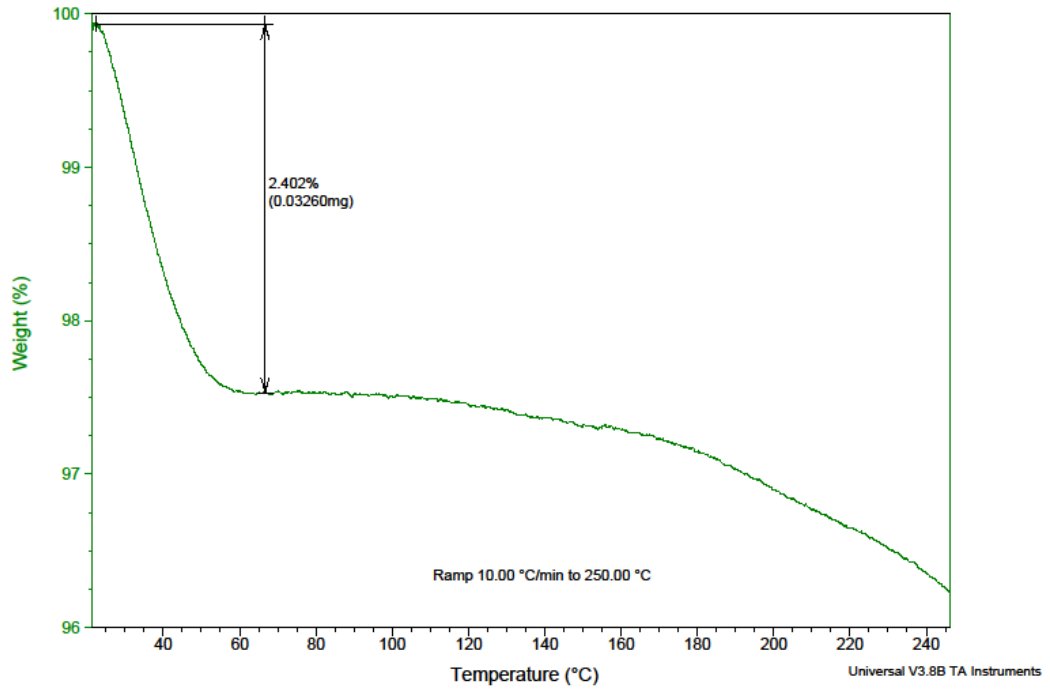


Figure 8.7 TGA plot for HPC film containing no drug substance

Sample: Placebo 5% HPC EE411574
Size: 0.8000 mg
Method: M0011383
Comment: HPC Film

DSC

File: I:\...DSCQ2000\DA0199X\DA01992.001
Operator: TE
Run Date: 22-Nov-10 16:36
Instrument: DSC Q2000 V24.4 Build 116

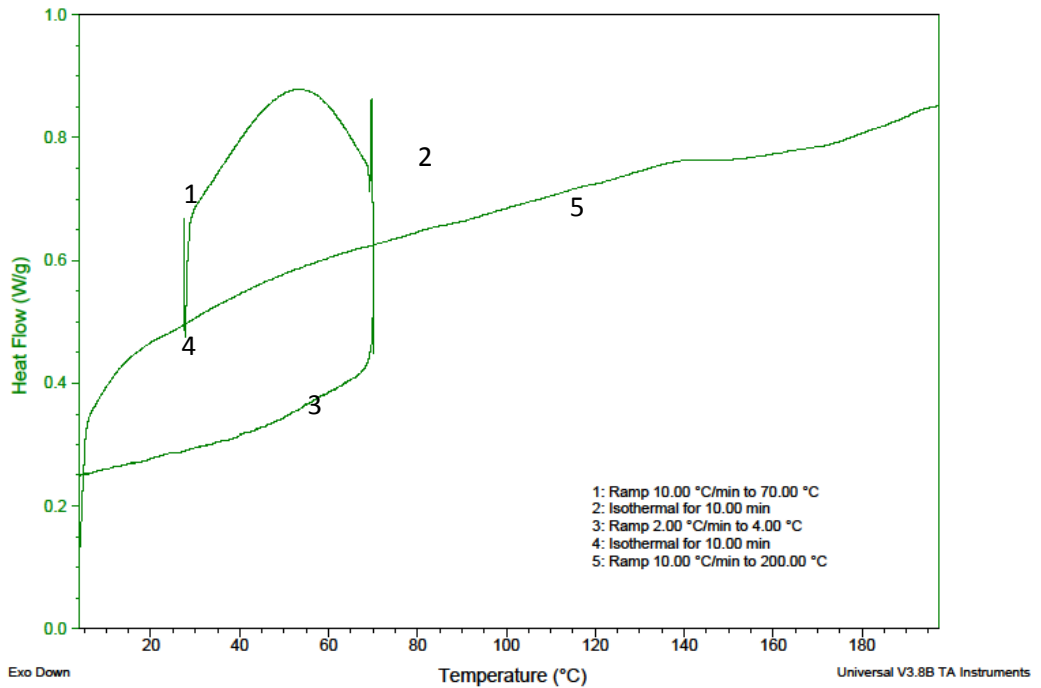


Figure 8.8 DSC plot for HPC film containing no drug substance

Sample: 5mg/g paracetamol EE583198/A
Size: 2.0430 mg

TGA

File: I:\...TGA Q500\Data\TA0091\TA00914.001
Operator: MKN
Run Date: 22-Nov-10 14:04
Instrument: TGA Q500 V6.7 Build 203

Comment: Performance Check

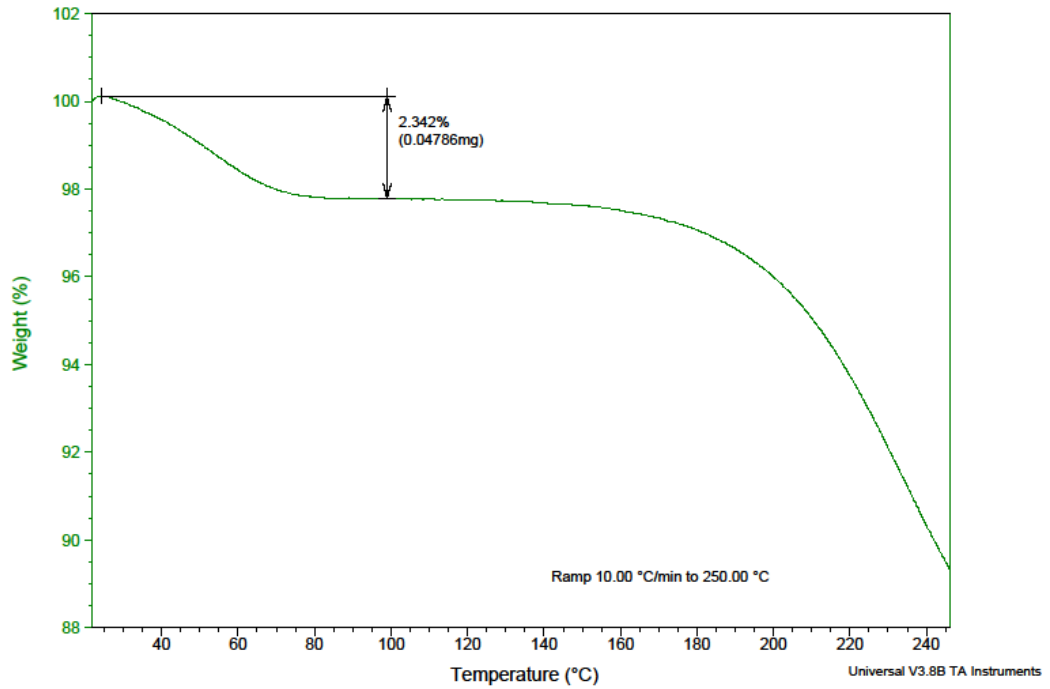


Figure 8.9 TGA plot for HPC film containing 5 mg/g paracetamol

Sample: 5mg-g Paracetamol EE583198
Size: 0.9500 mg
Method: M0011383
Comment: HPC Film

DSC

File: I:\...DSCQ2000\DA0199X\DA01990.001
Operator: MKN/TE
Run Date: 22-Nov-10 12:09
Instrument: DSC Q2000 V24.4 Build 116

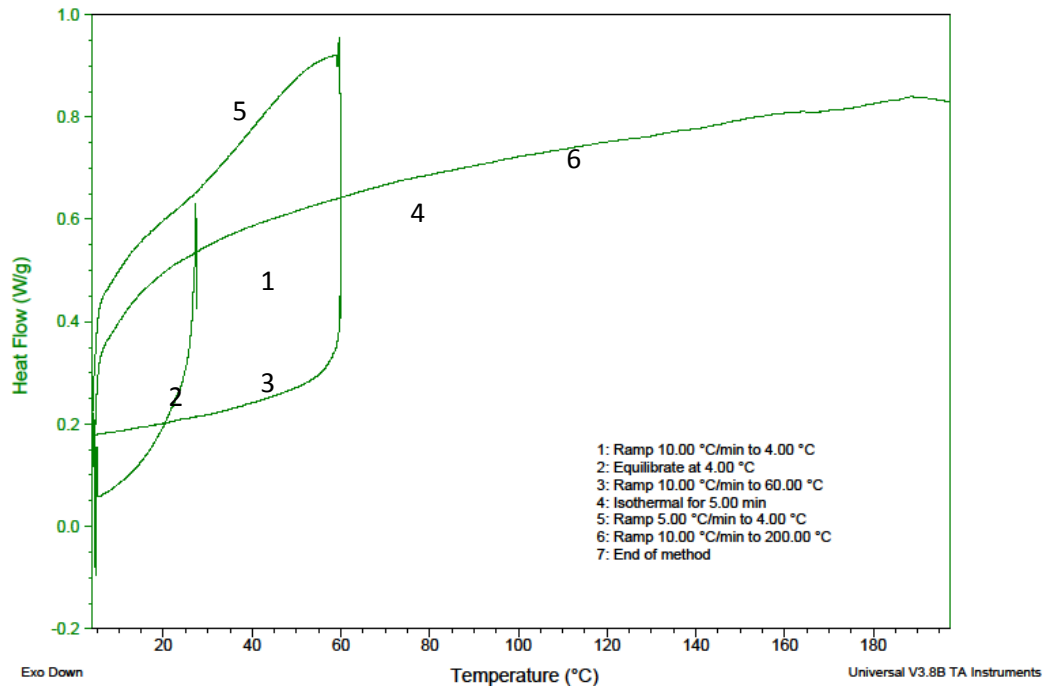


Figure 8.10 DSC plot for HPC film containing 5 mg/g paracetamol

The TGA plot in Fig. 8.9 for the HPC film containing 5mg/g paracetamol shows a residual moisture content of 2.342 %. This may be associated with the drying process employed as part of the casting or the equilibrium moisture content of the film after drying. The film may have reached equilibrium moisture content upon storage after manufacture.

Similar to Figure 8.8, the heating programme used in Fig. 8.10 was performed to remove the moisture from sample but first additionally explored temperatures below ambient to see if a T_g existed at lower temperature ranges (step 1 and 2). No T_g was observed for the 5 mg/g HPC film using DSC.

The TGA plot in Fig 8.11 for a HPC film containing 15mg/g paracetamol shows a residual moisture content of 2.876 %. This may be associated with the drying process employed as part of the casting or the equilibrium moisture content of the film after drying. The film may have reached equilibrium moisture content upon storage after manufacture.

Similar to Figure 8.9, the heating programme in Fig. 8.12 was performed to remove the moisture from sample and explore temperatures below ambient to see if a T_g existed at lower temperature ranges (step 3 and 4). No T_g was observed for the 15 mg/g HPC film using DSC.

Sample: 15mg/g paracetamol EE583198/B
Size: 2.3770 mg

TGA

File: I:\...TGA Q500\Data\TA0091\TA00915.001
Operator: MKN
Run Date: 22-Nov-10 16:36
Instrument: TGA Q500 V6.7 Build 203

Comment: Performance Check

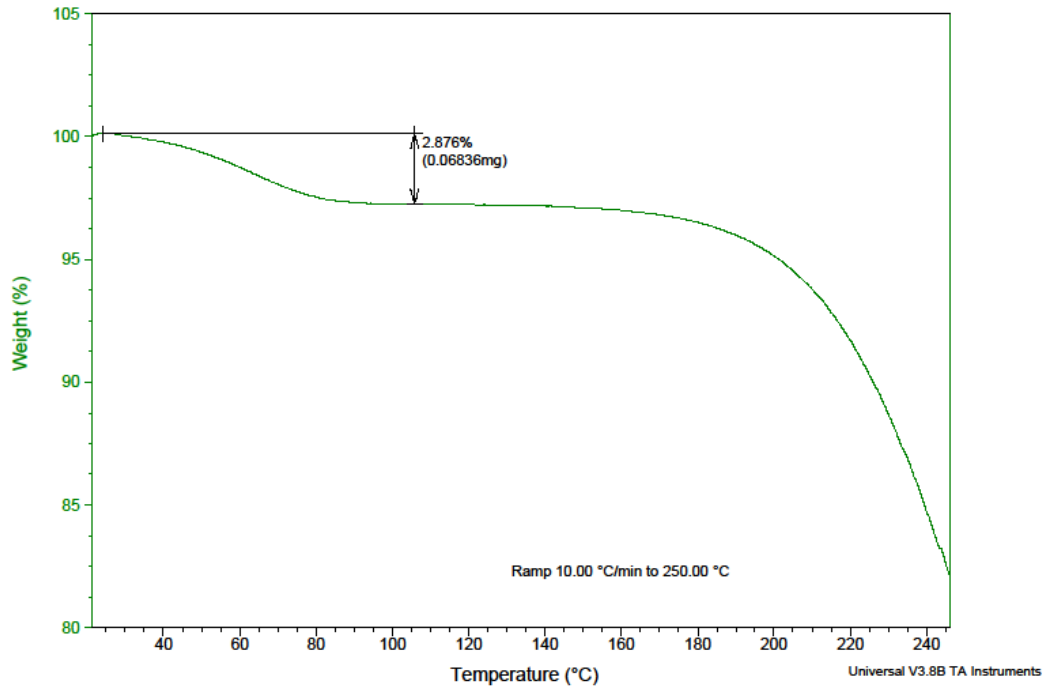


Figure 8.11 TGA plot for HPC film containing 15 mg/g paracetamol

Sample: EE583198/B
Size: 1.2040 mg

DSC

File: I:\...DSCQ2000\DA0202X\DA02022.001
Operator: MKN
Run Date: 14-Jan-11 16:59
Instrument: DSC Q2000 V24.4 Build 116

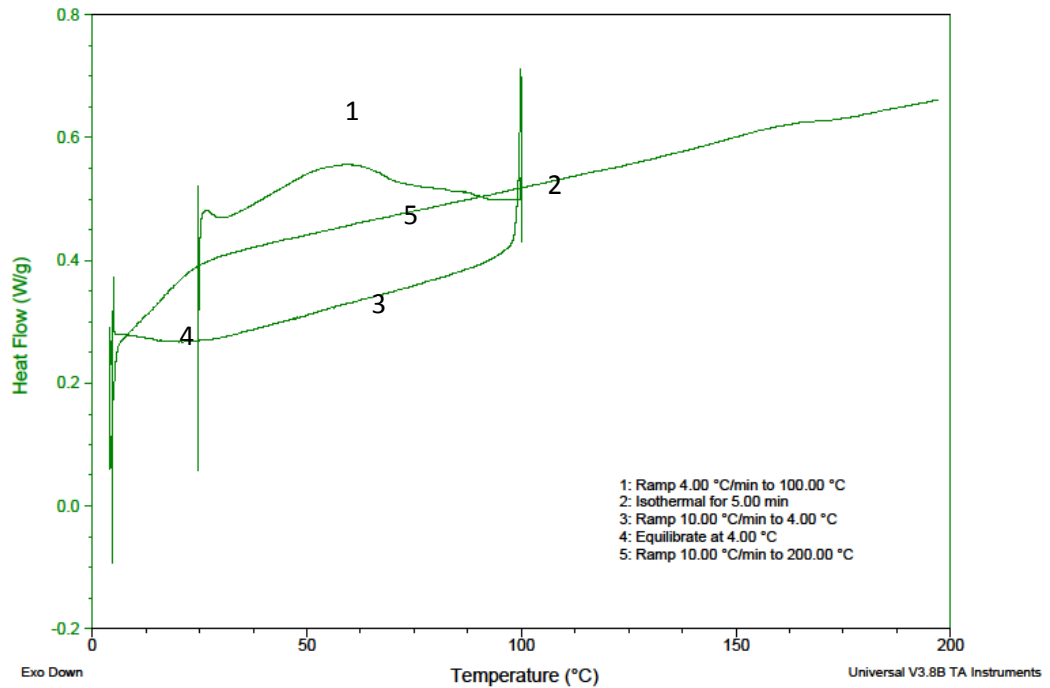


Figure 8.12 DSC plot for HPC film containing 15 mg/g paracetamol

These data indicate that no change in the baseline is present indicating an event such as the melting of paracetamol or gross degradation of the HPC film. The melting point of paracetamol is 169°C to 172°C so if present in the crystalline state it is likely that an endotherm would have been observed. These data therefore indicate that no crystalline paracetamol was present in the films and that the placebo and active HPC films were physically stable. These data also indicated that residual moisture of the films was between 2.342 % and 2.876 %. It was not possible to determine if this moisture remained following the drying process or if the films had reached equilibrium after drying and being stored at ambient conditions.

These data show that a glass transition temperature does not exist for the HPC films.

8.4 Conclusion

HPC films are able to retard dissolution rate of paracetamol. Retardation of dissolution rate is considered to be associated with the formation of liquid crystals as the film undergoes phase transformation prior to fully hydrating and solubilising in the dissolution media. HPC films may therefore have application for administering drug substance to paediatric or geriatric patients by overcoming swallowing difficulties; potentially providing taste masking and aiding oral cavity absorption. The drying conditions used to prepare the HPC films has no impact on the film characteristics. The presence of drug substance has a slight impacts on disintegration time.

9 General Discussion

9.1 Rationale and Aim

The availability of medicines designed specifically for and clinically evaluated in paediatric patients is significantly poor. Developing medicines for paediatric patients is challenging and is complicated by a number of factors due to the heterogeneous patient population. The paediatric population is made up of 5 sub-groups defined by ICH guidelines (EMA 2001). As described in Chapter 1, when considering the dosage form design for a product intended for use in paediatric patients it is important to consider aspects such as the physiological maturity of the child including key organs and metabolic pathways, the relative size differences between the sub populations, within populations and between geographic locations, the relative capabilities of each sub group, the ability for children to swallow products designed for oral delivery, adherence issues associated with taste and palatability. The correlation of safety data between adults and children must be carefully considered together with the potential need for juvenile toxicological testing of new chemical entities and excipients prior to administration to children (Salunke et al 2013). Consequently, regulatory guidance was recently enforced to encourage industry to consider this medically neglected population (FDA 2002 and EMA 2006).

Identifying a suitable oral dosage form that meets the needs of paediatric patients is difficult as most of the commonly used adult formulations, e.g., tablets and capsules pose issues for dosing to children. The aim of this research was to develop an oral dosage form that addresses these challenges whilst ensuring efficacy, safety and patient access (Sam et al 2012).

Based on their diverse application in oral dosage forms and safe toxicological profile, hypromellose and hydroxypropylcellulose (HPC) were considered as suitable polymers for this investigation. To minimise the quantity of functional polymer required in the dosage form by potentially enhancing the performance of the functional polymer, co-processing by spray-drying hypromellose was evaluated in Chapters 4 and 5. The use of HPC to form films containing paracetamol and

ranitidine was evaluated in Chapter 8 having explored the impact of temperature on aqueous solutions of HPC in Chapters 6 and 7. As described in Chapter 2, paracetamol and ranitidine were considered as 'model' drugs as they have different aqueous solubilities and are both listed by the EMA as drug substances for which greater research in paediatrics is required (EMA 2005 and EMA 2007).

9.2 Co-processing by Spray-Drying

Whilst spray-drying has been used extensively in the preparation of pharmaceutical products, spray-drying of hypromellose has not been significantly researched. In Chapter 4 spray-drying of hypromellose was evaluated.

Hypromellose was successfully spray-dried and though the process significantly changed the physical structure of the material, there was no change in the function of the polymer as determined by viscosity measurements. The spherical shape and reduced particle size of spray-dried hypromellose may offer processing advantages over non spray-dried hypromellose, for instance in modified release matrix tablets whereby spray-dried hypromellose may exhibit better flow characteristics and also improve gel layer formation based on its reduced size and spherical shape.

Though hypromellose was successfully spray-dried, the investigation also highlighted difficulties associated with spray-drying hypromellose which are mainly due to the high viscosity of its aqueous solutions. An increase in polymer content and molecular weight results in an increase in viscosity of the aqueous spray-drying solution. Only low molecular weight polymers at a maximum concentration of 5 %w/w could be spray-dried. Such low solids content results in significantly long processing times which are likely to render this process commercially unviable. Modification to the polymer viscosity is required to enable higher polymer concentrations to be processed.

Attempts were made to reduce the viscosity of polymer solutions by heating at 40°C and 60 °C. As temperature increased, solution viscosity began to decrease before eventually the gelation temperature was reached. Careful temperature control of the polymer solution during spray-drying may even enable higher polymer

concentrations or higher molecular weight polymers to be spray-dried by reducing the viscosity of the polymer solution. However, although temperature may be used to reduce solution viscosity, significant engineering controls such as temperature-controlled transfer pipework from the stock solution to spray nozzle would be required to ensure that the solution temperature is carefully controlled up to the point of atomisation.

Having successfully spray-dried hypromellose, co-processing hypromellose with paracetamol using spray-drying was investigated in Chapter 5. The intention was to determine the properties and functionality of spray-dried hypromellose and paracetamol. Chapter 5 investigated the effect of adding 15 % w/w paracetamol to 5 %w/w E5LV hypromellose solution. The addition of paracetamol to hypromellose solution resulted in significant flocculation at 40°C and 60 °C, and also to an increase in polymer solution viscosity at ambient temperature. Such an increase in polymer solution viscosity at ambient temperature following the addition of 15 % w/w paracetamol will reduce the achievable flow rate for spray-drying. It was not possible to spray dry aqueous hypromellose solutions containing 15 % w/w paracetamol due to the increase in viscosity at ambient temperature. Flocculation, caused by heating the hypromellose solutions containing 15 % w/w paracetamol, prevented spray-drying of these solutions.

Though aqueous hypromellose solutions may be spray-dried with the potential to use heat to reduce solution viscosity, hypromellose solutions containing paracetamol have a higher viscosity than solutions without paracetamol and require formulation optimisation if heating is to be used in the same way.

9.3 Investigating the Influence of Temperature on Aqueous Solutions of HPC

Having determined the effect of temperature on aqueous hypromellose solutions and aqueous hypromellose solutions containing paracetamol, the effect of temperature on aqueous solutions of HPC was determined in Chapter 6.

An increase in HPC polymer content and molecular weight results in an increase in viscosity of the aqueous polymer solutions (Chapter 6) similar to hypromellose (Chapters 4 and 5). Only low molecular weight grade ($\leq 370,000$ Daltons) of HPC at low concentrations (≤ 10 %w/w) could be considered for spray-drying. However, unlike hypromellose, HPC solutions did not exhibit a gelation temperature and increased heating to 60°C resulted in a continued decrease in polymer viscosity. When heated to temperatures $\geq 40^{\circ}\text{C}$ HPC solutions also became cloudy. The impact of temperature on aqueous HPC solutions was further investigated.

HPC solutions changed from clear to cloudy at a reduced temperature when the polymer concentration was increased. Polymer molecular weight appeared to have no impact on the onset temperature of this physical change. These observations supported the theory that the physical change was associated with polymer precipitation and the formation of liquid crystals that may be caused by polymer dehydration.

Viscosity testing of aqueous HPC solutions demonstrated that three phases of change were apparent when plotting viscosity versus temperature, illustrated by a sigmoid shape curve. The change in viscosity appears to occur in 3 phases; i) initially a linear reduction in viscosity ii) at 40°C the rate of change in viscosity is more significant and at phase iii) at 50°C the rate of change reaches a minimum and minimum viscosity is reached. Higher concentrations of aqueous HPC solutions exhibited the greatest decrease in viscosity with increase in temperature.

Data in Chapter 6 suggest that the change in per cent UV transmission is linked with a change in viscosity of aqueous HPC solutions. At the cloud-point, the viscosity of the HPC solution is significantly decreased. These changes are likely to be associated with the formation of liquid crystals as described by Werbowj and Gray (1980) and

Wang (1997). These changes may be described using the phase diagram proposed by Werbowyj (1980) and Guido (1995) and these data enable the phase diagram to be extended to include solutions of a lower HPC concentration (≤ 10 %w/w).

The impact of paracetamol and ranitidine on the properties of aqueous solutions of HPC was also investigated in Chapter 7. HPC solutions containing drug substance exhibit similar shape curves to solutions containing no drug substance. HPC solutions containing ranitidine reach 'phase ii' of the curve at a slightly higher temperature than solutions containing no drug substance, whilst solutions containing paracetamol reach 'phase ii' of the curve at a slightly lower temperature, which correlates well with the data obtained using UV transmission. Increased concentrations of the poorly soluble paracetamol further reduced the onset temperature whilst solutions containing the relatively higher soluble ranitidine had a slightly higher onset temperature than solutions containing HPC alone.

The physical changes, observed in Chapters 6 and 7, upon heating aqueous solutions of HPC may be caused by the HPC molecules dehydrating following heating and hydrogen bonds between the HPC molecules and water molecule breaking resulting in the formation of liquid crystals. The formation of liquid crystals causes the aqueous HPC solutions to go cloudy and the viscosity of the solutions to decrease. These data also indicate that the presence of drug influences the cloud-point temperature of aqueous HPC solutions. Paracetamol reduced the cloud-point temperature and ranitidine increased the cloud-point temperature of aqueous HPC solutions. These changes may be caused by the salting in effect of the hydrochloride salt of the ranitidine molecule or the poor solubility of the paracetamol. Further investigation is required to understand the impact of drug properties on the cloud-point of aqueous HPC solutions.

Aqueous solutions of HPC form liquid crystals at increased temperature so temperature could not be used to reduce the viscosity of aqueous HPC solutions to enable spray-drying. Spray-drying of aqueous solutions of HPC was therefore not considered.

Data obtained in Chapters 6 and 7 indicated that changes in viscosity of aqueous HPC solutions occurred at temperatures in the range of 35°C to 40°C which is close

to human body temperature (37 °C). Therefore the applications of these findings for a paediatric dosage form platform were examined. A HPC-based film was developed. Polymer films intended for oral administration may provide many benefits to the paediatric patient including ease of swallowing due to disintegration of the dosage form in the mouth cavity and dose flexibility based on unit film size.

9.4 HPC Film Preparation and Characterisation

As described in Chapter 8, films could be formed by drying aqueous solutions of 5 %w/w EXF HPC. The drying temperature used to form the films had no impact on the film characteristics measured. Films could be prepared to a consistent weight and thickness and disintegrated in water in <30 sec and fully dissolved in 350 seconds to 540 sec. Following the successful preparation of films from HPC solution, the inclusion of paracetamol and ranitidine in the HPC films was investigated.

Successful film formation with paracetamol and ranitidine was dependent upon the drug:polymer ratio within the solution. Films prepared containing 50 mg/g and 100 mg/g ranitidine were discoloured and contained cracks after drying. Films could be prepared from aqueous solutions containing paracetamol and ranitidine at concentrations ≤ 15 mg/g. A minimum polymer content of 3 times that of the drug substance was required to cast a fully integral film without damage observed around the edges of the film during drying. Films could be prepared to a consistent weight and thickness.

The presence of paracetamol in the film increased the disintegration time of the film in water slightly to <45 secs. Dissolution testing of paracetamol contained in a film showed a slower dissolution rate than that of paracetamol powder. This difference in dissolution of paracetamol from HPC films may be explained by the formation of liquid crystals with an increase in temperature, slowing the dissolution of paracetamol prior to the film fully hydrating and solubilising in the dissolution media. These dissolution data suggested that the films produced may provide some taste masking potential if the dissolution of paracetamol can be sufficiently delayed by the time taken for the film to fully dissolve in the oral cavity.

Uniformity of film weight and paracetamol assay data suggest that maximum dose flexibility could be provided by enabling the patient or caregiver to cut the required size of film as drug content can be expressed by weight of film or by surface area of film. Thermal analysis of the HPC films using DSC and TGA illustrated that the dried films had a residual moisture content of <3 % and that they do not exhibit a glass transition temperature.

The assessment of films produced from aqueous solutions of HPC containing paracetamol indicates that the dosage form may be a suitable for pharmaceutical application in paediatric patients.

10 General Conclusions and Recommendations for Further Work

10.1 General Conclusions

This investigation demonstrated that spray-drying of hypromellose is feasible. However, the viscosity of its solutions generally restricts the aqueous concentration of hypromellose and the hypromellose grade that may be spray-dried. An aqueous solution of 5 %w/w hypromellose E5LV was spray-dried but its viscosity significantly restricted the maximum achievable flow rate during spray-drying. Increasing the temperature may be used to reduce the viscosity of hypromellose solutions but requires careful control to avoid reaching the gelation temperature of the solutions whereby viscosity significantly increases.

Spray-dried hypromellose particles are much more spherical and uniform in size than non-spray-dried particles, and may offer improved flow and uniform gel formation due to their increased surface area. Polymer solutions prepared from spray-dried hypromellose have similar viscosity to those prepared from non-spray-dried hypromellose indicating that the functionality of the spray-dried material is unchanged.

The inclusion of 15 %w/w paracetamol in aqueous solutions of 5 %w/w E5LV hypromellose increased solution viscosity. Temperature could not be used to decrease the viscosity of this solution as flocculation of the suspension occurred. Co-processing hypromellose and paracetamol by spray-drying could not be achieved in this work.

Investigating the impact of temperature on aqueous HPC solutions showed that heating causes a reduction in solubility of HPC in water which results in its precipitation and the formation of liquid crystals. As a consequence of this precipitation, the aqueous HPC solutions appear 'cloudy' and their viscosity decreases. The temperature at which these changes occur is referred to as the 'cloud-point'. Based on the viscosity of aqueous solutions of HPC and the impact of temperature of these solutions, spray-drying of HPC was not investigated.

The effect of temperature on aqueous HPC solutions containing ranitidine and paracetamol was determined. Paracetamol decreased the temperatures of dehydration and onset of precipitation and ranitidine increased the temperatures of dehydration and precipitation. This is probably associated with a salting in effect. The effect of temperature on aqueous HPC solutions containing drug is dependent on the properties of the drug.

HPC was used to form films which are able to retard dissolution rate of paracetamol. Integral films may be formed which meet the pharmacopoeial content uniformity criteria typically applied to oral dosage forms. HPC films may therefore have application for administering drugs to paediatric or geriatric patients by disintegrating in the mouth and so overcoming swallowing difficulties; potentially providing taste masking and aiding absorption across the oral cavity.

HPC films offer significant benefits to the paediatric population. The manufacturing process is simple and transportation is easy as secondary packs are likely to be less bulky than currently used for tablets. The films may also be suitable for administering combinations of drugs in the same dosage form by layering or by combining the drugs at the HPC solution stage. For these reasons the HPC films may have particular application for diseases in the developing world and meet many requirements associated with WHO and other global regulatory guidelines.

10.2 Recommendations for further work

- Advantages of spray-dried hypromellose over non spray-dried hypromellose could be further assessed. Spray-dried material is more spherical, uniform and with a higher surface area than non spray-dried hypromellose and therefore it should hydrate more rapidly and form a stronger gel barrier more quickly.
- To understand the effect of drug properties on the formation of liquid crystals in aqueous HPC solution, drugs with different functional groups could also be assessed. Additionally different salts of the same drug could be considered to determine the impacts of the counter ion.
- Alternative manufacturing processes, such as microwave drying, could be considered for film formation to determine if film drying time may be reduced to support scale-up and commercialisation of the film formation.
- The development of an appropriate standardized disintegration test for films is required.
- A taste study in humans would determine if the delay observed in dissolution rate was sufficient to improve the taste of poorly tasting drug substances with a low taste concentration threshold. This test would also enable the palatability of HPC films to be determined.
- The impact of polymer loading on film formation, drug dissolution and palatability should also be determined so that the films are optimized for drug loading and *in-vivo* performance.
- To determine the potential for films to be used in drug combination therapy, the feasibility of preparing films containing more than one drug could be assessed.

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References 25 Nov 13

APPENDICES

Appendix 1: Attendance at Conferences and Seminars

British Pharmaceutical Conference, Sept 2006, Manchester, UK

British Pharmaceutical Conference, Sept 2007, Manchester, UK

Academy of Pharmaceutical Sciences, UK Pharm Sci, Sept 2010, Nottingham UK

Academy of Pharmaceutical Sciences, UK Pharm Sci, Sept 2011, Nottingham UK

Academy of Pharmaceutical Sciences, UK Pharm Sci, Sept 2012, Nottingham UK

**EuPFI 1st conference 'Formulating Better Medicines for Children', March 2009,
London, UK**

**EuPFI 3rd conference 'Formulating Better Medicines for Children', Sept 2011,
Strasbourg, France**

**EuPFI 4th conference 'Formulating Better Medicines for Children', Sept 2012,
Prague, Czech Republic**

**EuPFI 5th conference 'Formulating Better Medicines for Children', Sept 2013,
Barcelona, Spain**

Appendix 2: Publications

Ernest, T.B., Elder, D.P., Martini, L.G., Roberts, M., and Ford, J.L. (2007) Developing paediatric medicines: identifying the needs and recognizing the challenges. *JPP*, 59:1043-1055.

Specific aspects of gastro-intestinal transit in children for drug delivery design. Alexandra Bowles, Joanne Keane, Terry Ernest, David Clapham and Catherine Tuleu *Int J Pharm* 395(1-2):37-43 (2010)*

A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms - An application for paediatric dosage form selection. Tom Sam, Terry Ernest, Julie Williams, Jennifer Walsh and on behalf of the European Paediatric Formulation Initiative (EuPFI) *Int J Pharm*. 2012 Oct 5;435(2):115-23*

Preparation of medicines for children-a hierarchy of classification. Terry Ernest, Jo Craig, Anthony Nunn, Smita Salunke, Catherine Tuleu, Joerg Breitzkreutz, Rainer Alex and John Hempenstall *Int J Pharm*. 2012 Oct 5;435(2):124-30*

Application of in vitro biopharmaceutical methods in development of immediate release oral dosage forms intended for paediatric patients. Batchelor H, Kendall R, Desset-Brethes S, Rainer A, Ernest TB; on behalf of the European Paediatric Formulation Initiative (EUPFI), *Eur J Pharm Biopharm*. 2013 May 9*

* Published work in addition to this thesis

Appendix 3: Poster and Oral Presentations

Posters

Ernest, T.B., Elder, D.P., Martini, L.G., Roberts, M., and Ford, J.L., (2006) Ion Exchange Resins: Ion exchange resins: improving palatability without compromising bioequivalence, *JPP*, 58, 10; 211. Pharmaceutical Press Royal Pharmaceutical Society Great Britain

British Pharmaceutical Conference, Manchester, 2006

Ernest, T.B., Martini, L.G., Elder, D.P., Roberts, M., Ford, J.L., (2007). The influence of spray drying on the physical properties of hydroxypropyl cellulose and hypromellose. *JPP*, 59, A41. Pharmaceutical Press Royal Pharmaceutical Society Great Britain

British Pharmaceutical Conference, Manchester, 2007

Ernest, T., Martini, L., Roberts, M., Ford, J.L., (2010). Effects of Drug Solubility and Concentration on Phase Transformations of Hydroxypropyl Cellulose Aqueous Solutions. *JPP*, 62, 1328-1329. Wiley-Blackwell

UK Pharm Sci, Nottingham, 2010

Ernest, T.B., Martini, L.G., Elder, D.P., Roberts, M., Ford, J.L. (2011). Characterisation and Modified Release Properties of Hydroxypropyl Cellulose Films.

UK Pharm Sci, Nottingham, 2011

Ernest, T.B., Martini, L.G., Elder, D.P., Roberts, M., Ford, J.L. (2011). Hydroxypropyl Cellulose Films – The Spoonful of Sugar that Helps the Medicine Go Down?

EuPFI 3rd conference 'Formulating Better Medicines for Children', Strasbourg, France, 2011

Invited Oral Presentations

Pharmaceutical Development Considerations, Formulating Medicines for Children, GSK Academy, Annually since 2007

Development of Paediatric Formulations. An Industry Perspective. Final Year Pharmacy Students at Liverpool John Moores University (LJMU), and University College London (UCL) Annually since 2007

Pharmaceutical Development: Paediatric Formulation, 3rd DIA Paediatric Forum, EFGCP Children's Medicines Working Party, 5th Annual Conference, Integrating Paediatrics into Drug Development - From Concept towards Reality, London, Oct 2009

Session Chair, 'Focus Session: Extemporaneous preparations', EuPFI 3rd conference 'Formulating Better Medicines for Children', Strasbourg, Sept 2011

Challenges Associated with Developing Medicines for Children – An Industry Perspective, UK Pharm Sci, Nottingham, Sept 2012

Preparations of medicines for children – A hierarchy of classification, EuPFI 4th Conference, 'Formulating Better Medicines for Children', Prague, Sept 2012