THE CHARACTERIZATION AND COMPACTION PROPERTIES OF MANIPULATED PARACETAMOL CRYSTALS

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ABSTRACT

This thesis investigates the effects of modification of crystals, resulting from alternative crystallization techniques, on the compaction properties of paracetamol.

Paracetamol was subjected to different crystallization procedures in the absence or presence of polyvinylpyrrolidone (PVP) as an additive. The drug crystals were characterized using scanning electron microscopy, differential scanning calorimetry (DSC), infrared spectroscopy (IR) and X-ray powder diffraction (XPD) to assess their habit and solid state characteristics. Sieved fractions of untreated and the modified forms of paracetamol were compressed at different compaction forces and speeds using a high speed compaction simulator. The elastic recoveries and the crushing strengths of tablets, and the Heckel constants and energies involved during compaction were used to investigate their compaction properties.

Compression of two different particle sizes of untreated paracetamol produced extremely weak tablets with a high tendency to cap. The results of Heckel analyses, including low correlation coefficient of initial part of Heckel plot, low degree of strain rate sensitivity (SRS), and increase in mean yield pressure (MYP) with decrease in particle size, indicated that the main mechanism of compaction of paracetamol was fragmentation. The phase III of Heckel plots, elastic recoveries and elastic energies of tablets indicated that paracetamol underwent a high elastic deformation during compaction. The elastic energy/plastic energy (EE/PE) ratio indicated that the majority of energy involved during compaction was utilized as elastic energy which increased with increasing compaction force or speed.

Prismatic polyhedral crystals of paracetamol were prepared by cooling an aqueous saturated solution of paracetamol at 65°C to 25°C. Thin plate-like crystals were prepared by adding a concentrated solution of paracetamol in hot ethanol to water at 3°C. This was termed the watering-out method. IR, XPD and DSC studies confirmed that these two forms of crystals were structurally similar, therefore polymorphic modifications were ruled out. Compression of both polyhedral and plate-like crystals, similar to untreated paracetamol, produced very weak tablets with a high tendency to cap. The crystal habit had influenced the compression properties of paracetamol, the Heckel plots and their associated constants being dependent on the habits. The correlation coefficient of the initial part of Heckel plots, and also the values of SRS, were lower for thin plate-like crystals, indicative of greater fragmentation for the plate crystals as compared to polyhedral crystals. The tablets made from plate-like crystals exhibited higher elastic recoveries and elastic energies. These indicated that thin plate-like crystals underwent more elastic deformation during compaction than the polyhedral crystals.

Crystallization of paracetamol by a combination of watering-out and in the presence of 0.5% w/v of PVP 10000 or PVP 50000 produced near spherical, agglomerated particles, consisting of numerous rod-shaped microcrystals. Particles crystallized in the presence of PVP 2000 consisted of fewer microcrystals. IR, XPD and DSC proved that paracetamol crystallized in the presence of PVP had not undergone polymorphic modification. The tablets made from particles crystallized in the presence of PVP 10000 or 50000 exhibited excellent hardness and lack of tendency to cap, even at high compression speeds. The very low values of SRS for these particles was indicative of a high degree of fragmentation during compaction. Low deviations from the horizontal of the phase III of the Heckel plots and low elastic recoveries and elastic energies of tablets were indicative of less elastic behaviour than untreated paracetamol. The low EE/PE ratio for paracetamol crystallized in the presence of PVP, indicated that contrary to untreated paracetamol, a minor portion of compaction energy was utilised as elastic energy.

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CHAPTER 1 INTRODUCTION

1.1 GENERAL INTRODUCTION

Crystal morphology plays an important role in the physico-mechanical behaviour of drug substances. The performance of a drug in a pharmaceutical formulation may depend on its polymorphism and crystal habit. Certain habits of a particular drug may be disliked because they produce difficulties during or after production. For example, one crystal habit of a drug may tablet well while another may not. One polymorph may show better solubility and bioavaiability than another polymorph of the same drug (Haleblian, 1975). York (1992), in his review article, referred to the work of Hallas-Moler et al (1952) which revealed that the solubility of insulin was determined by its solid states (amorphous, crystalline or size of crystal) and also by other parameters such as the zinc content. Therefore, it is necessary to modify the type of drug crystals produced by control over the crystallization process.

Crystallization is widely employed for purification of the majority of drugs. However, as a result of changes in the crystallization conditions, alterations in the properties of the resultant crystals can occur. In recent years, a number of examples have been reported whereby improved control over the crystallization or particle preparation stage has produced material with the desired properties.

York (1992) referred to two major questions about this research area:

1-Is it possible to prepare "designer material" crystals with preferred processing properties giving optimised product characteristics?

2-How can such materials be efficiently manufactured?

The concept of engineering materials with improved properties is widely applied in many industries. Examples include the use of metallic alloys, semiconductors and polymer composites. However until recently, its application in the pharmaceutical industry has been minimal. There are a limited number of examples in the pharmaceutical literature of attempts to deliberately alter the properties of crystals by alternative crystallization procedures. This technique has been termed "crystal engineering".

Crystal and particle engineering of drugs can play a significant role in the design of materials for compaction. Therefore, the driving force for controlled modification must be to provide the required properties for direct compression or good compressional behaviour and to overcome the deficiencies in the unmodified material which lead to problems in tabletting and compaction (York, 1992). For example, different mechanical properties exhibited by various forms of lactose can be related to the crystallization and pretreatment procedures (Bolhuis, 1988). Slow crystallization of lactose produces single crystals with plane faces for α-lactose monohydrate, whilst rapid crystallization or dehydration of the crystals result in aggregates of microcrystals of anhydrous α-lactose and anhydrous β-lactose. These aggregates undergo an intensive fragmentation under compaction, leading to

higher tablet crushing strength compared with α-lactose monohydrate. The superior bonding ability of spray-dried lactose monohydrate can be attributed to the presence of an amorphous phase of lactose which exhibits plastic flow during compaction (Bolhuis, 1988).

Since, a study of the effect of alternative crystallization processes on the properties of a drug crystals and ultimately on their compaction behaviour will be presented in this thesis, it is now appropriate to examine the theory and relevant literature pertaining to the two major areas of this project, i.e. 1- Crystallization and crystalline states and 2- Compaction.

1.2 THE CRYSTALLIZATION PROCESS

Crystallization process is usually used to obtain drug substances with a high chemical purity (by leaving impurities in the mother solvent) or to achieve better or different crystal shapes and sizes. The crystallization process ranks high in the list of industrial processes devoted to the production of pure crystals (Mullin, 1993). Apart from the fact that its final product has an attractive appearance, crystallization frequently proves to be the cheapest and sometimes the easiest way in which a pure substance can be produced.

Crystals may be grown from the vapour of the substance (sublimation), from the melt or from a solution in a suitable solvent. However, crystallization from solution is of most interest because, firstly, most solids are purified by

recrystallization from solution and secondly, interesting changes of habit may be brought about either by changing from one solvent to another or by adding a second solute (additive) to the solution (Wells, 1946).

1.2.1 CRYSTALLIZATION STAGES

The process of crystallization consists of three main stages:

1.2.1.1 Production of a supersaturated solution

A solution that consists of solute and solvent in equilibrium is said to be saturated. However, if the concentration of solute is raised above that in the saturated state, the solution is considered to be supersaturated. Supersaturation can be achieved by both cooling a solution or removing the solvent by evaporation.

1.2.1.2 Formation of crystal nuclei

The condition of supersaturation alone is not sufficient cause for a system to begin to crystallize. Before crystals can develop there must exist in the solution a number of minute solid bodies, nuclei or seeds, that can act as centre of crystallization. Nucleation is the production of the smallest possible particles (or nuclei) in a supersaturated solution of a substance which is being crystallized. These nuclei then act as centres for further agglomeration of solute molecules or ions. This process may occur spontaneously or it may be induced by the addition of foreign particles, termed homogeneous and heterogeneous nucleation, respectively (Mullin, 1993).

The formation of crystal nuclei is a difficult process to envisage. The solute molecules (building units) have to become oriented into a fixed lattice. Before formation of nuclei, critical clusters are produced. Further addition of molecules to the critical cluster results in nucleation. The number of molecules in a stable nucleus can vary from about ten to several thousands and they are too small to observe directly.

1.2.1.3 Growth of the crystals

As soon as the stable nuclei have been formed in a supersaturated system, they begin to grow in crystals of visible size. There are three proposed mechanisms to explain crystal growth: 1- the diffusion mechanism, 2- the adsorption layer mechanism and 3- the surface energy mechanism (Mullin, 1993).

1.2.1.3.1 Diffusion mechanism

This mechanism is thought to consist of two steps:

1- diffusion of the solute molecules through the bulk of the supersaturated solution to the solid surface.

2- incorporation of these adsorbed molecules into the crystal lattice.

1.2.1.3.2 Adsorption layer mechanism

This mechanism proposes that growth occurs via adsorption onto a crystal surface, layer-by-layer and is controlled by the formation of two-dimensional surface nuclei.

1.2.1.3.3 Surface energy mechanism

According to this mechanism the equilibrium shape of a crystal is related to the free energies of the faces, suggesting that the crystal faces would grow at rates proportional to their respective surface free energies.

1.2.2 INDUCTION PERIOD

A period of time usually elapses between the achievement of supersaturation and the appearance of crystals. This time lag is known as the "induction period". This period is considerably influenced by the level of supersaturation and presence of impurities. The induction period may therefore be considered as being made up of several parts. For example a certain relaxation time (t_r) is required for the system to achieve a quasi-steady-state distribution of molecular clusters. Time is also required for formation of a stable nucleus (t_n) and then time is required for the nucleus to grow to a detectable size (t_g). The induction period (t_{ind}) may be written therefore as: $t_{ind}=t_r+t_n+t_g$ (Mullin, 1993).

Factors that can influence the induction time are: temperature, agitation, degree of supersaturation, seeding and the presence of impurity. The presence of seeds generally reduces the induction period. At very high supersaturation, the induction period can be extremely short. Induction times are often measured visually. However, when t_{ind} is less than about 5 s, a sensitive and fast method such as laser light scattering must be used for detection of changes in the system.

1.2.3 INFLUENCE OF IMPURITIES ON NUCLEATION, INDUCTION TIME AND CRYSTAL GROWTH

The presence of impurities in a crystallization system can have a profound effect on nucleation, induction time and crystal growth. It has long been known that the presence of small amounts of high molecular weight substances such as gelatin, sodium carboxymethylcellulose or polyacrylamide can suppress or inhibit the nucleation and subsequently increase the induction time during crystallization from an aqueous solution (Davey, 1982). Traces of foreign ions, especially Cr^{3+} and Fe^{3+}, can have a similar action on inorganic salts. The modes of action of high molecular weight substances and cations are probably quite different. The former renders the nuclei inactive by adsorbing on their surfaces, whereas the latter may act as structure-breakers of nuclei (Mullin, 1993).

Although some impurities can suppress growth, others may exert a highly selective effect on certain crystal faces and thus modify the crystal habit in specific directions which will be discussed later. Impurities can influence crystal growth rates. They can change the equilibrium solubility and hence the degree of supersaturation. They can alter the characteristics of the adsorption layer at the crystal-solution interface and influence the integration of growth units (Mullin, 1993).

1.2.4 HABIT MODIFICATION

Without altering the internal structure, crystals can change their habit

(external appearance) due to variations in face dimensions or the appearance or disappearance of some faces (Khamskii, 1976). An important parameter liable to be affected by the crystallization process is crystal habit. Under certain conditions of crystallization one set of crystal faces may be induced to grow faster than others, or the growth of another set of faces may be retarded. For example, one method of crystallization may favour an acicular (needle) habit, while another may give a tabular habit (plates or flakes). This variation is termed modification of habit. Figure 1.1 shows three different habits of a crystal belonging to the hexagonal system. The centre diagram (b) shows the predominant crystal with prismatic habit, whereas stunted growth in the vertical direction results in tabular crystals (a). An elongated growth in the vertical direction yields needle or acicular crystals (c).

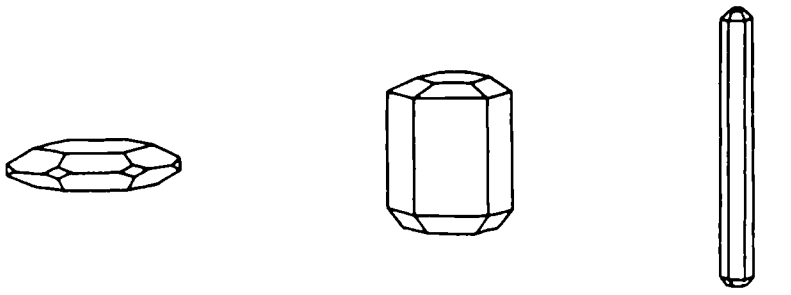


Figure 1.1 Different crystal habit of a hexagonal crystal.

1.2.4.1 Industrial importance of habit modification

Certain crystal habits are disliked in commercial industry because they may

give the crystalline mass a poor appearance, induce poor flow characteristics or give rise to difficulties in the handling or packaging of materials (Haleblian, 1975). Properties such as dissolution rate, powder flow and compressibility which are of pharmaceutical interest, can also differ for various habits of the same material (York, 1983; Marshall & York, 1991). Therefore, the reproducible modification of crystal habit using alternative crystallization techniques may facilitate the production of powders with desirable properties.

The different crystal forms of a particular drug possess different planes and thus differ not only in their specific surface, but also in their free surface energy. Therefore they may exhibit different physico-mechanical properties (Huttenrauch, 1983). Crystal habit can be an important parameter which may affect the compressibility of a particular drug. Poor compressibility of a specific habit of a particular drug can be attributed to the presence of crystal faces that give poor adhesion to each other and the absence of faces that are required for optimal adhesion (Milosovich, 1963).

1.2.5 FACTORS AFFECTING THE CRYSTAL HABIT

The morphology of a crystal depends on the growth rates of the different crystallographic faces. The growth of a given face is governed by the crystal structure on the one hand and by the local environmental conditions on the other. A number of factors which may affect the morphology of a crystal during crystallization process include; the presence of impurities, type of

solvent, degree of supersaturation and rate of crystallization, i.e. the rate of cooling or evaporation.

1.2.5.1 Influence of impurities on habit modification

One of the most common causes of habit modification is the presence of impurities in the crystallizing solution. Sometimes the impurities are added deliberately to produce desirable crystal habits (York, 1983). The case where a new chemical compound is formed as a result of chemical reaction between the impurity and the substance being crystallized, is not considered as a habit modification (Khamskii, 1976).

The presence of a small amount of an effective additive in the crystallization medium can dramatically reduce the nucleation and crystal growth and also change the crystal size and shape. These effects were attributed to the adsorption of the additive at the growth sites (Davey, 1982). The degree of interaction (adsorption) between the additive and the crystal surface depends on their chemical and structural properties such as anionic or cationic groups or to the possibility of the formation of hydrogen bonds (Khamskii, 1976; Davey, 1982).

The additives used in crystallization procedures may be classified into several groups (Davey, 1982; Mullin, 1993):

1- Surface active agents (surfactants), e.g. alkyl sulphates,

2- Low molecular weight organic substances e.g. citric or succinic acids,

3- Low molecular weight inorganic substances e.g. sodium triphosphate,

4- Polymeric materials e.g. polyvinylalcohol and alginates, and

5- Long chain proteinaceous materials e.g. gelatin.

A modification of habit will result if the impurity exerts a selectivity towards certain faces of the crystal. It has been suggested that the impurity molecules bind stereospecifically to growth sites in a similar manner to the substrate molecules. However, due to the modified side chain of the impurity, the regular deposition of substrate molecules in certain directions is disturbed. Thus, the growth rates in these directions are reduced, producing a change in crystal morphology (Mullin, 1993; Berkovitch-Yellin et al, 1982; 1985). A simple example in this case is the modification of benzamide crystals in the presence of three different impurities; benzoic acid, *o*-toluamide or *p*-toluamide. All these three substances, which have similar structure to benzamide but contain substituent groups, were capable of retarding the growth rates along specific directions (Berkovitch-Yellin et al, 1982).

One of the initial investigations into the effect of impurities on the crystal habits of pharmaceuticals was performed by Michaels and Colville (1960) using the excipient adipic acid. The facial growth rates of the adipic acid crystals were reduced by the presence of both anionic and cationic surfactants. An anionic agent (sodium tetrapropyl benzene sulphonate) caused the production of needle-like particles whereas a cationic surfactant (trimethyl dodecyl ammonium chloride) led to the formation of thin plates or

flakes. Fairbrother and Grant (1978, 1979) in similar studies, reported that the crystallization of adipic acid from solutions containing alkanols produced elongated rods and in the presence of alkanoic acids produced plate-form crystals. These studies were expanded by Chow et al (1984, 1985), who investigated the effect of these processes on the crystal properties, such as density, specific surface area, melting point, enthalpy of fusion and dissolution rate.

Chow et al (1985) and, Chow and Grant (1988a,b) crystallized paracetamol from water containing various concentrations of *para*-acetoxy-acetanilide as an additive. Negligible amounts of the additive were incorporated into the crystals. Its presence changed the crystal habit (shape), surface properties, melting point and dissolution rate of the crystals.

Sometimes the impurities are added to the crystallization medium to enhance the dissolution rates of poorly soluble drugs. Dissolution rates of chloramphenicol, sulphathiazole, and prednisolone were markedly increased by crystallization from aqueous solutions containing small amounts of a surfactant, polysorbate 80 (Chiou et al, 1976). Naggar et al (1980), Ismail et al (1987), El-Bary et al (1990), El-Gindy et al (1982), Shawky and Mesiha (1988) reported the enhancement of the dissolution rates of the poorly soluble drugs phenylbutazone, phenacetin, chlorpropamide, nalidixic acid, and lorazepam following different crystallization techniques from solutions containing small amounts of polymers or surfactants such as

polyvinylpyrrolidone or polysorbate. These additives adsorbed onto the crystals. Chiou et al (1976) suggested that the presence of small amounts of surfactant in treated crystals would increase the wettability of the powder and thereby increase its dissolution rate.

Mackellar et al (1994 a,b) investigated the effect of the surfactant, poloxamer 188, on the crystallization of ethyl-*p*-hydroxybenzene. The surfactant resulted in a decreased particle size and changed the habit from plate to prismatic.

1.2.5.1.1 Assessment of additive activity

Davey (1982) introduced a number of methods to assess the activity (effectiveness) of additives in influencing the crystallization processes. One frequent manifestation of an effective additive is that it produces crystals of a different shape to those formed from a solution in the absence of additive.

The simplest quantitative assessment of the activity of an additive is obtained by measurement of the time required for the appearance of the solid phase in the presence or absence of additive. Active additives invariably extend induction times. Davey (1982) referred to the work of Smith and Alexander (1970) who showed that during crystallization of $CaSO_4.2H_2O$ the induction times greatly increased as the amount of the impurity, polyacrylic acid, increased.

Effective additives normally decrease the crystal growth rate resulting in a

decrease in the mass of crystals deposited. Therefore, measuring the crystallization yield is useful index of the ability of an additive to influence the crystallization process.

It was explained that the observed effects of additives on crystal habit, nucleation and crystal growth are due to their adsorption on to the crystal surfaces. Therefore, measuring the amount of adsorbed additive in the harvested crystals may also be used to assess the activity of an additive (Davey, 1982). Chow and Hsia (1991), Gordon and Chow (1992), and Chow et al (1995) reported that the crystallization of phenytoin in the presence of three different esters homologue of diphenylhydantoin changed the crystal habit from needles to elongated plates. They observed a drastic reduction in crystal yield and also an increase in the amount of adsorbed additive as the concentration of additives in the crystallization medium increased. The authors suggested that the most active additive was that one which changed the crystal habit at the lowest concentration and caused greatest reduction in crystal yield.

1.2.5.2 Influence of solvent on habit modification

A change of solvent will often result in a change of crystal habit. In general, the interaction (adsorption) between the solvent molecules and the different crystal faces is believed to play a major role in determining the crystal morphology. If adsorption is selective, i.e. only on to specific faces of crystals, or to different extents on the different faces, different growth rate of faces

and hence habit modification will be produced (Mullin, 1993).

Berkovitch-Yellin (1985) proposed a method for predicting the habits of crystals grown from various solvents. He suggested that polar solvents are preferentially adsorbed by polar faces and non-polar solvents by non-polar faces. The polarities of the faces, which are governed by the atoms exposed normal to the face, were calculated by analyzing their structures. Davey et al (1982) demonstrated that crystallization of succinic acid from water or isopropanol produced plate and needle habits, respectively. They suggested that the carboxylic acid groups of succinic acid interact presumably through hydrogen bonding, more strongly with isopropanol than with water. The stronger adsorption would reduce the growth rate of faces containing carboxylic acid groups, leading to modifications in the crystal habit.

Garti and Tibika (1980), and Marshall and York (1989) demonstrated that when nitrofurantoin was crystallized from formic acid and formic acid/water, its crystal habit was modified. The crystals from formic acid had a tabular habit whilst those from formic acid/water (a more polar solvent) were needle-like. These two forms of crystals exhibited different compaction properties (Marshall & York, 1991).

Gordon and Amin (1984) reported that when ibuprofen was crystallized from hexane or heptane (the less polar solvent) the crystals were rod or needle shape, while when it was crystallized from C1-C3 alkanols (polar solvents),

the crystals were essentially grain-like or hexagonal shape. It was claimed that the latter crystals exhibited better flow, less static charge, improved dissolution rate and compaction and binding ability.

Gonda et al (1985) reported that crystallization of hexamethylmelamine from polar solvents (e.g water, methanol and dichloromethane) yielded predominantly acicular crystals, but crystallization under similar conditions from solvents with zero dipole moments (e.g. cyclohexane or benzene) produced hexagonal crystals. These were habit modifications.

Watanabe et al (1982) reported that crystallization of aspirin from different types of solvents gave various habits. Aspirin crystals obtained from water were thin-plate; from methanol, ethanol or acetone were plates or prisms,and from dioxane or *n*-heptane were thin needles or elongated prisms. These different habits, exhibited different dissolution rates.

1.2.5.3 Influence of the degree of supersaturation

The degree of supersaturation of a system, S, can be expressed as shown in equation 1.1.

$$S = c/c^* \qquad \text{Equation 1.1}$$

c is the solution concentration and c* is the equilibrium saturation (solubility) at the crystallization temperature (Mullin, 1993). The degree of

supersaturation may have a major effect on crystal growth and crystal habit.

By raising or lowering the degree of supersaturation, it is sometimes possible to cause the preferential growth of crystals in one particular direction and therefore to produce a considerable control over the crystal habit.

1.2.5.4 Influence of cooling rate

When naphthalene was crystallized by rapid cooling from ethanol or methanol, it gave thin plates and when it was slowly crystallized, it yielded compact crystals (Wells, 1946). Garti and Tibika (1980) demonstrated that by increasing the cooling rate during the crystallization of nitrofurantoin from a mixture of formic acid/ethanol, more elongated crystals were collected. These two examples reveal that the rate of cooling is effective in altering the crystal habit. The cooling rate influences the degree of supersaturation and consequently the crystal growth and crystal habit. Decreasing the crystallization temperature will cause the value of c* in equation 1.1 to decrease. Consequently the degree of supersaturation, S, will increase.

1.2.6 CRYSTALLIZATION PROCEDURES

The methods available for crystallization are many and varied but in all cases a state of supersaturation has first to be achieved. The way in which supersaturation is produced depends on the characteristics of the crystallizing system. In this section an account of the most common ways in which crystallization can be performed, is given.

1.2.6.1 Cooling and evaporation

The most common method by which the supersaturation can be achieved is by means of the cooling process. If the solubility of the solute in the solvent decreases with a decrease in temperature, some of the solute will be deposited on cooling. If the solubility characteristics of the solute in the solvent are such that there is little change with a reduction in temperature, some of the solvent may have to be deliberately evaporated from the system in order to affect the necessary supersaturation and crystal deposition.

1.2.6.2 Crystallization by solubility reduction

Another method by which a supersaturated solution can be formed, is by the addition of a substance that reduces the solubility of the solute. Such a process is known as salting-out. The added substances may be liquid, solid or gas. This method is commonly used during crystallization of organic substances from water-miscible organic solvents, by the controlled addition of water to the solution. The term "watering-out" is used in this case.

Salting-out has many advantages. For example, very concentrated initial solutions can be prepared by dissolving the crystals in a small amount of suitable solvent and a high solute recovery can be made by cooling the solution in addition to salting it out. However, salting-out can have the disadvantage of needing a separation device if the solvents and precipitant have to be recovered (Mullin, 1993).

1.2.6.3 Spray crystallization

The term spray crystallization is really a misnomer, because crystals are not grown by this method. The solid is simply deposited from a very concentrated solution similar to spray drying. The size and shape of the solid particles depend to a large extent on those of the spray droplets. The spray method is often employed when a product with better handling properties can be produced.

1.2.6.4 Spherical crystallization

One interesting technique for transforming fine crystals into dense spherical agglomerates during the crystallization process is spherical crystallization. The method is based on the addition of a small amount of an immiscible liquid to a crystallizing system which preferentially wets the developing fine crystals during agitation. In fact the immiscible solvent acts as a "bridging agent", encourages the particles to aggregate into spherical agglomerates. Chloroform, toluene, hexane, hexanol or octanol appear to be the preferred organic bridging agents in most studies. The original idea was introduced by Farnand et al (1961) and Sutherland (1962) and the method was developed by Kawashima et al (1982a, 1984) and kawashima (1984) using salicylic acid as a model drug. Agitation of a mixture of ethanol-water-chloroform containing salicylic acid yielded spherically agglomerated particles (Kawashima et al, 1982a).

Several pharmaceutical substances have been successfully processed by this

technique in order to improve their flowability, compressibility and dissolution rate. Examples include; aminophylline (Kawashima et al, 1982b), phenytoin (Kawashima et al, 1986), tolbutamide (Sano et al, 1987), naproxen (Gordon & Chowhan, 1990), meprobamate (Guillaume et al, 1993) and bucillamine (Morishima et al, 1993; Morishima et al, 1994).

1.2.6.5 Sublimation

So far, only the crystallization of a solid phase from a liquid phase containing a suitable solvent has been considered. However, the crystallization of a solid substance can be induced from a supersaturated vapour by the process generally known as "sublimation". Sublimation refers only to a phase change of solid to vapour without the intervention of a liquid phase. In its industrial application, however, sublimation is include the condensation process as well, i.e. solid to vapour to solid. Organic compounds which can be purified by sublimation include naphthalene, camphor, benzoic acid and salicylic acid (Mullin, 1993).

1.2.6.6 Cooling of a melt

In this case, a melted compound is cooled and if the melt is not pure, the crystals appearing above the eutectic temperature are pure. This method is not generally used. Rapid cooling of the melt often produces amorphous solids.

1.3 SOLID AND CRYSTALLINE STATES

Characterization of a solid involves verifying its chemical nature, determining the internal structure and describing the habit of its crystals. The internal structure of a compound can be classified in a variety of ways, as shown in figure 1.2. Drugs are mostly organic compounds and are usually crystals or amorphous substances. Therefore, the first major distinction is whether the solid is crystalline or amorphous.

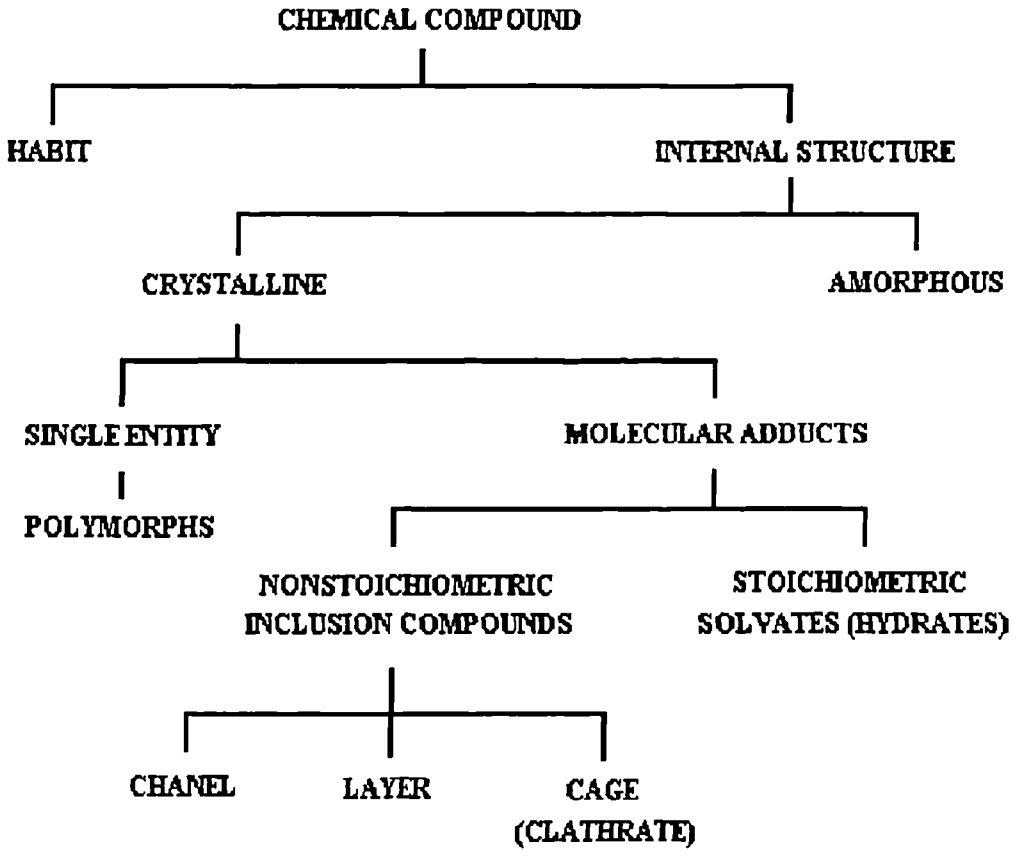


Figure 1.2 Outline of the differentiation of habit and crystal chemistry of a compound (after Haleblian, 1975).

1.3.1 INTERNAL STRUCTURE

Internal structure is the arrangement of building units (atoms, molecules or ions) in a solid, which are responsible for the characteristics of the substance. The internal structure of a solid may be investigated by X-ray diffraction.

1.3.2 CRYSTALLINE SOLIDS

A crystalline substance is one in which the molecules, atoms or ions are positioned and arranged in fixed geometric patterns or lattices. The crystal lattice can be regarded as a highly ordered structure which repeats itself regularly in three directions. Crystalline solids show definite melting points, passing rather sharply from the solid to the liquid state. Most crystals are anisotropic, i.e. their physical properties such as hardness or optical properties, can vary according to the direction in which they are measured. However, crystals belonging to the cubic system are the exception to this rule, their highly symmetrical internal arrangement renders them isotropic (Mullin, 1993).

1.3.2.1 Types of crystalline solids

Four main types of crystalline solids may be specified according to the method of bonding in the solid state, i.e. ionic, covalent, molecular and metallic.

1- *Ionic crystals*, e.g. sodium chloride, are composed of charged ions held in place in the lattice by electrostatic forces.

2- *Covalent crystals*, e.g. diamond, in which the constituent atoms do not

carry effective charges, they are connected by a framework of covalent bonds, the atoms sharing their outer electrons.

3- *Molecular crystals*, e.g. organic compounds such as paracetamol, are composed of discrete molecules held together by weak attractive forces like π-bonds or hydrogen bonds.

4- *Metallic crystals*, e.g. copper, are comprised of ordered arrays of identical cations. The constituent atoms share their outer electrons, but these are so loosely held that they are free to move through the crystal lattice and confer metallic properties on the solid.

1.3.3 AMORPHOUS SOLIDS

Amorphous solids may be considered as substances in which the molecules are arranged in a random manner somewhat as in the liquid state. In fact, the unit building blocks are put together in a non-uniform array. Amorphous solids are isotropic, i.e. their physical properties are the same, no matter in which direction they are measured (Mullin, 1993).

Amorphous forms are typically prepared by rapid precipitation, lyophilization, spray drying or rapid cooling of a melt. Lyophilization of fluprednisolone in *tert*-butanol produced the amorphous form of the drug (Haleblian & Koda, 1971). Mullin and Macek (1960) identified two forms of novobiocin; crystalline and amorphous. The crystalline form was more stable chemically but poorly adsorbed orally. Production of an amorphous form of frusemide using spray drying was reported by Matsuda et al (1992).

1.3.4 POLYMORPHISM

Polymorphism is the ability of a compound to crystallize in more than one crystalline state with a different internal lattice. The best examples of polymorphs are diamond and graphite. Both are pure carbon but the arrangement of the atoms is different. Polymorphs generally have different properties such as melting points, X-ray diffraction patterns, density, hardness, crystal shape, solubilities, dissolution rate and bulk behaviour, even though they are chemically identical. They consist of the same atoms, molecules or ions but in different arrangements (Haleblian & McCrone, 1969).

Two polymorphic forms of tolbutamide have been reported to posses different powder flow and compaction characteristics (Simmons et al, 1972). Polymorphic form B was responsible for both powder bridging in the hopper and extensive capping problems during tabletting. This behaviour was attributed to the plate-shaped crystals of form B and could be corrected by using the non-plate-like form A. Tulodhar et al (1981) reported different dissolution characteristics for phenylbutazone polymorphs. Summers et al (1977) demonstrated that different polymorphs of sulphathiazole, barbitone and aspirin differed significantly in their compression characteristics. The diuretic frusemide has been reported to occur only in one crystal form. However, Doherty and York (1988), demonstrated that a second polymorph of frusemide can be crystallized under certain conditions. This polymorph exhibited a 63% increase in aqueous solubility and a 58% increase in the dissolution rate, relative to usual form.

1.3.5 SOLVATES OR STOICHIOMETRIC ADDUCTS

A solvate is a molecular complex in which the molecules of crystallizing solvent have been incorporated into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called a hydrate. Attention must be given to potential solvate formation during crystallization as well as wet granulation, since the latter process involves the use of a solvent. Alternatively if the crystal form is initially a solvate, the drying process associated with many manufacturing procedures may cause transition to a desolvated form and alter its properties (York, 1983).

Different dissolution behaviours of the dihydrate, monohydrate and anhydrate of erythromycin (Allen et al, 1978) and differences in the dissolution rates and therefore absorption rates of ampicillin in its trihydrate and anhydrate forms have been reported (Poole et al, 1968). Muller (1977) suggested that the different crystalline forms of pure magnesium stearate, plate and needles, were associated with different hydration states and indicated that its lubricating efficiency could be correlated with its crystalline structure. Abugela and Grant (1979), and Grant and Abugela (1981) reported that griseofulvin can form solvates with *n*-alkanoic acids (C1-C9) during crystallization from these fatty acids. It has been reported that the crystallization of nitrofurantoin from a mixture of formic acid and water caused the production of a monohydrate (Marshall & York, 1987, 1989).

Agbada and York (1991), found different mechanical properties for the

anhydrous and monohydrate forms of theophylline. The hydrate form showed better compressibility and produced tablets with higher crushing strengths compared to anhydrous form. Lerk et al (1983) demonstrated that dehydration of α-lactose monohydrate strongly increased its binding properties during compaction.

1.3.6 CLATHRATES OR NONSTOICHIOMETRIC ADDUCTS

A crystalline compound may contain non-stoichiometric amounts of crystallization solvent which are entrapped solvent molecules within cavities provided by the crystal lattice. Usually these adducts are undesirable, owing to a lack of reproducibility and should be avoided (Haleblian, 1975).

1.3.7 CRYSTAL HABIT

Habit is the description of the outer appearance of crystals. The environment of a crystal may affect its habit. Although crystals can be classified according to six general systems (cubic, tetragonal, hexagonal, rhombic, monoclinic and triclinic) (Martin et al, 1983), the relative size of the faces of a particular crystal can vary considerably. Crystal habit may be modified under certain conditions of crystallization procedures (see sections 1.2.4 and 1.2.5).

1.3.8 IMPERFECTIONS IN CRYSTALS

As mentioned in section 1.3.2, the crystal lattice can be regarded as a highly ordered structure which repeats itself regularly in three directions. However, in practice, disturbances and imperfections are extremely numerous within

a crystal. In fact, crystals are never completely ordered and perfect, because during crystal growth the lattice undergoes some imperfections. Spray drying may cause a relative high degree of imperfection and disorder (Huttenrauch, 1983).

1.3.8.1 Different types of lattice imperfections

There are three main types of lattice imperfection; point defects, line defects and surface defects. The common point defects are shown in figure 1.3. The two main types of line defect which can play an important role in the mode of crystal growth are edge and screw dislocations (figure 1.4). Both of these are responsible for slip or shearing in crystals. A variety of surface imperfections, or mismatch boundaries, can be produced in crystalline materials as a result of mechanical or thermal stresses or irregular growth (Mullin, 1993).

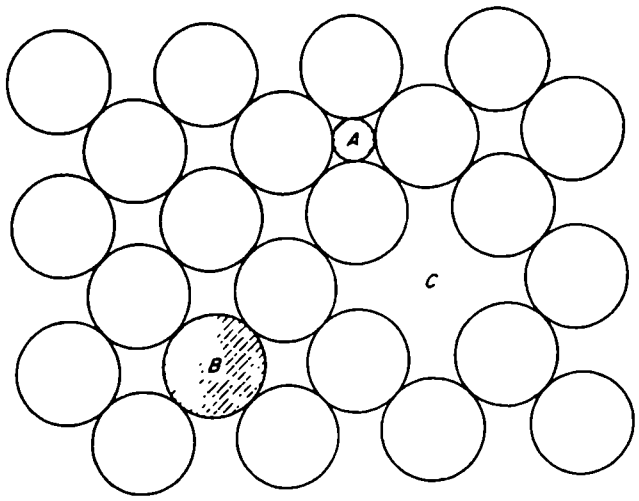
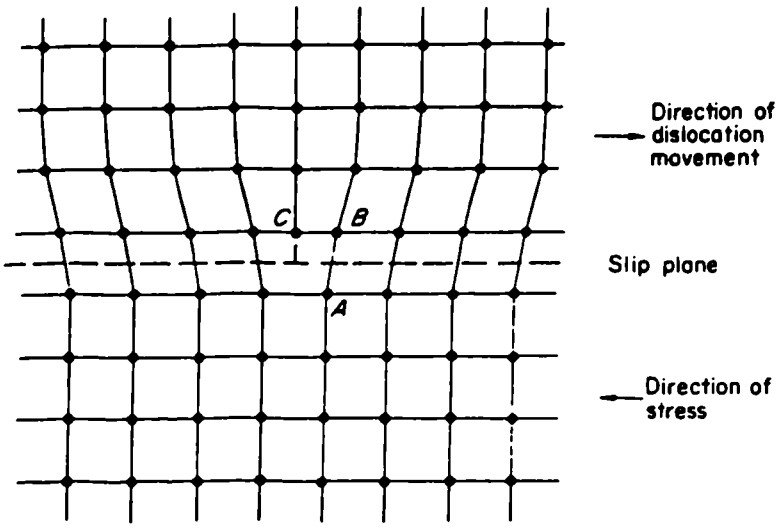


Figure 1.3 Representation of some common point defects: (A) interstitial impurity, (B) substitutional impurity, (C) vacancy (after Mullin, 1993).

(a)



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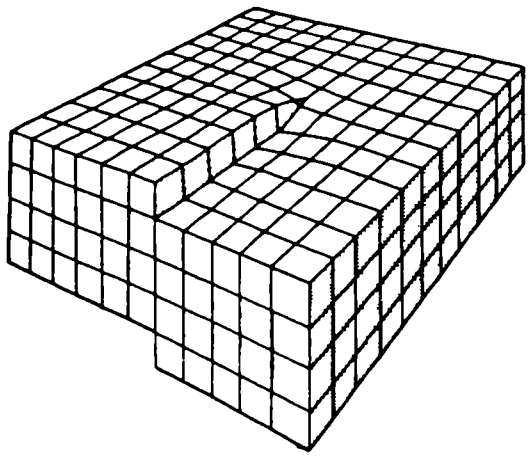


Figure 1.4 Two types of line distortion: (a) movement of an edge dislocation through a crystal, (b) screw dislocation (after Mullin, 1993).

These defects can influence some important physical and mechanical properties of crystalline drugs during processing (York, 1983). The frequency of defects can be related to the ease of fracture during milling (Pilpel, 1977) as well as deformation during compression (Wert & Thomson, 1970; Huettenrauch, 1977). The fracture of crystals in brittle materials is also

associated with crystal lattice defects and imperfections (Hess, 1978).

1.4 COMPACTION OF PHARMACEUTICAL POWDERS

A pharmaceutical powder is a complex physico-chemical system comprising of particles with different size and shapes. The process of forming powders into tablets was first described by Brockendon (1843). A tablet is produced by the compression and consolidation of a known weight of powder between two punches in a die cavity to a coherent unit as a result of applied pressure. Variation in the physico-chemical properties of powders may have significant influence on their compaction behaviour (Jones, 1981).

1.4.1 DIRECT COMPACTION

Direct compression is the process of preparing tablets from mixtures of drug and excipient powders. The simplicity of this process leads to improved reliability with a reduction in the complexity of the tablet formulation. The oldest and widely used tableting technique requires the preparation of granules. Figure 1.5 highlights the relative complexity of granulation techniques compared to direct compression. Thus, granulation is a multi-stage process, certainly involving additional expenditure on equipment, material handling, personnel and time (Armstrong, 1986). Therefore, the most important advantages of direct compression are the low cost and rapid production.

Since, the manufacture of tablets by direct compression offers advantages

over conventional granulation procedures, the question that may be asked is "Why are not more tablets made by the direct compression route?" The answer is that some compounds can not be compressed into tablets without preliminary treatment such as granulation.

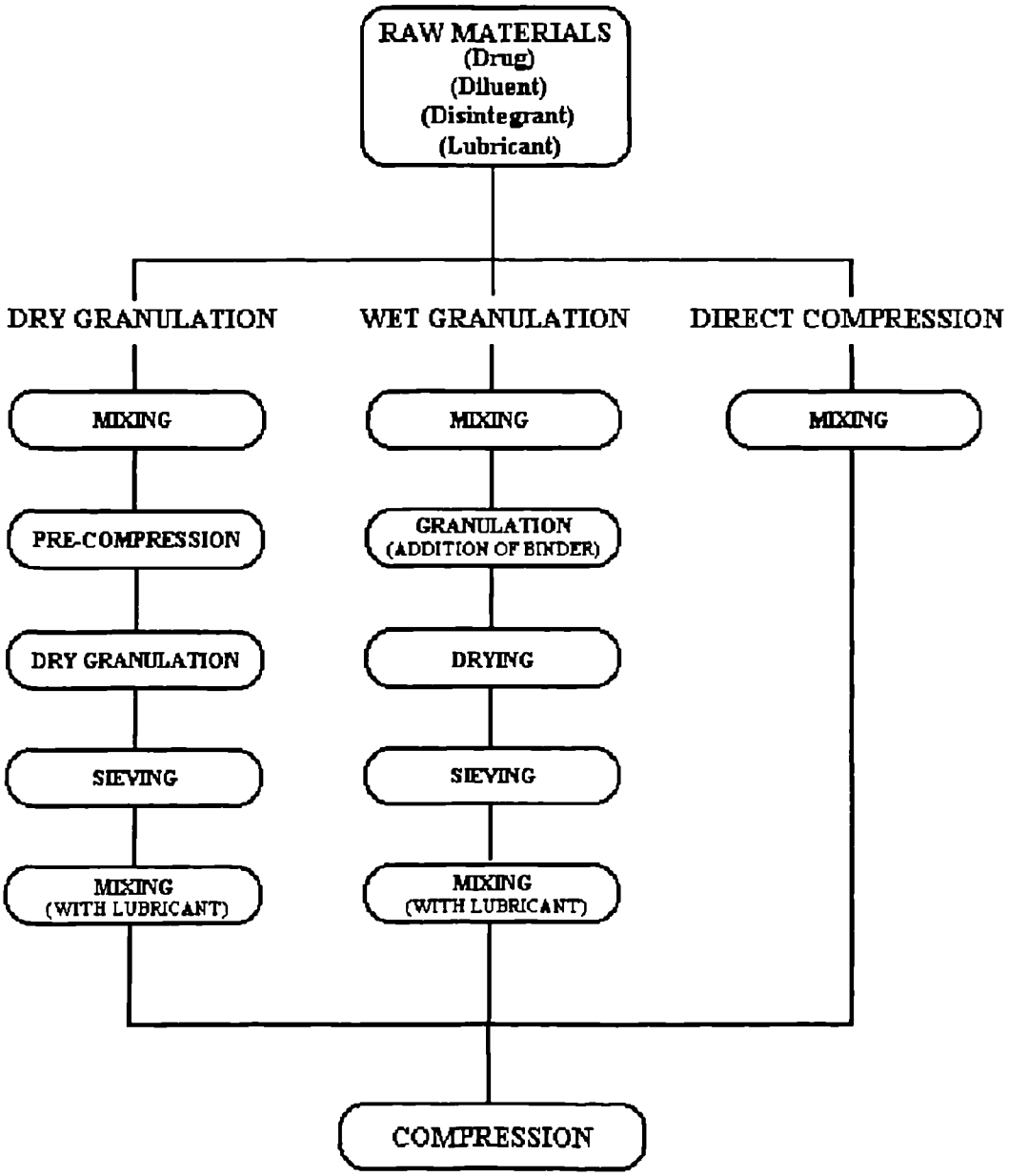


Figure 1.5 Tablet production by granulation techniques and direct compression.

The great majority of drugs do not have the necessary compressibility, but many of them do not need to. Approximately one third of marketed tablets contain less than 10 mg of drug and another third contain 10 to 100 mg of drug (Armstrong, 1986). These two groups of drugs can be compressed into tablets using a large amount of a suitable direct compression excipient. It is clear that for these two groups the compressibility of the direct compression excipient will be the major controlling factor in the compressibility of blends. Since, the maximal carrying capacity of a direct compression excipient is limited to 25% of a non-compressible drug (Armstrong, 1986), a drug of a dosage >100 mg could not be directly compressed because the weight of tablet will be too large.

1.4.2 MECHANISM OF COMPACTION

Compaction is the general term used to describe the situation when a powder mass is subjected to some level of mechanical force in a die. The effects of such forces are particularly important in the manufacture of tablets. Densification of powders was initially described in terms of "compressibility" and "compactibility" by Schwarzkof (1947). Leuenberger (1982) defined compressibility as the ability of a powder to decrease in volume under pressure while, compactibility was defined as the ability of a powder to be compressed into a coherent compact of specific strength. A tablet is produced by the compression and consolidation of a two-phase (particulate solid-gas) system, due to applied force. Compression means a reduction in the bulk volume of the material as a result of displacement of the gaseous phase and

consolidation is an increase in the mechanical strength of material resulting from particle-particle interaction.

1.4.3 STAGES OF POWDER COMPACTION

Seelig and Wulf (1946) suggested that the process of compaction of powders in a die may be divided into three stages: a) packing, b) elastic and plastic deformation and c) cold-working with or without fragmentation. Later the compression of powders was considered to be as a three stage process: a) die filling, b) particle movement and rearrangement and c) particle deformation (Heckel, 1961a,b). All the stages involved during powder compaction (including compression and decompression) are illustrated in figure 1.6. These phases do not necessarily occur sequentially and there is sometimes considerable overlap of the various stages.

1.4.3.1 Die filling

The first step in the compaction process is the filling of the die cavity. In a single punch tablet press, die filling is achieved by passing a feed hopper containing the powder over the die space, leading to the formation of a powder bed. Free flowing powders or granules will permit the uniform filling of the die specially in a high speed tabletting machine. Poor flow properties cause a high variation in tablet weights. Particle size and shape have a major effect on this process. With a small particle size, the initial powder packing, due to die filling, is decreased. This has been attributed to an increase in the number of contact points and therefore higher interparticular cohesive forces

between particles which oppose dense packing (York, 1978).

1.4.3.2 Particle slippage and rearrangement

When powder flows into a die cavity, it will have an untapped (bulk) density. The onset of compaction load, when the upper punch makes contact with the surface of crystals, is usually accompanied by closer repacking of the powder particles. In most cases, this is the main mechanism of initial volume reduction as shown in figure 1.6. This process is referred to as particle rearrangement. Heckel (1961b) reported that the amount of particle rearrangement is dependent upon the particle size and shape while the type of material has no recognizable effect on this process. De Blaey (1972) reported that the magnitude of the applied pressure required to cause particle slippage and rearrangement depends on the particle size, particle shape and the surface characteristics of the particles.

1.4.3.3 Plastic and elastic deformation

During compaction, as the load increases, further compression involves some type of particle deformation. When any solid particle is subjected to opposing forces, there is a finite change in its geometry, depending upon the nature of the applied load (Marshall, 1986). The relative amount of deformation produced by such forces is a dimensionless quantity called strain. Three of the commonest types of strain are illustrated in figure 1.7. For example, if a solid particle (figure 1.7b) with initial length, H_o, is compressed by forces acting to each end to cause a reduction in length of ΔH, then the compressive

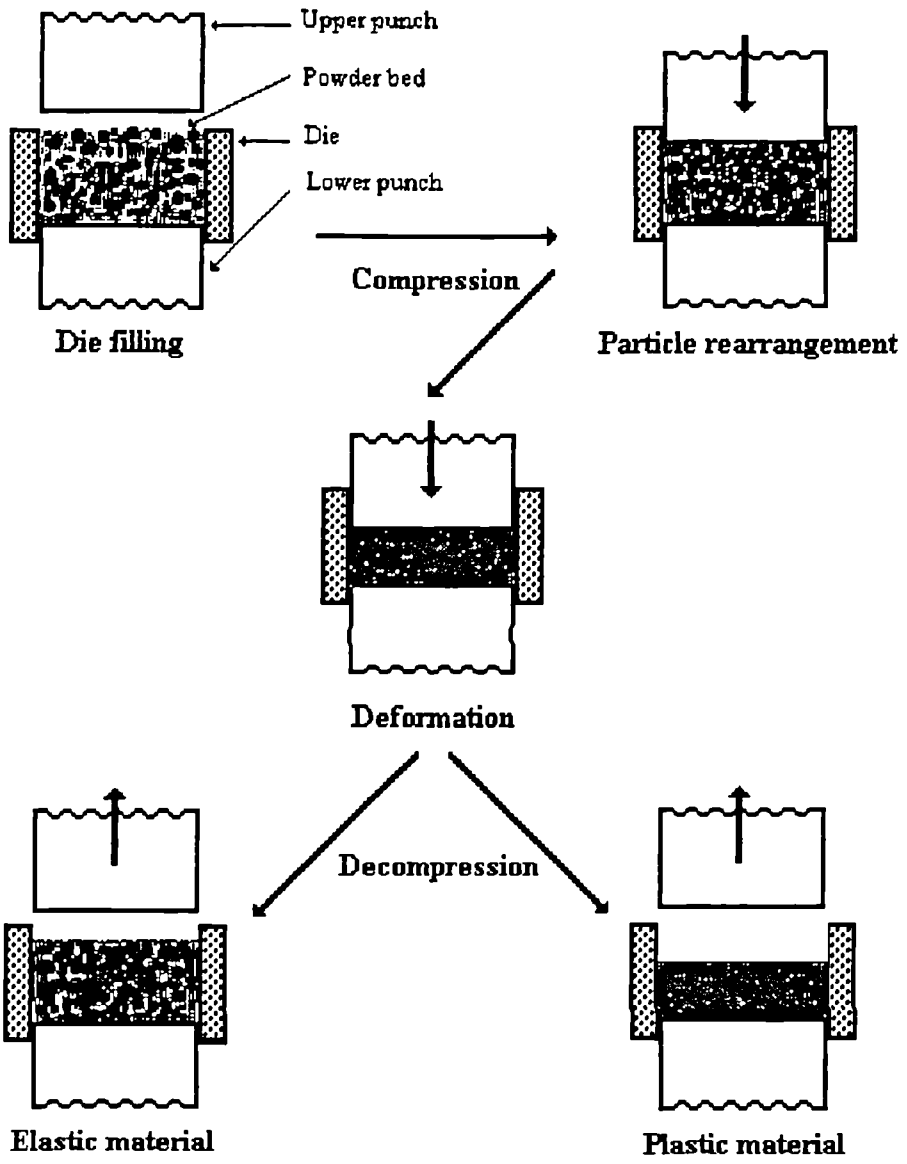


Figure 1.6 Diagram of the effect of compressional force on a bed of powder.

strain Z is given by equation 1.2:

$$Z = \Delta H/H_o \qquad \text{Equation 1.2}$$

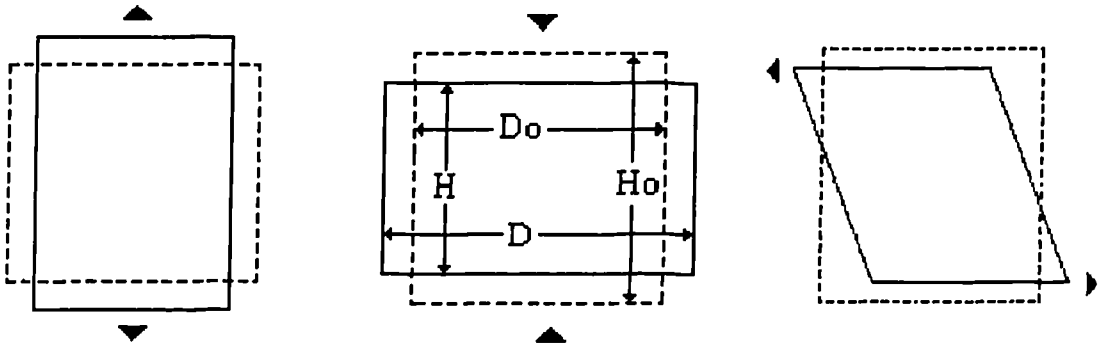
The ratio of force F necessary to produce this strain to the area A over

which it acts, is called the stress σ, as shown in equation 1.3:

$$\sigma = F/A \qquad \text{Equation 1.3}$$

If on removal of the load, the deformation is to a large extent spontaneously reversible, i.e., if it behaves like rubber, then the deformation is said to be elastic. All solids undergo some elastic deformation, when subjected to external forces. In other groups of solids, the resulting deformation is not immediately reversible on removal of the applied force. Bulk volume reduction in this case results from the plastic deformation, where the particles are squeezed into the remaining spaces. The ability of a powder to undergo irreversible plastic deformation during compaction is essential for tableting. The mechanism of plastic deformation predominates in materials where the shear strength is less than the tensile or breaking strength (figure 1.7). Conversely, when the shear strength is greater, particles may be preferentially fractured and the smaller fragments then help to fill up any adjacent air space. This is most likely to occur with hard, brittle particles and in fact is known as brittle fracture.

Train (1956) investigated the mechanism of powder compaction using magnesium carbonate. He suggested that two types of ideal powder compaction mechanisms exist, namely brittle fracture and plastic flow. During the compression event, most powders exhibit an initial fragmentation



(a) (b) (c)

Figure 1.7 Changes in the geometry (strain) of a solid body resulting from various types of applied force: (a) tensile strain, (b) compressive strain and (c) shear strain (after Marshall, 1986).

stage followed by plastic flow. Ionic crystalline materials such as sodium chloride and potassium chloride are compressed by plastic deformation (Cole et al, 1975). Potassium chloride exhibits ideal plastic behaviour due to the presence of a highly symmetrical ionic crystal lattice containing numerous slip planes (Hess, 1978).

1.4.3.4 Consolidation (particle bonding)

The ability of a powder mass to reduce in volume during compression does not ensure the formation of a tablet. It is essential that the powder should cohere into a suitable form after removal of the applied load. Therefore plastic deformation and less elasticity are necessary for compression but are not enough for tableting. There are two hypotheses which purport to explain the bonding between particles during compaction.

1- When the surfaces of two particles approach each other closely enough (less than 50 nm), their free surface energies result in an attractive force which is known as cold welding. The nature of the bonds so formed are similar to those of the molecular structure of the interior of the particles. This hypothesis is favoured as a major reason for the increase in the mechanical strength of a bed of powder, when subjected to rising compressive forces (Higuchi et al, 1953; Armstrong & Griffiths 1970; Marshall, 1986).

2- Another hypothesis is fusion bonding (asperitic bonding). Any load applied to the powder bed must be transmitted through the interparticulate contacts. Under appreciable forces, this transmission may result in the generation of considerable frictional heat. If this heat is not dissipated, the local rise in temperature could be sufficient to cause melting of the contact areas of the particles. On solidifying, the mechanical strength of the mass is increased. Asperitic bonding primarily occurs in materials with low melting points (York & Pilpel 1972, 1973; Marshall, 1986).

In both cold and fusion welding, the process is influenced by several factors, including the chemical nature of the materials, the extent of available surface, and the inter-surface distance. In general, the type of crystal in a particular material influences its consolidative behaviour under applied force. More importantly, different polymorphic forms and crystal habits of the same compound may not behave in the same way during compaction (Milosovich, 1963; Marshall, 1986).

1.4.3.5 Removing compression (decompression)

At the end of a compression cycle, when the upper punch rises, pressure on the compact is released and the elastically deformed particles start expanding toward their original volume and shape. In this process, the weak bonding between particles is broken. At zero pressure, the bed has expanded and the degree of bonding is reduced greatly. The expansion and subsequent rupture of bonds between particles may cause a cleavage and the tablet can be readily separated into two parts. This phenomena is called capping. In general, in the case of a high degree of elastic deformation, the tablet would be soft and unacceptable (Milosovich, 1963).

When the particles undergo plastic deformation, materials can be compressed into good tablets. On increasing the compression pressure, at the point where elastic deformation begins, plastic flow also occurs. As the pressure is removed there will be some expansion in the tablet, but it will be much less than described above since less elastic deformation occurred.

1.4.4 CAPPING TENDENCY

Capping is a problem which frequently occurs in tablet manufacture in which the top of tablet lops off after compression. Capping has been attributed either to the expansion of air trapped within interstices of tablet or to the deformational (plastic or elastic) properties of the material.

The presence of air entrapped in the pores of tablets during compression,

which then expands on decompression, has been reported to cause failure and capping (Gregory 1962; Burlinsun 1968). However, it has been shown that there was no significant difference in the capping tendency of tablets made in vacuum or at normal atmospheric pressure (Shotton & Ganderton 1961; Ritter & Sucker 1980). Mann et al (1983) examined the effect of air pressure on the capping tendency of two formulations at high compression speed. Reducing the surrounding air pressure caused a reduction in the incidence of capping. However, lamination replaced the capping and apparently was unaffected by changes in air pressure. Mann et al (1981) investigated the influence of punch and die tolerance (the gap between the punch and die which allows the release of air from the powder bed) and compression speed on the capping behaviour of three formulation. They observed that if the rate of release of air was restricted by reducing the punch tolerance or by increasing the compression speed, the capping tendency was increased.

As early as 1963, Milosovich attributed capping to the expansion of elastically deformed particles and subsequent rupture of interparticulate bonds. Malamataris et al (1984) noted that the incidence of capping and lamination during production of tablets following ejection from the die, depended on the plastic and elastic behaviour of the materials. Ritter and Sucker (1980) studied extensively different variables during compression. They reported that with increase in compression force, the capping tendency increased. This was attributed to an increase in the elastic energy of the tablets with increasing compaction force. Ritter and Sucker (1980) found that the ability

of particles to deform elastically or plastically is important determinant of capping. Materials which deform plastically, such as Avicel (microcrystalline cellulose), with very low elastic deformation show no evidence of capping. Garr and Rubinstein (1991a) reported that increase in the elastic energy/plastic energy ratio with increase in compression speed are important factor, which increase the tendency of paracetamol tablets to cap.

1.4.5 INTERPRETATION OF COMPACTION DATA

Powder compaction was initially quantitatively described by pressure/volume relationships and subsequently by relating compaction pressure to tablet hardness. The use of compaction simulators and instrumented tablet machines, which monitor upper and lower punch pressures and displacements, has lead to the availability of a large number of parameters which may be used to evaluate compaction and the compressibility of pharmaceutical powders.

The criteria most widely employed for interpreting compaction data are the crushing or tensile strengths of tablets, the energy required for elastic and plastic deformation using force-displacement curve, pressure/density (volume) relationships and elastic recovery measurements.

1.4.5.1 Mechanical properties of compacts

One of the most direct means of comparing the tableting characteristics of powders is to plot tablet crushing force against compaction pressure. The

evaluation of tablet strength consists of breaking or crushing the compacts by application of a compressive load. The crushing strength is dependent on tablet dimensions, thus it is difficult to compare the strengths of tablets of different sizes. However, Fell and Newton (1970) overcame this problem by introducing the radial tensile strength (T_s) of tablets. This can be calculated from the equation 1.4.

$$T_s = 2P/\pi DT \qquad \text{Equation 1.4}$$

P is the load necessary to cause diametral fracture, D is the tablet diameter and T is the tablet thickness. Newton et al (1971) found that tensile strengths determined by equation 1.4 were satisfactory except for thin tablets.

1.4.5.2 Pressure-density relationships based on the Heckel equation

There are a large number of equations used to describe the degree of densification of a powder bed under an applied load (Walker, 1923; Bal'shin, 1938; Heckel, 1961a,b; Lude & Kawakita, 1966). The Heckel equation (equation 1.5) is the most informative because it provides information on the mechanisms of powder consolidation and, in addition, the Heckel's constants K and A have valuable physical significance (Hersey & Rees, 1970; Hersey et al, 1972).

In the Heckel equation (equation 1.5), D is the relative density (the ratio of

tablet density to true density of the powder) at applied pressure P; A and K are constants.

$$\ln[1/(1 - D)] = KP + A \qquad \text{Equation 1.5}$$

A schematic diagram of a Heckel plot based on equation 1.5 is illustrated in figure 1.8. The initial curved region is due to densification as a result of particle slippage and rearrangement. The linear region at higher pressures is a result of deformation of the particles. From B, the place where the Heckel plot intercepts the ln 1/1-D axis, the density of powder at zero pressure, D_o, is obtained (equation 1.6). D_o can be defined as the densification due to the die filling or to initial powder packing.

$$D_o = 1 - e^{-B} \qquad \text{Equation 1.6}$$

From the intercept of the linear portion of this plot, A, the total densification of a powder bed due to die filling and particle slippage and rearrangement, D_a, may be obtained, from equation 1.7.

$$D_a = 1 - e^{-A} \qquad \text{Equation 1.7}$$

The extent of particle slippage and rearrangement, (D_b), is determined by subtracting of D_o from D_a. The values of D_o, D_a and D_b are dependent on the shape and size of the particles (Heckel, 1961b).

The constant K is the slope of the straight line region of the Heckel plot and the reciprocal of K is known as the mean yield pressure, which is an important compressibility index. Mean yield pressure is considered to be a material constant. Low values of mean yield pressure reveal an ability of a material to deform plastically and high values are indicative of brittle materials.

Rue and Rees (1978) suggested that the Heckel equation should be used with caution, since the Heckel plot for a given material would vary, depending on the experimental conditions. Fell and Newton (1971) demonstrated that the mean yield pressures obtained from Heckel plots depended on whether the

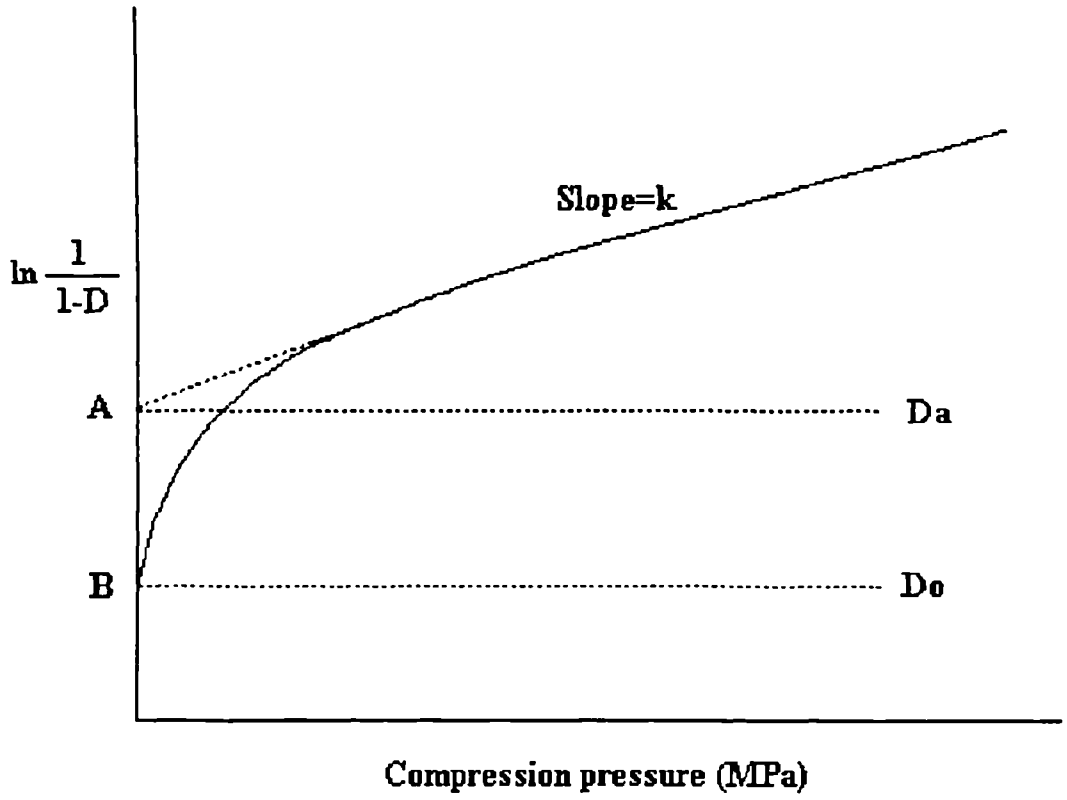


Figure 1.8 A schematic diagram of a Heckel plot.

volume of the tablets was measured under load or after ejection from the die. They concluded that volume measurements recorded with the compacts under load included an elastic component which increased the value of ln 1/1-D, especially at higher compaction forces. This gave a false, low value of the mean yield pressure.

The limitation in using a Heckel plot to distinguish between elastic and plastic deformation, evaluated from the slope of the linear portion of profile, has been emphasized by some workers (Humbert-Droz, 1983; Duberg & Nystrom, 1986). Duberg and Nystrom (1986) applied the Heckel equation to both compression and decompression phases in an attempt to distinguish between the plastic and elastic deformations of materials. They divided the Heckel plot into three stages, as illustrated in figure 1.9.

During phase I, when the applied pressure is low, particle slippage and rearrangement take place. At higher pressure (phase II) elastic and/or plastic deformation are the dominating mechanism. During decompression (phase III) the elastic propensities of the particles could result in an increase in porosity or a decrease in the density of the tablets. The decompression curve should be approximately horizontal when no elastic deformation is present i.e. the instantaneous elastic expansion of the tablet is negligible (the continuous line, figure 1.9). A considerable deviation from the horizontal in phase III (dashed line, figure 1.9) indicate the elastic behaviour of material under pressure. Of course a false low value of the mean yield pressure in this

case is obtained. Therefore a low value of the mean yield pressure, is real and acceptable when the decompression phase (phase III) does not show a large deviation from the horizontal i.e. the tablet does not undergo a massive elastic deformation.

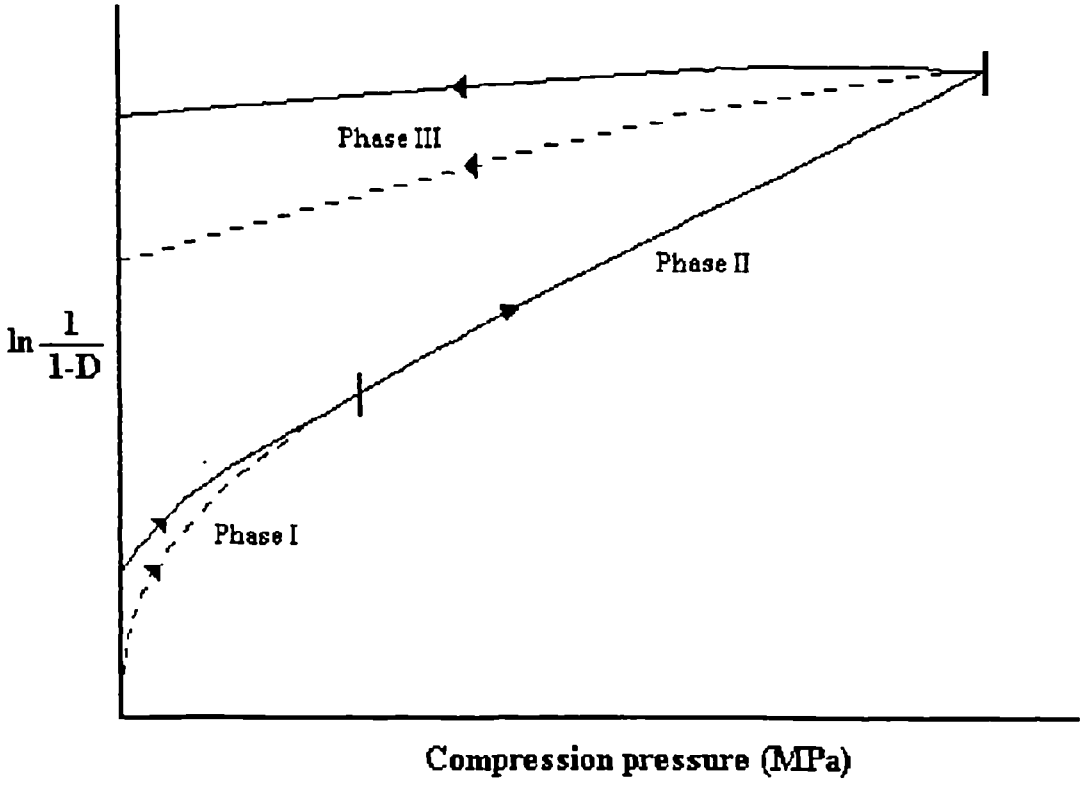


Figure 1.9 Schematic diagram of a Heckel plot showing compression and decompression cycles.

1.4.5.3 Force-displacement curves

By simultaneously monitoring the displacement of the upper punch and the force it applies during compression, force-displacement curves can be

constructed. This was first performed by Higuchi et al (1952, 1954) who suggested that the area under such curves is equal to the work of compression.

De Blaey and Polderman (1970, 1971) and De Blaey et al (1971) investigated the force-displacement curves for the total compression cycle (figure 1.10). The area under the curve CBD is elastic energy due to expansion of the compact during the compression cycle. The area ABD is the gross energy of compression. The area under curve ABC is the net compaction energy, which is utilized by die wall friction, interparticle friction, particle slippage and rearrangement, plastic deformation, fragmentation and the formation of bonds. The work of die wall friction is the difference between the upper and lower punch work. The lower punch work can be plotted as the force transmitted to the lower punch against the displacement of the upper punch. De Blaey et al (1971) mentioned that no distinction can be made between the amount of work used for plastic deformation and the amount of work for formation of bonds.

Compression energy is a powerful tool for comparing the compaction properties of different materials in preformulation studies (Graffner et al, 1985). The mechanical properties of compacts versus compaction energy, appears to be a useful parameter for evaluating the utilization of the compression energy (Hiestand et al, 1981).

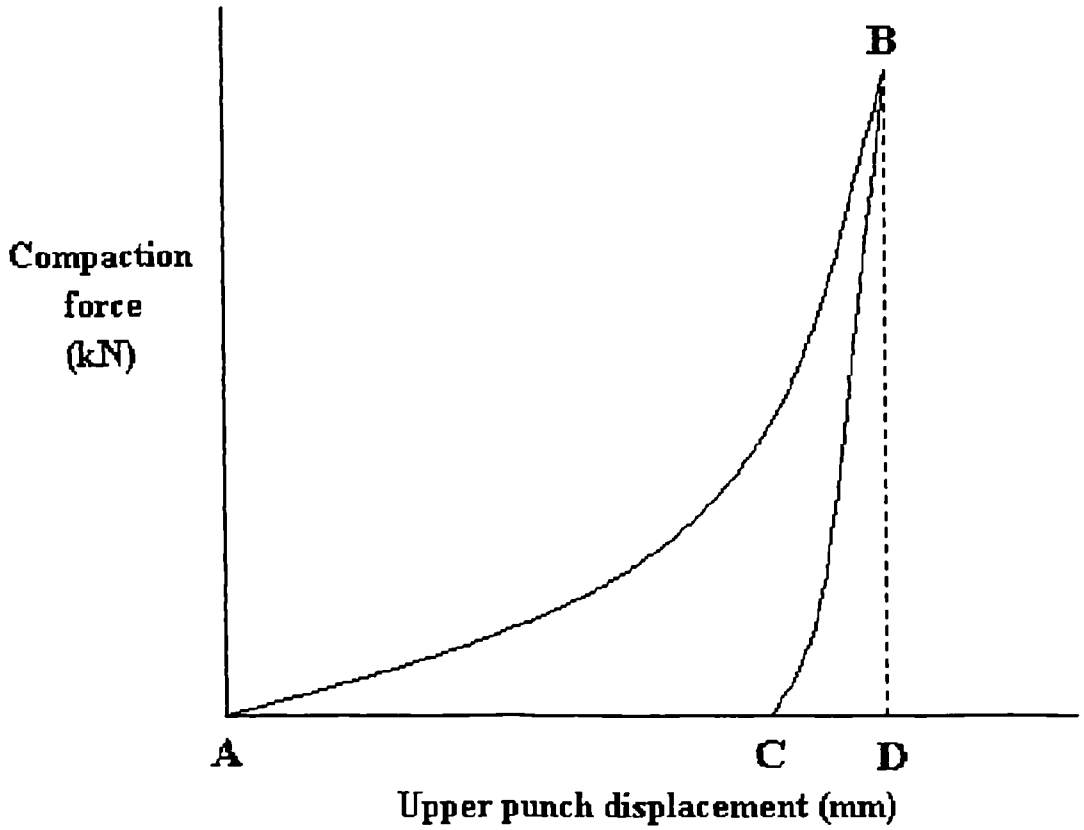


Figure 1.10 Schematic diagram of a force-displacement plot.

1.4.5.4 Determination of elastic recovery

Elastic recovery is axial expansion of tablet following the removal of the compression force. The precise quantification of elastic recovery is useful in elucidation of the dominant mechanisms of powder consolidation. Elastic recovery has been associated with the storage of elastic energy during compression as deformation energy under stress and subsequent release of this energy after the removal of axial pressure. Huffine and Bonilla (1962)

measured the percentage axial recovery of compacts in the die. Carless and Leigh (1974) observed that the percentage of elastic recovery of tablets after ejection was considerably higher than in the die.

The most widely used equation for measuring the elastic recovery (ER) was proposed by Armstrong and Haines-Nutt (1972), in which elastic recovery was defined as equation 1.8.

$$\mathbf{ER = [(H - H_c)/H_c] \times 100} \qquad \text{Equation 1.8}$$

H_c and H are the heights of the compact under pressure and 24 h after ejection, respectively. In the case of measuring the elastic recovery in the die, the value of H (equation 1.8) would be the height of tablets after the compression force is removed.

1.4.6 ESTIMATING THE DEGREE OF FRAGMENTATION OF PARTICLES DURING COMPACTION

A pharmaceutical powder may be classified into one of three main categories according to their mechanism of densification during compaction, i.e. those mainly undergoing plastic deformation, those mainly undergoing fragmentation and those undergoing both plastic deformation and fragmentation (Humbert-Droz et al, 1983).

Fragmentation is defined as the formation of smaller discrete primary

particles from an initial particle. Therefore an adequate approach for characterizing fragmentation seems to be measurement of the surface area of the material before, during or after compaction (Alderborn et al, 1985). Higuchi et al (1953) measured the surface area of sulphathiazole compacts as a function of compaction pressure. They observed an initial increase in surface area due to brittle fracture, followed by a decrease ascribed to bonding between particles. Huffine (1953) reported that the surface area of sodium chloride compacts decreased as the compression pressure increased suggesting that sodium chloride consolidated by plastic deformation. Alderborn et al (1985) measured tablet surface area by a permeametry technique. They observed that sodium chloride showed a small increase in tablet surface area with increase in pressure whereas Emcompress (dicalcium phosphate dihydrate) showed a dramatic increase in surface area with increase in pressure. These observations confirmed that sodium chloride consolidated mainly by plastic deformation but Emcompress fragmented extensively during compaction.

Duberg and Nystrom (1986) suggested that during phase I of the Heckel plot (figure 1.9) when the applied pressure is relatively low, many materials undergo particle fragmentation. At this stage, the interparticulate friction may be sufficient to cause fragmentation of weaker particles (Armstrong & Haines-Nutt, 1970). The curvature of the plot at phase I, which can be evaluated as the deviation from straight line, indicates fragmentation (Humbert-Droz, 1983). The correlation coefficient of this region (phase I) can

serve as a tool to quantify the degree of fragmentation. A linear segment (with a high value of the correlation coefficient) is obtained for non-fragmenting materials such as sodium chloride. A non linear curve (with a low correlation coefficient) for phase I and a high mean yield pressure should correspond to material which consolidates by fragmentation rather than plastic deformation, e.g. Emcompress (Duberg & Nystrom, 1982).

By using scanning electron microscopy, it is possible to see if changes in particle size or shape have occurred during compression. Hardman and Lilley (1970), and Duderg and Nystrom (1982), using scanning electron microscopy, showed that there was no particle fragmentation for sodium chloride particles after compaction, although a slight change in the shape of the particles was observed. It was impossible to distinguish any original particle of sucrose or Emcompress after compaction, because of the high degree of fragmentation of these particles.

Another useful method for estimating the degree of fragmentation is measuring the strength of tablets with or without a lubricant such as magnesium stearate (Duberg & Nystrom, 1982). In the case of a plastically deforming material (e.g. sodium chloride), addition of lubricant decreased the adhesion and bonding properties between the particles and therefore the crushing strengths of tablets were decreased dramatically. Tablets made from fragmenting materials, such as Emcompress, showed little or no reduction in their strength on addition of the lubricant. This was attributed to the

formation of new, fresh, clean and unlubricated surfaces which were able to form bonds between particles (Bolhuis et al, 1975; De Boer et al, 1978).

Changes of mean yield pressure with compaction speed can be quantified using equation 1.9 which defines strain rate sensitivity (SRS) (Robert & Rowe, 1985).

$$\mathbf{SRS = [(P_{Y2} - P_{Y1})/P_{Y2}] \times 100} \qquad \text{Equation 1.9}$$

P_{Y1} and P_{Y2} are the mean yield pressure at minimal and maximal punch speed, respectively. SRS is a useful index which can show the plastic or brittle nature of a material. Due to the time dependent nature of plastic deformation, the mean yield pressure increases with increasing punch velocity for plastic materials such as Avicel and sodium chloride, which consequently show higher values of SRS (Robrts & Rowe, 1987a). Materials which consolidate by fragmentation such as Emcompress or magnesium carbonate showed no change in their mean yield pressure with increase in compaction speed. A low value of SRS was obtained for them (Roberts & Rowe 1985, 1987).

Since plastic deformation is a time dependent phenomenon, it has long been recognised that compaction speed will affect significantly the extent of plastic flow. Decrease in the crushing strengths of compacts with an increase in the rate of compaction, has been ascribed to a reduction in the time available for

plastic deformation and thus interparticulate bond formation (Seitz & Flessland, 1965; Hiestand et al, 1977). David and Augsburger (1977) observed that an increase in the duration of the compression cycle resulted in a significant increase in the tensile strength of tablets prepared from Avicel, but not for lactose suggesting that the former underwent plastic deformation while the latter underwent fragmentation. The crushing strengths of tablets made from plastic materials such as Avicel exhibited a dramatic decrease with increase in compaction speed, while tablets made from Emcompress which consolidates by a dominant fragmentation mechanism were independent on compression speed (Garr, 1992). Therefore measuring the crushing strength of tablets at different compression speeds serves as a useful technique for estimating the degree of fragmentation during compaction.

1.5 STUDIES ON THE COMPACTION OF PARACETAMOL

1.5.1 PROBLEMS IN COMPACTION OF PARACETAMOL

It is well known that paracetamol exhibits poor compressibility during compaction, often resulting in weak and unacceptable tablets with a high tendency to cap (Krycer et al, 1982). In general, production of weak and capped compacts of paracetamol has been attributed to a low degree of plastic flow and high elasticity (Duberg & Nystrom, 1986), weak bonding (Obiorah & Shotton, 1976; Doelker & Shotton, 1977) and a high brittle fracture propensity (Hiestand et al, 1977; Alderborn et al, 1985) during compaction.

Garr and Rubinstein (1991a) reported that the relative high elastic energy due to elastic deformation of paracetamol particles during compaction, appeared to be an important factor in tendency of paracetamol tablets to cap.

In section 1.4.1, the advantages of direct compression, compared to granulation techniques, were reviewed. Low cost and rapid production were most important aspects of direct compression. Paracetamol is a widely used analgesic. Therefore it would be useful to improve the direct compression characteristics of paracetamol.

1.5.2 TABLET FORMATION OF PARACETAMOL MIXTURES WITH DIRECT COMPRESSION EXCIPIENTS

Wells and Langridge (1981) evaluated dicalcium phosphate dihydrate-microcrystalline cellulose binary mixtures as direct compression vehicles. Where in excess of 50% microcrystalline cellulose was present, using normal compression forces, tablets of high tensile strength and low friability were obtained. Wells and Langridge (1981) investigated the capacity of these binary mixtures (>50% microcrystalline cellulose) to form tablets with paracetamol. Good tablets were prepared from formulations containing 20% paracetamol. Unsatisfactory tablets were produced with formulation containing above 30% paracetamol due to poor flow, capping and lamination. Malamataris et al (1984) investigated the compaction properties of various mixtures of paracetamol and Avicel. They found that by increasing the amount of Avicel in the mixtures, more acceptable tablets could be produced.

They also found that the incidence of capping and lamination of tablets was greatest when the fraction of Avicel was less than 25% w/w. In a similar study, Yu et al (1988) reported that as far as tensile strength, friability and absence of capping were concerned, the optimal mixture of the two powders was 50% w/w Avicel and 50% w/w paracetamol. Mollan and Celik (1994) evaluated the tabletability of five maltodextrin-paracetamol mixtures. Maltodextrins exhibited adequate binding potential at drug loading levels of up to only 25% w/w paracetamol.

As was mentioned in section 1.4.1, in the case of tablet formulations which require a high amount (>100 mg) of a non-compressible drug, direct compression excipients can not be used, because the weight of tablet will be too large. Paracetamol tablets are mainly formulated as tablets containing 300 to 500 mg of drug. The above studies clearly show that, for example, in the case of using 25% w/w of paracetamol mixed with direct compression excipients, the weight of a formulated tablet will be between 1200 to 2000 mg. Obviously, this is an unacceptable weight for oral tablets.

1.5.3 MODIFICATION OF PARACETAMOL CRYSTALS TO IMPROVE ITS COMPRESSIBILITY

Crystal and particle engineering of drugs play a significant role in the design of materials for direct compaction. Therefore, the driving force for controlled modification must be to provide the required properties for direct compression or good compressional behaviour and to overcome the deficiencies in the

unmodified material which lead to problems in tableting and compaction (York, 1992).

In recent years, some attempts have been made to modify the properties of paracetamol crystals using different crystallization techniques, in order to improve the compaction properties of unmodified crystals. Fachaux et al (1992, 1993) prepared a sintered form of paracetamol crystals by crystallization from dioxane followed by a controlled drying process. The paracetamol interacted with this solvent to form a solvate. The porous texture of desolvated crystals induced plasticity and improved the compressibility of paracetamol. One disadvantage of this form of paracetamol was the difficulty in the complete elimination of residual solvent from the final product.

Di Martino et al (1994, 1995, 1996) prepared a polymorph of paracetamol (orthorhombic form) by melting the drug at 170°C in an anhydrous nitrogen atmosphere. After slow cooling to room temperature, the solidified material was ground. The obtained crystals exhibited better compressibility than untreated crystals. The increased compressibility was attributed to the presence of sliding planes in the crystal structure which lead to a possible increase in plasticity. The disadvantage of this work was that a high temperature was required and therefore the atmosphere and time have to be strictly controlled.

Abdelillah et al (1995) prepared agglomerated particles of paracetamol using

a spherical crystallization technique. The agglomerated particles were obtained by adding a paracetamol solution in tetrahydrofuran into either hexane or a hexane/chloroform mixture. The agglomerated particles exhibited good compressibility compared to untreated paracetamol. The most obvious disadvantage of this method was that a relatively high tetrahydrofuran content remained in the final agglomerates even after drying.

1.6 AIMS AND OBJECTIVES

Paracetamol is a model drug with well known poor tableting properties. As detailed in section 1.2.4 and 1.2.5, the crystal morphology of a drug plays an important role in its physico-mechanical behaviour. Therefore the main aim of this project was to study the consequences of altering the crystal properties of paracetamol on its compaction behaviour. The main objectives of this work were:

-to modify the crystal habit of paracetamol by using selected crystallization techniques in the presence or absence of polyvinylpyrrolidone as an additive.

-to assess the solid state characteristics of the modified crystals.

-to investigate the role of these modifications on the compaction properties.

The following is a brief outline of the contents of this thesis. Chapter 2 describes the general materials and methods used in this study. A comprehensive study of the compaction properties of untreated paracetamol

crystals is given in chapter 3. Chapter 4 describes the effect of crystallization solvent and crystallization temperature on the production of some modified paracetamol crystals. The compaction properties of these modified crystals are investigated in chapter 5.

Since polyvinylpirrolidone (PVP) was used as an additive during the crystallization of paracetamol, chapter 6 details the possible interactions between PVP and paracetamol. Chapter 7 describe the modification of paracetamol particles using crystallization in the presence of PVP. The compaction properties of these particles are given in chapter 8. The dissolution characteristics of the paracetamol particles obtained in the presence of PVP are detailed in chapter 9. Whilst the conclusions of each chapter are presented following a discussion of the results, a general discussion of the main findings of the project is provided in chapter 10. Suggestions for further work, and a summary of the contents of this thesis is presented in chapter 11.

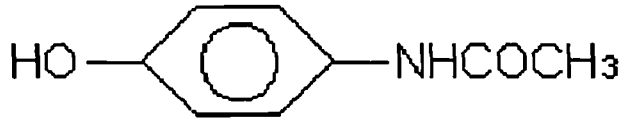
CHAPTER 2. MATERIALS AND EXPERIMENTAL METHODS

2.1 MATERIALS

The following materials were used throughout this study:

2.1.1 PARACETAMOL

Paracetamol (*para*-hydroxy-acetanilide) (figure 2.1) is a white crystalline powder, soluble 1:70 in water at 25°C, 1:20 in boiling water, 1:7 to 10 in ethanol, 1:9 in propylene glycol, 1:13 in acetone, (all at 25°C), slightly soluble in chloroform, insoluble in ether and benzene, and soluble in a solution of alkaline hydroxide (El-Obeid & Al-Badr, 1985). Its melting point is 169-172°C. Its ultraviolet spectrum in water has a maximum absorbance between 244-247 nm (Moffat et al, 1986).



$C_8H_9NO_2$

Mol. Wt=151.16

Figure 2.1 The chemical structure of paracetamol.

Paracetamol is very stable in aqueous solution and its maximum stability is in the pH range 4 to 7 (Koshy & Lach, 1961; Connors et al, 1976). Instability of paracetamol is due to its hydrolysis which yields *p*-aminophenol and acetic acid.

Paracetamol used in this study was obtained from Sterling Organics, Northumberland, U.K.

2.1.2 POLYVINYLPYRROLIDONE

Four soluble grades of polyvinylpyrrolidone (PVP) were obtained from BASF, Aktiengesellschaft, 67056 Ludwigshafen, Germany, as trade names Kollidon 12PF, Kollidon 17PF (PF = pyrogen free), Kollidon 30 and Kollidon 90.

Soluble grades of PVP are obtained by free radical polymerisation of vinylpyrrolidone in water or isopropanol, yielding the chain structure of polyvinylpyrrolidone as shown in figure 2.2.

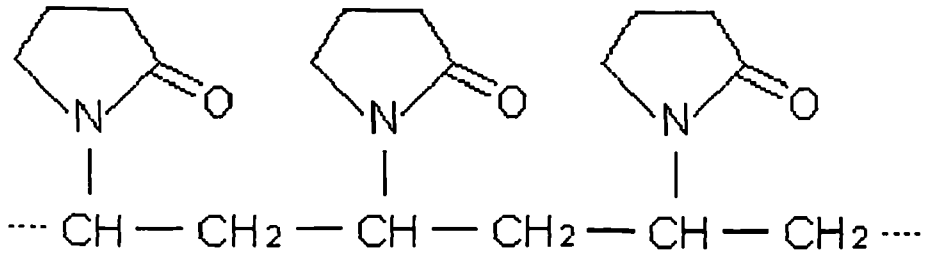


Figure 2.2 The chemical structure of polyvinylpyrrolidone.

One of the interesting features of the soluble grades of PVP is their universal solubility, which extends from extremely hydrophillic solvents, such as water, to hydrophobic liquids, such as butanol. In general they are soluble in water, alcohol and in chloroform but practically insoluble in ether (Raynolds, 1993).

However, higher molecular weights of PVP, specially Kollidon 90, dissolve more slowly than the lower molecular weight grades (Kollidon, Technical information, 1992).

The average molecular weights of Kollidon grades are given in table 2.1. Recent results do not always agree well with older results, as the techniques used have been improved significantly over the years. However, the products themselves have not changed.

Table 2.1 The average molecular weights of soluble grades of Kollidon (Kollidon, Technical information, 1992).

	Average molecular weight	
Kollidon grade	Recent determinations	Measured before 1975
Kollidon 12 PF	2000- 3000	2500
Kollidon 17 PF	7000- 11000	9000
Kollidon 30	44000- 54000	40000
Kollidon 90	1000000-1500000	700000

The viscosities of aqueous solutions of the soluble grades of Kollidon, which depend on their average molecular weight, are considerably different. The average molecular weights of the soluble grades of Kollidon are expressed in terms of the K-value in pharmacopoeias used in Europe and the USA. The K-value is calculated from the relative viscosity in water and always forms a part of the commercial name. Table 2.2 shows the K-values and typical viscosities for 10% w/v solutions of various grades of Kollidon in water at

20°C.

Table 2.2 K-values and typical viscosities of 10% w/v solutions of Kollidon in water at 20°C (Kollidon, Technical information, 1992).

Product	K-value range	Typical viscosity range
Kollidon 12 PF	11-14	1.3-2.3 mPa s
Kollidon 17 PF	16-18	1.5-3.5 mPa s
Kollidon 30	28-32	5.5-8.5 mPa s
Kollidon 90	85-95	300-700 mPa s

The various grades of Kollidon, Kollidon 12 PF, Kollidon 17 PF, Kollidon 30 and Kollidon 90, are expressed according to their molecular weight in this study as PVP 2000, PVP 10000, PVP 50000 and PVP 10000000, respectively.

2.1.3 ETHANOL

Absolute ethanol B.P, containing not less than 99.5% v/v of C_2H_5OH, used in this study was obtained from Hayman Ltd, Witham, Essex, UK.

2.1.4 OTHER REAGENTS USED IN THIS STUDY

Resublimed iodine, potassium iodide, anhydrous citric acid, magnesium stearate, acetone (all General Purpose Reagents) and potassium bromide (Analar Grade) were obtained from British Drug Houses (BDH) Chemicals Ltd, Poole, Dorset, UK.

2.2 EXPERIMENTAL METHODS

2.2.1 CRYSTALLIZATION PROCESSES

For the purposes of convenience, the techniques for crystallization used in this study are explained in the relevant chapters.

2.2.2 X-RAY POWDER DIFFRACTION (XPD)

An important technique for establishing the reproducibility of a crystalline form is X-ray powder diffraction. Random orientation of a crystal lattice in a powder sample causes the X-ray to scatter in reproducible patterns of peaks at distinct angles (Fiese & Hagen, 1986). If the patterns are identical, the crystals have the same internal structure. If the patterns are different, then the crystals have different internal structures and are different polymorphs. Amorphous forms do not produce a distinct pattern (Byrn, 1982). This method is very useful to determine whether a pair of crystals are polymorphs or crystal habits.

2.2.2.1 Methodology

X-ray diffraction spectra of powder samples were obtained using an X-ray generator model Phillips, PW 1729 fixed with PW 1710 diffractometer (Phillips, Almelo, Netherlands). The cavity of the metal sample holder was filled with the powder sample which had previously been ground by a mortar and pestle, and then smoothed with a spatula. A scanning rate of 0.04°2θ s^{-1} over the range of 10 to 70°2θ was used to produce each spectrum.

2.2.3 INFRARED SPECTROSCOPY (IR)

Infrared spectroscopy is a useful method for the analysis of solids. The infrared spectrum is extremely sensitive to structure and conformation of a compound and thus can be used to compare the structure of a compound in different solid states (Byrn, 1982).

2.2.3.1 Methodology

Infrared spectra were recorded using a Perkin Elmer FTIR 1600 spectrophotometer (Norwalk, Connecticut, USA) utilising potassium bromide discs. These discs were made by grinding 2-3 mg of paracetamol crystals with 25-50 mg of potassium bromide and compressed by a hydraulic press model M-30 (Industrial instruments Co Ltd, UK) at 10 tons pressure for 2 min.

2.2.4 THERMAL ANALYSIS (TA)

Thermal analysis is a method which can be used to characterize the alterations of physical or chemical properties of substances induced by temperature changes. Melting, desolvation, sublimation, polymorphic transition (solid-solid transformation), degradation and crystallization may be examined. The most common types of thermal analysis are differential scanning calorimetry, differential thermal analysis, thermomechanical analysis and hot stage microscopy (Ford & Timmins, 1989).

2.2.4.1 Differential scanning calorimetry (DSC)

Differential scanning calorimetry measures the heat loss or gain resulting

from physical or chemical changes within a sample as a function of temperature (Fiese & Hagen, 1986). Differential scanning calorimetry is a very useful method for studying solid states and can be used to determine the accurate temperature and enthalpy of phase transformations (Byrn, 1982).

2.2.4.1.1 Calibration of DSC

DSC measurements were carried out with a Differential Scanning Calorimeter model DSC7 (Perkin Elmer, Baconsfield, UK) which was controlled by a Perkin Elmer TAC7. The differential scanning calorimeter was calibrated using indium (melting temperature, 156.6°C and ΔH_f 28.45 J g^{-1}) and zinc (melting temperature, 419.47°C). Samples (2-4 mg) were heated at 10°C min^{-1} in crimped aluminium pans under a nitrogen atmosphere. A similar empty pan was used as reference. Melting points and enthalpies of fusion of samples were automatically calculated by the instrument. The calculated enthalpy of indium and the melting temperatures of indium and zinc were programmed into the DSC as calibration data.

2.2.4.1.2 DSC methodology

Samples of paracetamol crystals (2-4 mg) were heated at 10°C min^{-1} in crimped aluminium pans under a nitrogen atmosphere. A similar empty pan was used as the reference. Melting points, onset temperatures and enthalpies of fusion were automatically calculated. The onset temperature is the point of intersection of the extrapolation from the peak to the baseline. Thus the onset temperatures used in this study are extrapolated onset temperatures

(Ford & Timmins, 1989). A minimum of four determinations for each sample was carried out.

2.2.4.2 Hot stage microscopy

This method involves the direct observation of the behaviour of materials during heating or cooling. This technique is useful for studying the melting, desolvation and polymorphic transitions in solids.

2.2.4.2.1 Methodology

For each sample, about 1 mg was spread on a microscope slide and covered with a cover slip. The sample was observed using an optical microscope during heating at 5°C/min using a Mettler FP82 Hot Stage and FP80 central processor.

2.2.5 SCANNING ELECTRON MICROSCOPY (SEM)

Scanning electron microscopy is a powerful tool for studying the crystal habit, surface properties of crystals and structural imperfections and dislocations in crystals (Byrn, 1982).

2.2.5.1 Methodology

Electron micrographs of powder samples were obtained using a scanning electron microscope (Jeol model JSM T200, Tokyo, Japan). The specimens were mounted on a metal stub with double sided adhesive tape. The stubs were then placed in the coating chamber of a Polaron E5000 diode sputter

coating unit (Holywell Industrial Estate, Watford, England). The chamber was evacuated, refilled with argon and samples coated with gold emitted at 1.2 kV. The coated samples were individually placed on the specimen holder of scanning electron microscope in a vacuum chamber. The chamber was evacuated and a voltage of 15 kV was selected for accelerating the electrons from the electron gun onto the specimen. The image formed was viewed directly via a screen or recorded photographically.

2.2.5.2 Particle size measurement

Particle size measurements were carried out directly from the scanning electron micrographs. For grain-like crystals the longest dimension was taken as the length and the shortest dimension as width. The thickness of the grain-like crystals was approximately equal to their width. The thickness was only determined for plate-like crystals. Each determination was carried out on a minimum of 30 crystals and the distributions of size reported.

2.2.6 QUANTITIVE DETERMINATION OF PVP IN AQUEOUS SOLUTION

2.2.6.1 Basic principle of method

The reaction of iodine and PVP (figure 2.3) is considered as a sensitive photometric method for determining small quantities of PVP in aqueous solution (Levy & Fergus, 1953). This reaction causes a considerable intensification of the iodine colour, such that very small quantities of PVP can be determined. A linear relationship between absorbance and PVP

concentration between 5-50 μg ml^{-1} was obtained (Levy & Fergus, 1953). The enhancement of colour, was achieved by control of pH, by carrying out the reaction in citric acid solutions. The colour intensity is dependent on the molecular weight of PVP (Levy & Fergus, 1953). For this reason calibration curves were produced for each grade of PVP.

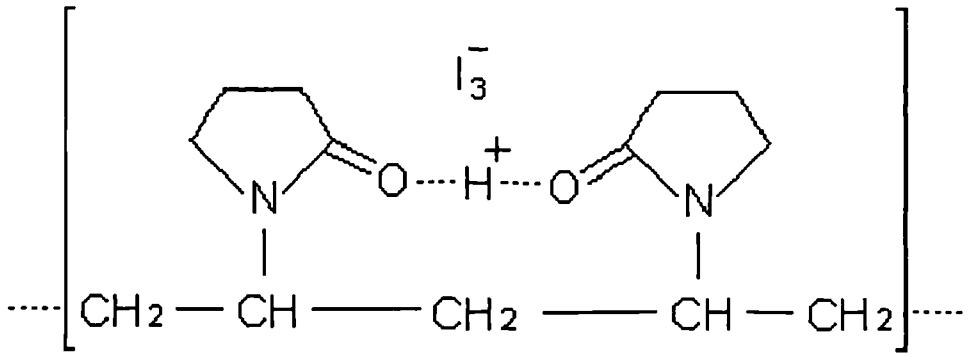


Figure 2.3 Complex formation between PVP and iodine (Schenck et al, 1979).

2.2.6.2 Calibration curve for different grades of pvp

Aqueous solutions of the four different grades of PVP, concentration of 10, 30 or 50 μg ml^{-1}, were prepared. 50 ml of these solutions were taken and mixed with 25 ml of 0.2 M aqueous citric acid and 10 ml of 0.006 N iodine solution (appendix 1). After 5 min, the absorbances of these solutions were measured against a blank solution without PVP (appendix 1) at 470 nm, using a Philips spectrophotometer (PU 8625, Cambridge, UK) (Kollidon, Technical information, 1992). Each determination was carried out three times and the mean values were reported. Figure 2.4 shows the calibration curves of different grades of PVP. The best fit equations for the Beer's law plots of the UV absorbance versus concentration of PVP 2000, PVP 10000, PVP 50000

and PVP 1000000 are given by equations 2.1, 2.2, 2.3 and 2.4, respectively.

Y = 0.005 + 0.009 C	(r = 0.9992)	Equation 2.1
Y = 0.007 + 0.013 C	(r = 0.9994)	Equation 2.2
Y = 0.012 + 0.018 C	(r = 0.9992)	Equation 2.3
Y = 0.011 + 0.020 C	(r = 0.9993)	Equation 2.4

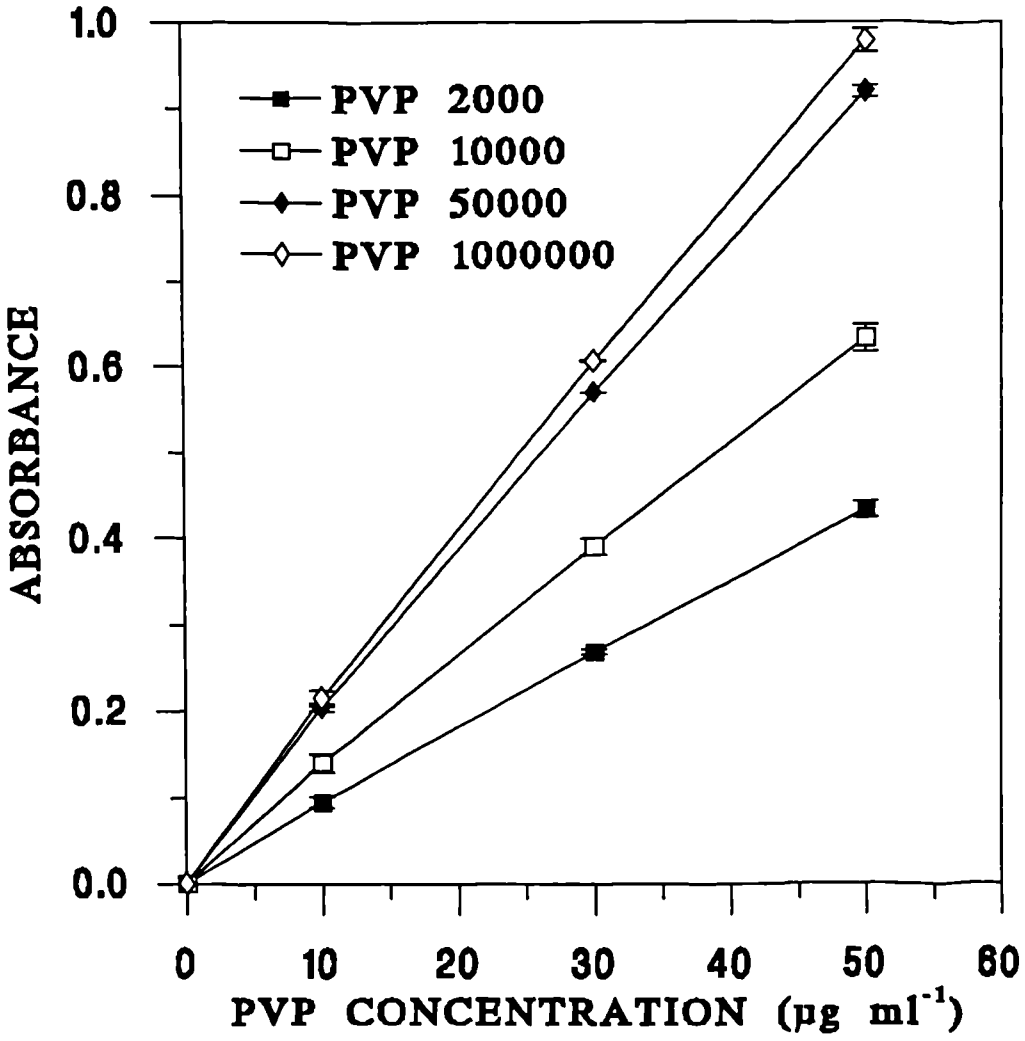


Figure 2.4 Ultraviolet absorbance against PVP concentration (µg ml^{-1}) for different grades of PVP at 470 nm (each point is the mean ±SD of three determinations).

In equations 2.1 - 2.4, Y is the absorbance of solution at 470 nm and C is the concentration of relevant grades of PVP in solutions (μg ml^{-1}).

2.2.6.3 Experimental method

The amount of PVP present in paracetamol particles crystallized from media containing PVP, was determined by photometric analysis as described above. An appropriate amount of sample (about 30 mg) was dissolved in 50 ml of water. This solution was then mixed with 25 ml of 0.2 M aqueous citric acid and 10 ml of 0.006 N iodine solution (appendix 1). After 5 min, the intensity of the colour was measured as described in section 2.2.6.2. The PVP contents were determined from the calibration curves for the relevant grade of PVP (figure 2.4). Each test was carried out at least three times.

2.2.7 CALIBRATION CURVE OF PARACETAMOL

The UV absorbance for solutions containing different concentrations of paracetamol (0.0 to 0.035 mg ml^{-1}) in freshly distilled water at 244 nm were determined (figure 2.5), using a Diode Array spectrophotometer (Hewlett Packard HP 8452A, Waldbronn, Germany). The best fit equation for the Beer's law plot of UV absorbance versus paracetamol concentration is given by equation 2.5.

$$\mathbf{Y = 0.007 + 62.9\ C} \qquad (r=0.9993) \qquad \text{Equation 2.5}$$

In equation 2.5, Y is the absorbance of paracetamol solution at 244 nm and

C is the concentration of paracetamol (mg ml^{-1}).

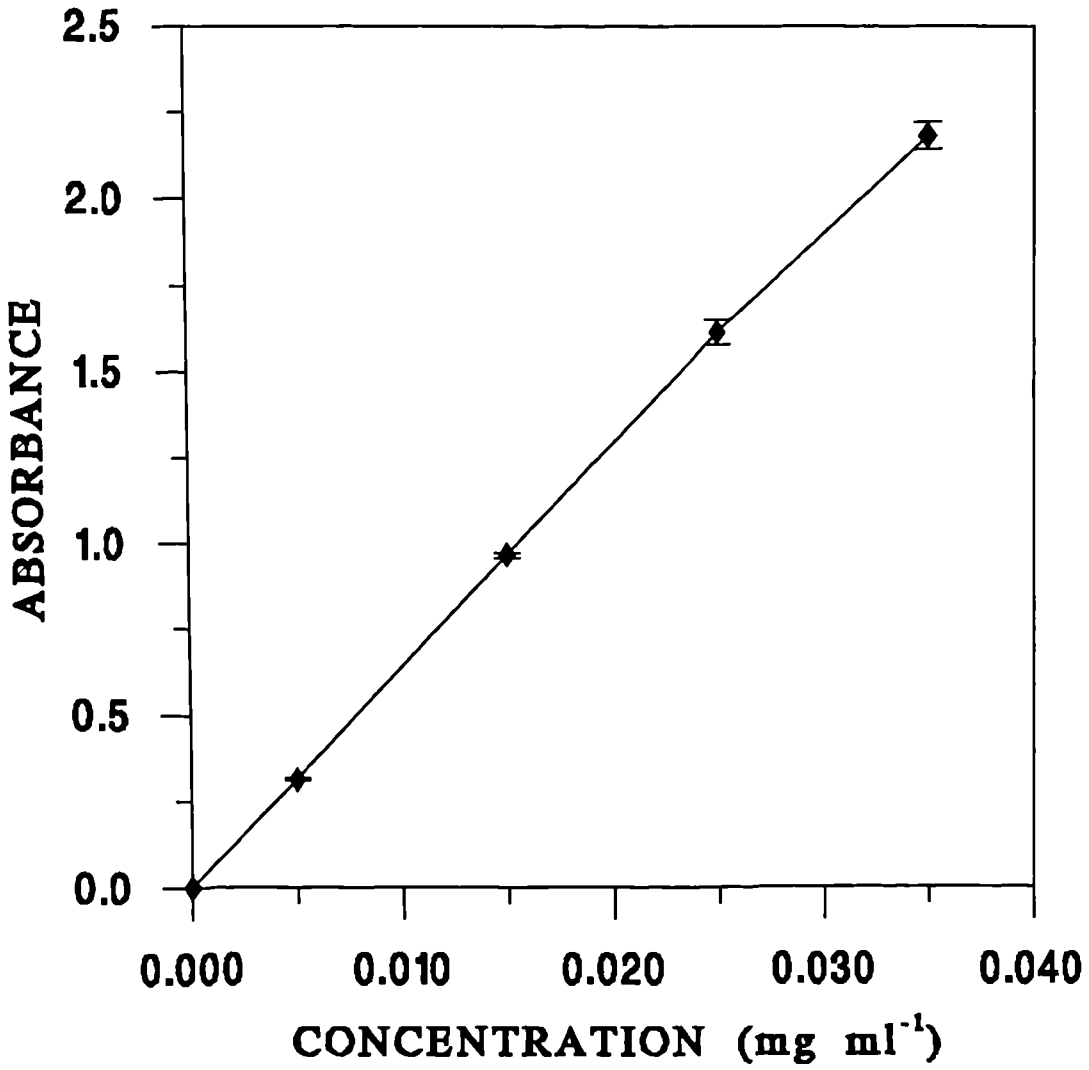


Figure 2.5 Ultraviolet absorbance against concentration (mg ml^{-1}) of paracetamol in distilled water at 244 nm (each point is the mean ±SD of three determinations).

2.2.7.1 Determination of paracetamol solubility

In order to investigate the aqueous solubility of paracetamol, the following was carried out. Samples (2.5 g) of paracetamol were dispersed in 100 ml of

freshly distilled water or aqueous solution of PVP in stoppered 100 ml conical flasks in a shaking water bath (Companstat 882942, England) at 37°C for 24 h. Then the suspended solids were allowed to settle and the supernatants were sampled and filtered through a Whatman No. 1 filter paper. The first 10 ml of the each filtrate was discarded. The paracetamol concentrations were determined spectrophotometrically at 244 nm after appropriate dilutions using equation 2.5. The mean of three determinations was used to calculate the solubility of paracetamol in aqueous media.

2.2.8 DISSOLUTION TESTING OF PARACETAMOL POWDERS

The dissolution rates of paracetamol samples were determined using a Pharmatest dissolution tester (GmbH, Hainburg, Germany), coupled with a Diode Array spectrophotometer (Hewlett Packard HP 8452A, Waldbronn, Germany). The USP XXII apparatus II was used, at 50 rpm rotating in 1000 ml distilled water at 37±1°C. Paracetamol powder was weighed accurately (35 mg) and placed into small bags (2 × 3 cm) made from metal gauze with 25 μm mesh size. The metal mesh bags containing drug powder were placed into dissolution medium under the dissolution paddles. The media were automatically sampled at every minute using an Ismatec peristaltic pump (IPS 8/B, Carshalton, UK) at 50 ml min^{-1} flow rate. The amount of dissolved paracetamol was analyzed spectrophotometrically at 244 nm.

2.2.9 DETERMINATION OF TRUE DENSITY OF POWDERS

The ratio of mass to volume is known as density of a material. If the true

volume (the volume of a sample excluding its pores) of a known weighed solid particles is measured, then the true density may be calculated. The true densities of powder materials used in this study were determined using an air comparison pycnometer Model 930, Beckman Instruments Ltd, UK. Each determination was carried out five times and the mean values obtained.

2.2.10 COMPACTION SIMULATOR

Initial research into compaction behaviour of materials began in 1954 when Higuchi et al employed an instrumented tableting press. They attached strain gauges to various parts of a tableting machine to facilitate the accurate measurement of force. Subsequently, instrumentation of single punch machines developed. Piezoelectric transducers and linear variable differential transformers (LVDTs) were applied to monitor the force and punch displacement during compaction (Shotton et al, 1963; De Blaey & Polderman, 1971). Although, some useful data may be obtained by such machines, it was not always possible to establish a correlation with the actual production simulation where high speed rotary machines are employed.

Hunter et al (1976) presented the design of a compaction simulator to mimic the compression and ejection cycle of any tableting process in real time and to record all important parameters during a compaction cycle. Celik and Travers (1985) used a compaction simulator, which was controlled by a computer. This machine consisted of a servo controller hydraulic actuator mounted in a frame.

Compaction simulators have numerous potential applications in pharmaceutical research, development and production. The basic compaction mechanisms of materials and process variables on tablet properties, and also the effect of particle characteristics of a drug or excipient on their compaction properties may be investigated using compaction simulators.

2.2.10.1 Design of compaction simulators

All simulators have similar design and construction. Compaction simulators are essentially high speed hydraulic presses modified for making tablets. A compaction simulator, such as that one used in this study, consists of three main sections; the load frame, the hydraulic power supply and electronic console. These sections are shown in figure 2.6.

(1) The load frame

The load frame consists of upper and lower actuators and a die table which are supported by four vertical columns. One ±25 mm LVDT is mounted on each actuator to control their movement. A ±50 kN load cell is located at the other end of each actuator. The die is positioned in the centre of die table along with two ±10 mm LVDTs which monitor the punch movement within the die.

(2) Hydraulic unit

This provides the energy to move the actuators. It consist of an oil reservior pressurised to 4000 psi by an electric pump.

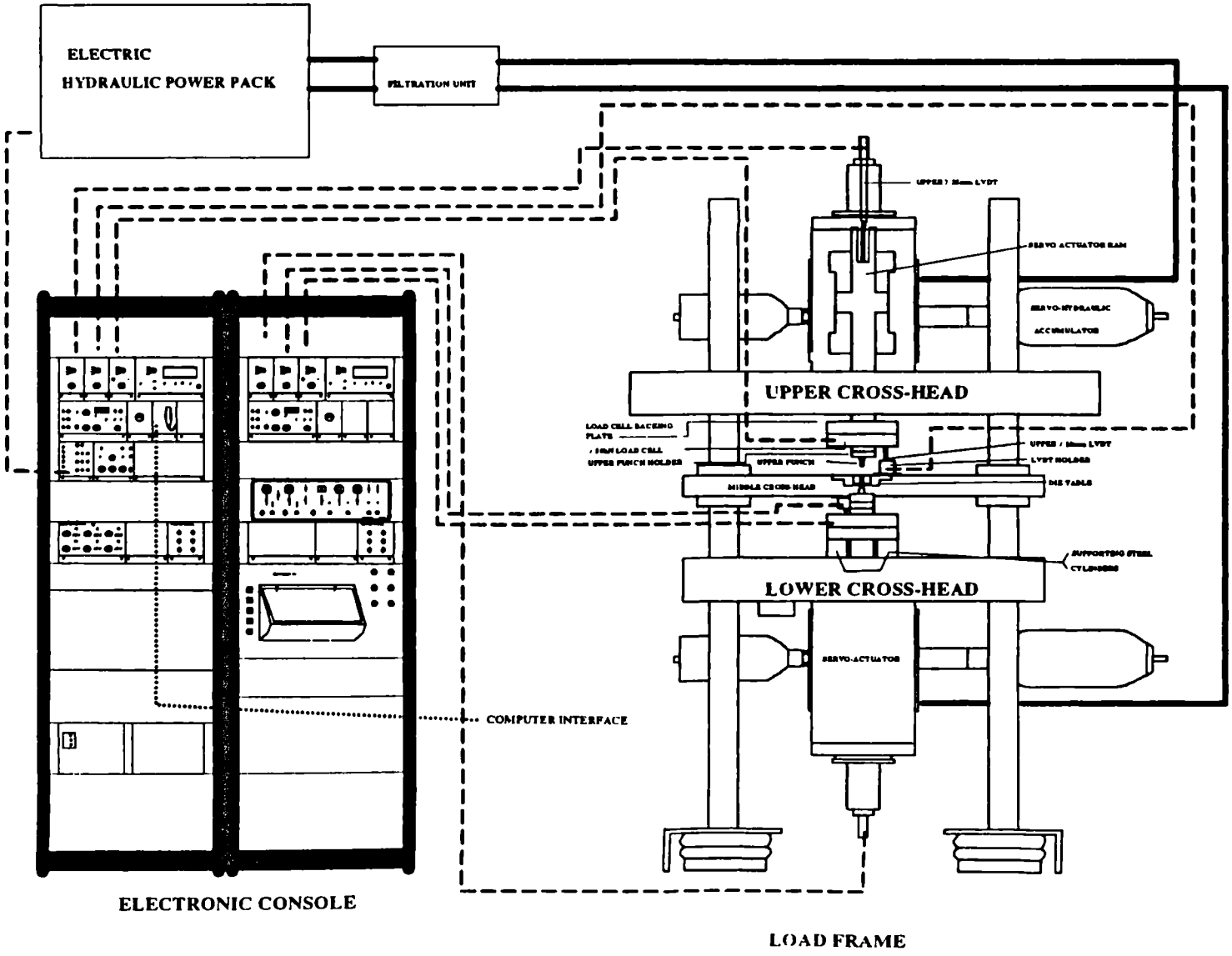


Figure 2.6 A diagram of Liverpool School of Pharmacy Compaction Simulator (with permission of Mr C.J. Okpala).

(3) The control unit

The control unit consists of two consoles which control the major parameters of load, position and strain associated with each punch. Data are captured via a microlink transient recorder, which provides a hard copy and a computer link for analysis.

2.2.10.2 Mode of operation

The microcomputer is able to generate a displacement-time profile similar to that experienced by the upper and lower punches of the tableting machine which is being simulated. The data points of the profile are output at a predetermined rate via a digital/analogue converter to the servo controller in the main control unit and on to the control valves situated on the load frame. The signal supplied to the valves determines the flow of hydraulic fluid from the power pack through the valves to the actuators. It is this flow of fluid which causes movement of the actuators according to the intended profile.

The amount of powder used is that required to produce one tablet, may be hand-filled into the die. During a compression event, force and displacement data from the upper and lower load cells and LVDTs are captured using the transient recorder. The data may then be plotted or transferred via the microcomputer to the mainframe computer for analysis.

2.2.11 COMPRESSION PROCEDURE

All compressions were carried out using the High Speed Compaction

Simulator (ESH Testing Ltd Brierley Hill, West Midlands, U.K.) modified by the Liverpool School of Pharmacy and Chemistry, fitted with 12.5 mm flat faced punches. This simulator is capable of compacting powders at rates up to 3000 mm s^{-1} and at forces up to 50 kN. A sawtooth time-displacement profile was used to control both upper and lower punches.

The die wall was cleaned with acetone and prelubricated with 4% w/w magnesium stearate in acetone before each compression. Particle size fractions of paracetamol (see section 2.2.13) were hand filled into the die. Four tablets were produced at compression speeds of 10, 50, 100 or 250 mm s^{-1} up to a maximum 30 kN compaction force. A constant weight of 400 mg was maintained for all the samples.

2.2.12 ANALYSES OF COMPACTION DATA

From the data obtained during compaction, it was possible to calculate the energy involved, the Heckel constants and the percentage of elastic recovery in the die for each tablet.

2.2.12.1 Energy analysis

For a system in which both punches are mobile, the punch separation may be plotted against upper punch force. The area under this curve will be the work done or energy (section 1.4.5.3). The net work of compaction (plastic energy) and expansion work (elastic energy) of compaction were measured using energy analysis on force-punch separation plots. Plastic energy is

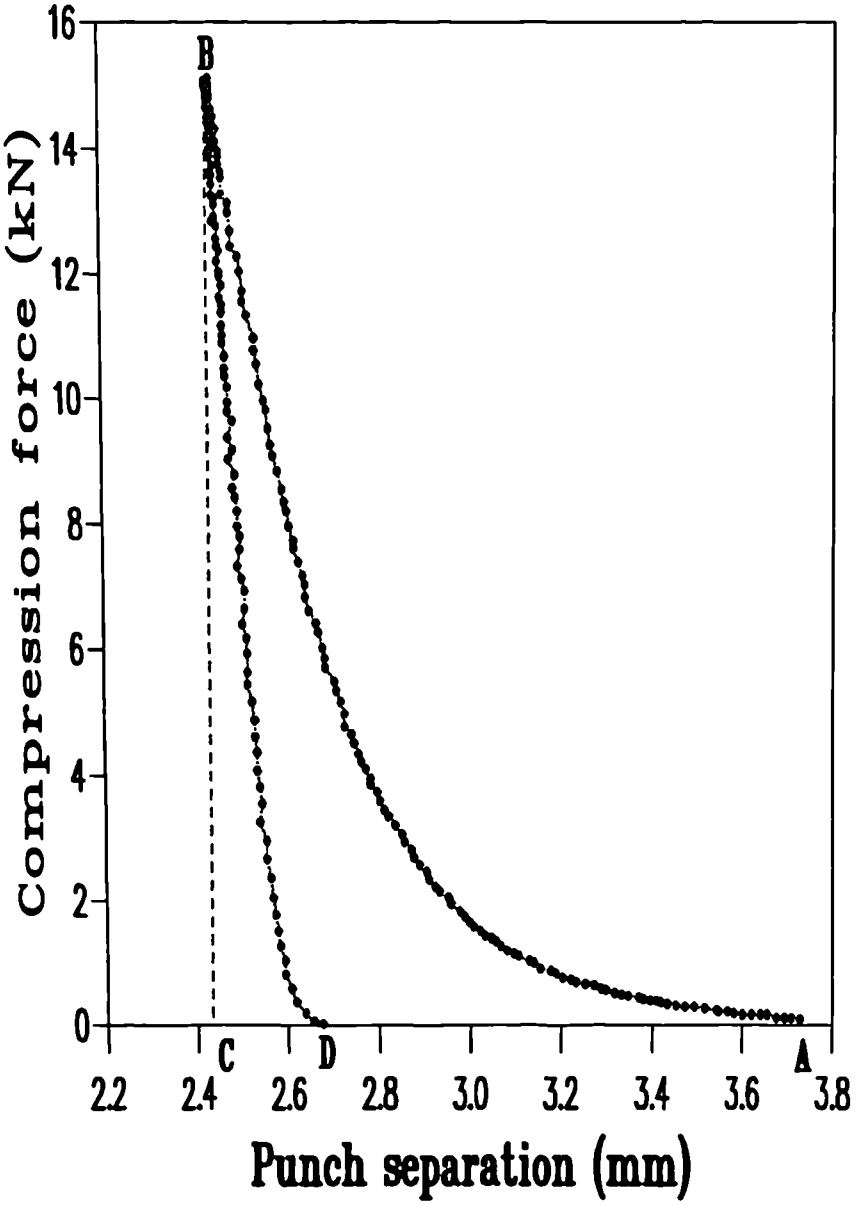


Figure 2.7 Typical force-punch separation plot for untreated paracetamol (particle size 105-210 μm) obtained at a compression speed of 10 mms^{-1}.

energy permanently imparted to the tablet but elastic energy is energy of expansion of tablet which is transferred to the punch during decompression phase.

Figure 2.7 illustrates a typical force-punch separation plot, where A is the punch separation at the first measurable force. B is the peak force at minimal punch separation, C represent the minimum punch separation and D is the separation after decompression. The area ABC gives the gross energy, and the area under curve CBD corresponds to the decompression energy or elastic energy. The net compaction energy or plastic energy (the area under curve ABD) was determined from the difference between area ABC and area CBD. A computer programme was employed to calculate gross, plastic and elastic energies from data obtained during compaction.

2.2.12.2 Heckel analysis

A computer programme was employed to fit data obtained during compaction to Heckel equation (equation 2.6).

$$\ln [1/(1 - D)] = KP + A \qquad \text{Equation 2.6}$$

Details of Heckel equation were described in section 1.4.5.2. Figure 2.8 illustrates a typical Heckel plot. Regression analyses were carried out on the Heckel plots for data obtained between 20 to 65 MPa and the slope of these straight line portions and subsequently the mean yield pressures determined.

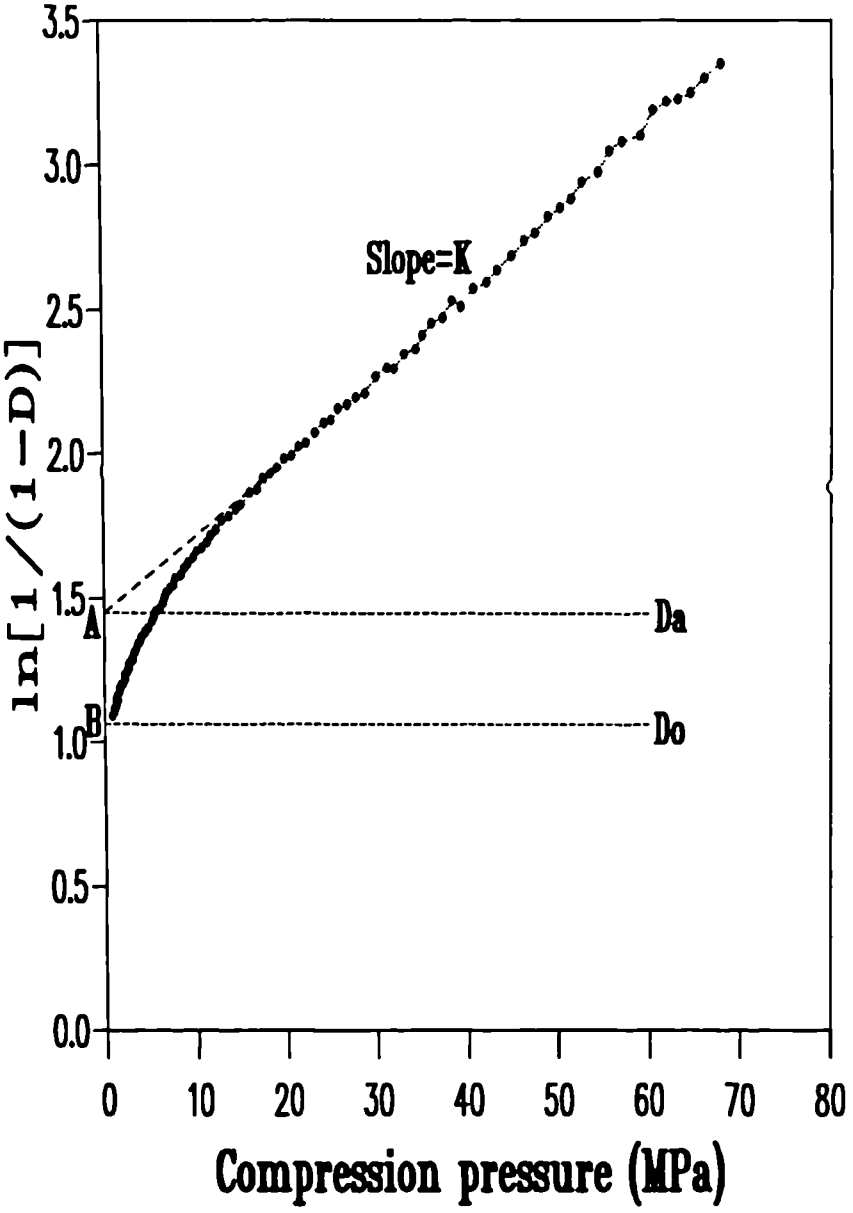


Figure 2.8 Typical Heckel plot for untreated paracetamol (particle size 105-210 μm) obtained at a compression speed of 10 mms^{-1}.

The relative densities of the powders, D_o, at the point when a measurable force is applied, and the relative densities, D_a, obtained from the intercept of the Heckel plot (figure 2.8), were also calculated.

2.2.12.3 Determination of elastic recovery of tablet in the die

Tablets made from untreated and some of the modified forms of paracetamol were too weak and capped after ejection, so that it was impossible to handle them and monitor their thickness outside the die. Therefore, the percentage of elastic recovery in the die of each tablet was calculated using equation 2.7.

$$\% \text{ Elastic recovery} = [(H - H_c)/H_c] \times 100 \qquad \text{Equation 2.7}$$

where H_c and H are the thickness of tablet under maximum pressure and after the compression force has been removed, respectively.

2.2.13 PARTICLE SIZE FRACTIONS

Particle size fractions (<90 and 105-210 μm) of untreated and modified paracetamol were obtained by sieving the materials through test sieves (Endecotts Ltd., London, U.K) on a mechanical sieve shaker (Pascall Ltd, Sussex, England).

2.2.14 DETERMINATION OF TABLET CRUSHING STRENGTH

The crushing strength was determined from the force required to fracture tablets by diametral compression on a motorised tablet hardness tester

(Schleuniger, Model 2E, Switzerland). Crushing strengths were employed instead of tensile strengths because it was not possible to determine an accurate thickness of paracetamol tablets due to their tendency to cap.

2.2.15 STATISTICAL METHODS

All compaction data were analyzed statistically by two way analysis of variance and/or Tukey's multiple comparison test. Results are quoted as significant where $P<0.05$.

Two way analysis of variance estimates the effects of two independent variables on a dependent variable. For example, in figure 3.4 the dependent variable is elastic recovery of tablet, one of the independent variables is particle size (<90 and 105-210 μm) and other is compression force. Two way analysis of variance showed that there is significant difference between the elastic recoveries of tablets made from the two different particle sizes of paracetamol. The next step was to determine for which compression forces the differences were significant. The Tukey's multiple comparison test is used for this purpose.

CHAPTER 3. COMPACTION PROPERTIES OF UNTREATED PARACETAMOL

3.1 INTRODUCTION

Paracetamol exhibits poor compressibility during compaction, resulting in weak and unacceptable tablets with a high tendency to cap (Krycer et al, 1982). Malamataris et al (1984) noted that the incidence of capping and lamination during the production, and following ejection of tablets from the die, depended on the plastic and elastic behaviour of the material used. It has been suggested that materials undergoing plastic deformation, in contrast to elastic deformation, display enhanced bond formation and produce strong tablets (Duberg & Nystrom, 1982).

In general, the strength of a compact depends on the inherent ability of the powder to reduce in volume during compression and the amount of interparticulate attraction in the final compact (Milosovich, 1963). The decrease in compact volume with increasing compression load is attributed normally to particle rearrangement, elastic deformation, plastic deformation and particle fragmentation. Pharmaceutical materials normally consolidate by more than one of these mechanisms (De Boer et al, 1978, Duberg & Nystrom, 1986).

The aim of the work presented in this chapter was to investigate the fundamental compression characteristics of paracetamol. Two different

particle size fractions of paracetamol were compressed at different compaction forces and compaction speeds. Heckel analyses, elastic recoveries, elastic energies and plastic energies were studied.

3.2 MATERIALS AND METHODS

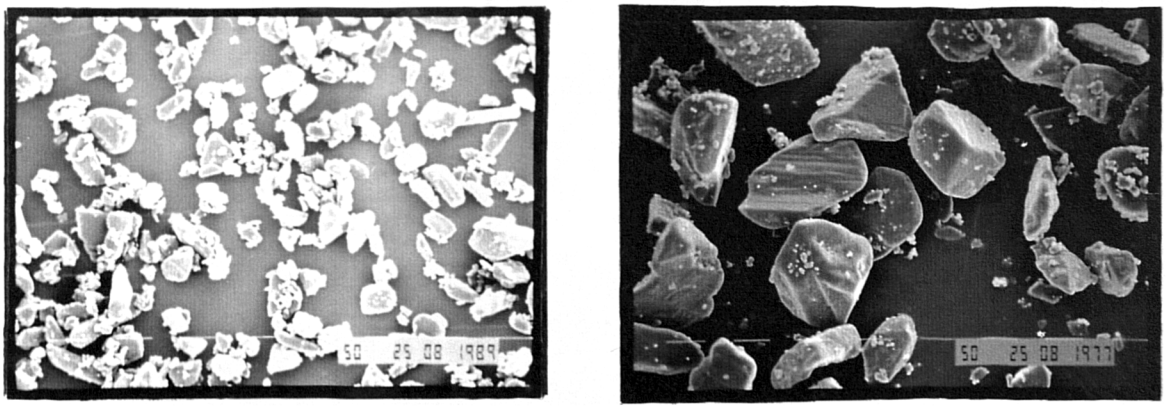
3.2.1 MATERIAL

Paracetamol powder, as described in section 2.1.1, was used.

3.2.2 METHODS

3.2.2.1 Particle size fractions of paracetamol

Two different sieve fractions of paracetamol, <90 μm and 105-210 μm, were obtained as detailed in section 2.2.13. Figure 3.1 exhibits the scanning electron micrographs of these two particle size fractions.



(a) (b)

Figure 3.1 Scanning electron micrographs of untreated paracetamol: a) the <90 μm and b) the 105-210 μm fractions (magnification ×100).

3.2.2.2. Compression

Compression was carried out using the compaction simulator (section 2.2.11). Four tablets, 400 mg weight each, were made at compression speeds of 10, 50, 100 or 250 mm s^{-1} up to a maximum compaction force of 30 kN. To eliminate the effect of moisture on the compaction properties of paracetamol (Garr & Rubinstein, 1992), the sieved fractions were dried in an oven at 55°C for 24 h and stored in tightly closed jars before use.

3.2.2.3 Analyses of compaction data

Analyses of the data according to the Heckel equation were carried out as detailed in section 2.2.12.2. Mean yield pressures (MYP), the relative densities of the powders at zero pressure (D_o) and before appreciable load (D_a), and the extent of particle rearrangement (D_b) were determined.

The plastic and elastic energies were measured using energy analysis on the force-punch separation plots (section 2.2.12.1).

Paracetamol tablets were too weak and capped after ejection, and it was impossible to monitor their thickness outside the die. Therefore the percentage of elastic recovery in the die at different compaction forces were determined, as detailed in section 2.2.12.3.

3.3 RESULTS AND DISCUSSION

3.3.1 CRUSHING STRENGTHS

Compression of both particle size fractions of paracetamol at all compression forces, even at the lowest compression speed, produced extremely weak tablets which had no measurable strength and a high tendency to cap. It was obvious that the capping and failure increased with increase in either compaction force or compaction speed.

3.3.2 HECKEL ANALYSES

Figure 3.2 shows typical Heckel plots of the different particle size fractions of paracetamol obtained at a compaction speed of 10 mms^{-1}. This figure indicates that the larger particles (105-210 μm) exhibited higher relative densities for a given applied pressure than the small fractions (<90 μm). Thus, the degree of densification that occurred during compression was greater for the larger particle size fraction. This can be attributed to increased frictional and cohesive forces associated with the smaller size range, which tend to restrict particle sliding and thus reduce densification (York, 1978; Roberts & Rowe, 1986). Furthermore, during compaction, the smaller particles yielded from fragmentation of the larger angular shaped particles (figure 3.1a), could tend to fill the remaining interparticulate voids between the crystals. This could lead to a further increase in the relative density of the compacts made from larger particle fractions. In contrast, it would be expected that only a relatively small amount of fragmentation

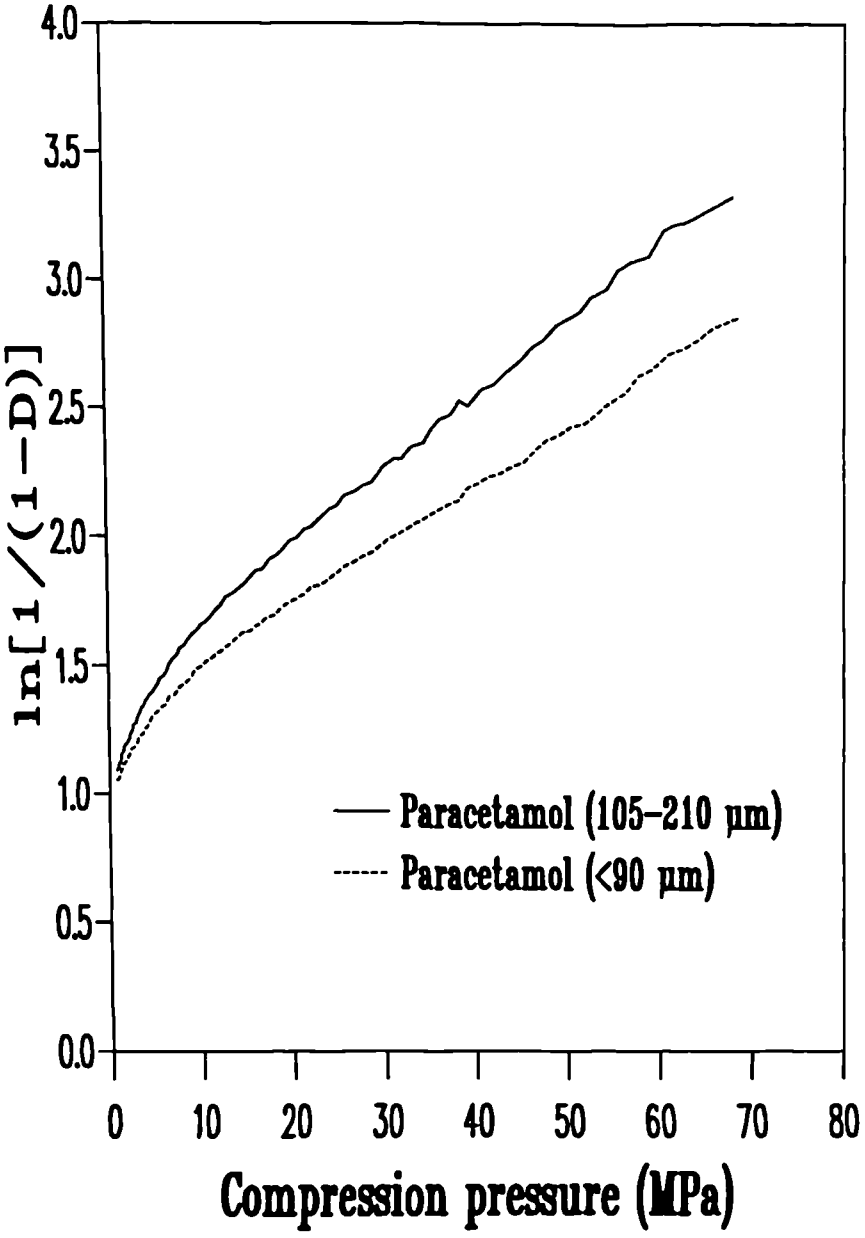


Figure 3.2 Typical Heckel plots of the <90 µm or 105-210 µm size fractions of paracetamol obtained at a compaction speed of 10 mm s^{-1}.

would occur in the small particle size fractions (<90 μm) due to the spherical shape of these particles (figure 3.1b) as reported by McKenna and McCafferty (1982) and Roberts and Rowe (1986).

Figure 3.2 also exhibits that the slope of Heckel plot for the 105-210 μm fraction was greater than for the <90 μm fraction. Table 3.1 indicates that the value of slope (K) was greater for the larger fraction and therefore the reciprocal of K, which is mean yield pressure, was lower. The values of D_a,

Table 3.1 The values derived from the Heckel plots of figure 3.2 of the <90 μm or 105-210 μm fractions of paracetamol compressed at a compaction speed of 10 mm s^{-1}.

	(105-210 μm)	(<90 μm)
K	0.029	0.022
1/K=Mean yield pressure (MPa)	34.2	45.5
D_a	0.72	0.70
D_o	0.67	0.65
r*	0.957	0.972
r**	0.996	0.992

r*=Correlation coefficient of initial curve of Heckel plot (0-20 MPa)

r**=Correlation coefficient of straight line portion of Heckel plot (20-65 MPa)

D_o and D_b (table 3.1) indicate that densification due to die filling and particle rearrangement for the tablet made from the 105-210 μm particles was higher than for the tablet made from the <90 μm fraction.

The correlation coefficient of the initial part of Heckel plot (0-20 MPa) was lower for the 105-210 μm fraction (table 3.1), indicating a higher degree of fragmentation for the larger particles than smaller particles (Duberg & Nystrom, 1986; Humbert-Droz et al, 1983). As mentioned in section 1.4.6, the correlation coefficient of the initial curve of Heckel plot serves as a tool which may be used to quantify the tendency of particles to fragment.

The Heckel plot and the constants derived from it, were thus dependent on the particle size of paracetamol.

A low mean yield pressure (less than 50 MPa) obtained for materials such as Avicel® (microcrystalline cellulose), indicates a high degree of plastic deformation under pressure (Roberts & Rowe, 1987b; Garr & Rubinstein, 1991b). York (1978) and Duberg and Nystrom (1986) reported that the value of mean yield pressure derived from the slope of the linear portion of the Heckel plot depends on the elastic and plastic deformation of the material under applied load. Therefore, for elastic materials a false, low mean yield pressure is obtained (Fell & Newton, 1971). It is difficult to distinguish between elastic and plastic deformation evaluated from the slope of the linear portion of Heckel plot. In an attempt to distinguish between plastic and

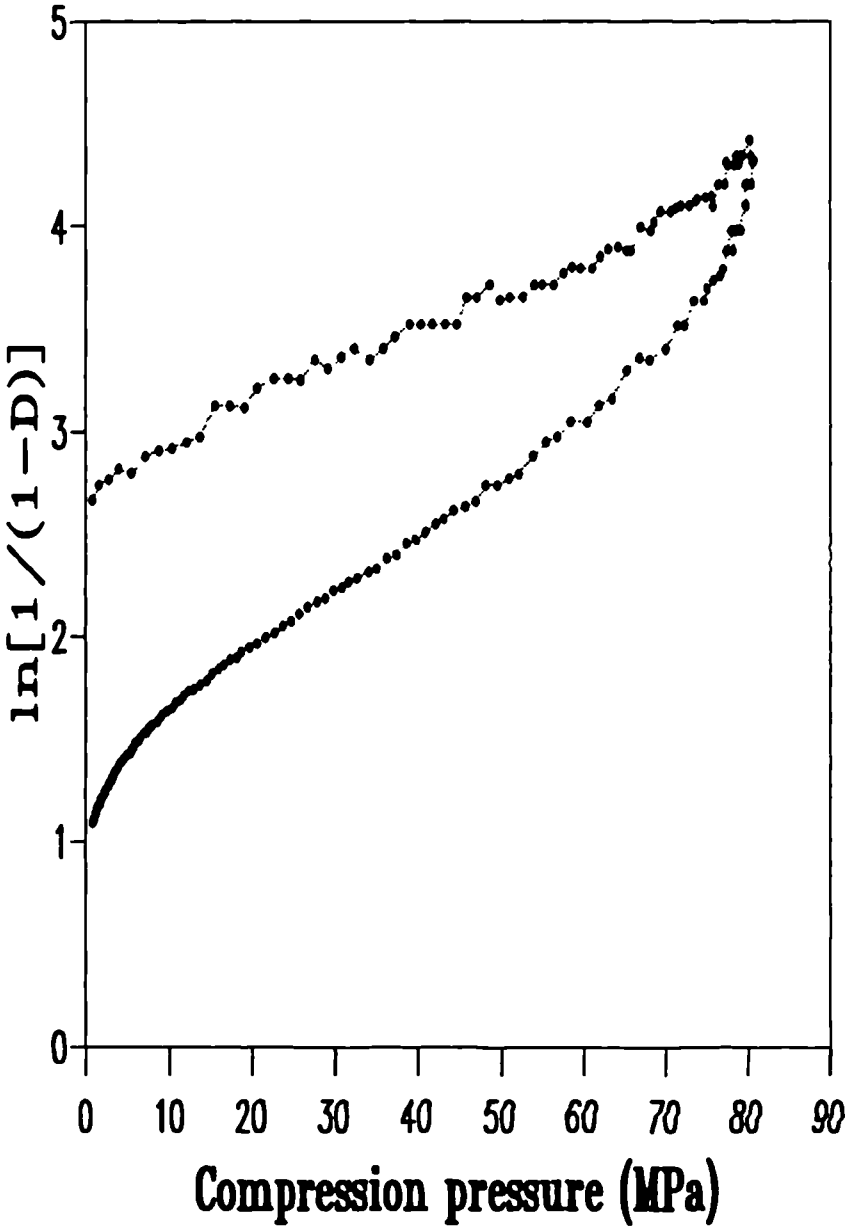


Figure 3.3 Heckel plot, including compression and decompression phases, of the 105-210 μm fraction of paracetamol, obtained at a compression speed of 10 mm s^{-1}.

elastic deformation of materials, Duberg and Nystrom (1986) divided the Heckel plot into three stages as illustrated in figure 1.9. As was mentioned in section 1.4.5.2, a considerable deviation from the horizontal in phase III indicate elastic behaviour of material under pressure. Figure 3.3 shows the whole compression cycle (compression and decompression phases) for the 105-210 μm fraction of paracetamol. The large deviation from horizontal during decompression (phase III) is indicative of a high degree of elastic propensity of these particles under pressure. Therefore the low mean yield pressure found for paracetamol (table 3.1), is attributed to its elastic behaviour not to plastic deformation. The high values of elastic recovery and elastic energy of paracetamol tablets, which will be discussed later in sections 3.3.3 and 3.3.4.2, confirm the extensive elastic behaviour of paracetamol particles during compaction.

3.3.2.1 Influence of compression speed on Heckel constants

The effects of compression speed on the constants derived from Heckel plot (mean yield pressure, D_o, D_a and D_b) of the two particle size fractions of paracetamol were investigated and the results are presented in this section. The effects of compression speed on MYP of the <90 μm and 105-210 μm fractions are shown in table 3.2. As the compaction speed increased, the mean yield pressure for each particle size increased. One way analysis of variance showed that there was a significant difference ($P<0.05$) between the mean yield pressures obtained at different compaction speeds for both particle fractions. Tukey's test revealed that there were no significant

differences (P>0.05) between the mean yield pressures obtained at 10 and 50 mm s^{-1} for both fractions. Additionally, the mean yield pressures obtained at 100 and 250 mm s^{-1} for the <90 μm fraction could not be differentiated.

Table 3.2 The effect of compression speed on the mean yield pressures (MYP) of the <90 μm and 105-210 μm particle size fractions of paracetamol.

Compression speed (mm s^{-1})	MYP±SD (MPa)	
	(105-210 μm)	(<90 μm)
10	34.4±2.0	44.5±1.5
50	35.5±1.2	44.8±1.2
100	38.6±0.6	48.7±1.5
250	42.3±1.6	51.5±2.7

The changes of mean yield pressure with compaction speeds can be quantified using equation 3.1 which allows the calculation of percentage of strain rate sensitivity (SRS) (Roberts & Rowe, 1985).

$$\mathbf{SRS = [(P_{Y2} - P_{Y1})/P_{Y2}] \times 100} \qquad \text{Equation 3.1}$$

P_{Y1} and P_{Y2} are the mean yield pressure at 10 mm s^{-1} and 250 mm s^{-1} punch velocity, respectively. The calculated values of SRS for the <90 μm and 105-

210 μm fractions of paracetamol were 13.6 and 18.7%, respectively.

SRS is a useful index which can show the plastic or brittle nature of a material (see section 1.4.6). Due to the time dependent nature of plastic deformation, the mean yield pressures increase with increasing punch velocity for plastic materials such as Avicel® and sodium chloride, which consequently show high value of SRS (>40%) (Roberts & Rowe, 1985, 1987a). However, for lactose, which deforms by a combination of particle fracture and plastic deformation, the SRS was about 16% (Roberts & Rowe, 1985).

The rather low degree of SRS found for both particle size of paracetamol, is indicative that fragmentation is the dominant mechanism during compaction. Roberts and Rowe (1985) and Duberg and Nystrom (1986) studied the Heckel equation during compaction of paracetamol and similarly reported that the dominant mechanism of compaction of paracetamol is by extensive fragmentation.

Table 3.2 also indicates that, at each punch velocity, the mean yield pressure increased as the particle size decreased. This supports the findings of Hersey et al (1973) and Roberts and Rowe (1986, 1987a) who suggested that as particle size decreases, the stress necessary to cause fracture of particles increases. It would be expected that as the particle size decreases, the brittleness of particles would be reduced because of the lower probability of cracks being present in the crystal structure. Roberts and Rowe (1989)

showed that larger particle size of sodium chloride undergo some degree of fragmentation during compaction whereas smaller particles (<35 μm) undergo plastic deformation, with no evidence of fragmentation.

It has been reported that for plastically deforming materials such as sodium chloride and potassium chloride (Hersey et al, 1973; Humbert-Droz et al, 1982), microcrystalline cellulose (Roberts & Rowe, 1986) and starch (McKenna & McCafferty, 1982), the measured mean yield pressures were independent of particle size. However for materials that deform by particle fragmentation such as lactose and calcium carbonate, the mean yield pressures increased with reduction in particle size (Hersey et al, 1973; York, 1978; Roberts & Rowe, 1986).

The findings of this study indicate that paracetamol belongs to group of materials which deform by fragmentation. The massive fracture of paracetamol particles under applied load has been also confirmed by other techniques such as permeametry (Alderborn et al, 1985).

Table 3.3 shows the values of D_o, D_a and D_b derived from Heckel plots at various compaction speeds. For each particle size, the values of D_o and D_a generally tended to decrease with increasing punch speeds. One way analysis of variance showed that there were significant differences ($P<0.05$) between the values of both D_o and D_a, obtained at different compaction speeds, for both particle fractions. Tukey's test revealed that there were no significant

differences ($P>0.05$) between the values of D_o at 10 and 50 mm s^{-1} for both particle sizes, and also between the values of D_a at 10 and 50 mm s^{-1} for the 105-210 μm fraction, and between values of D_o at 100 and 250 mm s^{-1} for 105-210 μm fraction. The decreases of relative densities with increasing compaction speed may be due either to an increase in the frictional and adhesive forces between particles or due to restriction of the air escape from the powder bed (Roberts & Rowe 1985).

Table 3.3 The values of D_a, D_o and D_b ($\times 10^{-1}$) (±SD) of different particle size fractions of paracetamol at different punch speeds.

Speed (mm s^{-1})	105-210 μm			<90 μm		
	D_o	D_a	D_b	D_o	D_a	D_b
10	6.57 ±0.08	7.18 ±0.04	0.61 ±0.08	6.45 ±0.05	7.03 ±0.04	0.58 ±0.04
50	6.50 ±0.08	7.10 ±0.07	0.63 ±0.08	6.45 ±0.05	6.93 ±0.04	0.48 ±0.04
100	6.25 ±0.05	6.90 ±0.04	0.63 ±0.07	6.16 ±0.05	6.72 ±0.04	0.56 ±0.04
250	6.20 ±0.00	6.70 ±0.04	0.53 ±0.05	5.93 ±0.04	6.48 ±0.05	0.55 ±0.05

Table 3.3 also indicates that at each compaction speed, the smaller particle fraction of paracetamol showed apparently lower values of D_o and D_a than the larger fractions. Two way analysis of variance showed that there were significant differences ($P<0.05$) between the <90 μm and the 105-210 μm particle fractions in terms of D_o and D_a. Tukey's test revealed that the values

of D_o obtained for the two fractions were significant only at 250 mm s^{-1} ($P<0.05$). However, the differences between the values of D_a were significant ($P<0.05$) at all compaction speeds. Decrease in values of D_o and D_a for smaller particles, may be attributed to increase frictional and cohesive forces between the smaller size fractions and/or more fragmentation of the 105-210 μm fraction as compared to the <90 μm fraction, which were discussed earlier.

3.3.3 INFLUENCE OF COMPACTION FORCE ON THE ELASTIC RECOVERY OF PARACETAMOL TABLETS

The effect of compression force on the elastic recoveries in the die of tablets made from the two size fractions of paracetamol are shown in figure 3.4. Increasing the compaction force resulted in an increase in the elastic recoveries of the tablets. Tablets made from the <90 μm fraction exhibited higher elastic recoveries than larger particles. Two way analysis of variance showed that there were significant differences ($P<0.05$) between the elastic recoveries of the tablets made from the <90 μm fraction and tablets made from the 105-210 μm fraction. However, there were no significant differences (using Tukey's test) between the elastic recoveries of the tablets made from the two particle sizes at 20 and 25 kN ($P<0.05$).

Although the paracetamol tablets made from either particle sizes had no measurable hardness, the values of elastic recoveries, which were lower for the larger particles, may indicate a higher interparticulate bondings for the 105-210 μm fraction. At all compaction pressures, the larger particles produced

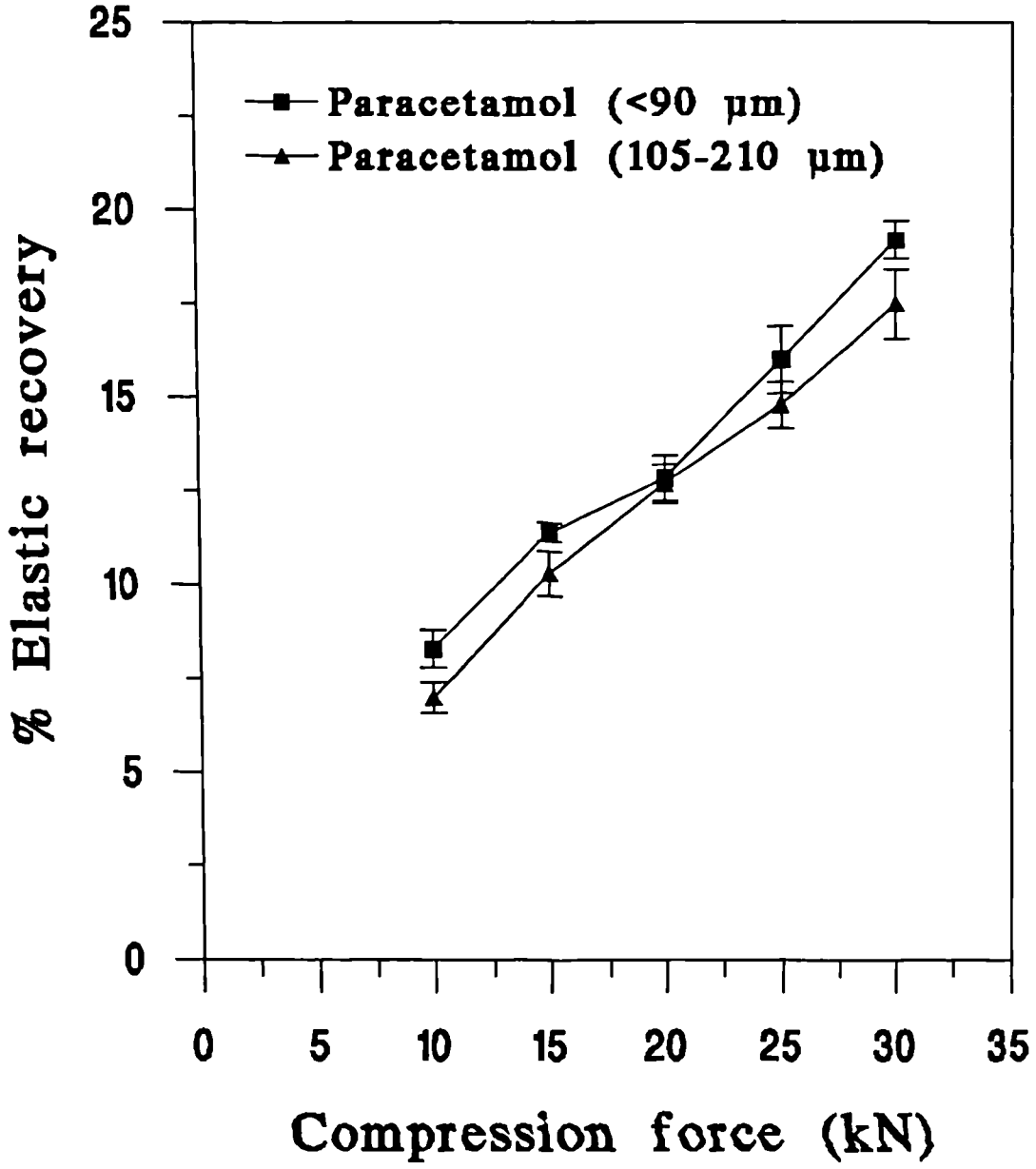


Figure 3.4 Effect of compression force on the elastic recovery in the die of tablets made from <90 µm or 105-210 µm fractions of paracetamol, at a compression speed of 10 mm s^{-1}.

denser compacts than the smaller particles (section 3.3.2). It may be argued that the increased fragmentation of the larger size fraction of paracetamol, should result in increased interparticulate bonding due to the formation of fresh and clean surfaces (McKenna & McCafferty, 1982).

For materials which fragment during compaction, such as Emcompress® (dicalcium phosphate dihydrate), the main mechanism of particle bonding is due to the creation of numerous new, fresh and clean surfaces which are able to form bonds (Duberg & Nystrom, 1982; Nystrom & Glazer, 1985; Alderborn et al, 1985). Therefore for a brittle substance, the greater fragmentation, producing more fresh and clean surfaces, results in the more bondings between particles.

3.3.4 ENERGY ANALYSIS OF PARACETAMOL TABLETS

3.3.4.1 Effect of compression force or speed on the gross energies

The effects of compaction force or compaction speed on the gross energies of tablets made from the <90 μm and 105-210 μm fractions of paracetamol are illustrated in figures 3.5 and 3.6, respectively. Increasing the compaction force or compaction speed, resulted in an increase in gross energies for both particle size fractions. These figures also indicate that at all compaction forces or speeds the gross energies of tablets made from the <90 μm fraction were greater than the 105-210 μm fraction. The gross energy is a combination of elastic and plastic (net compaction) energies. Therefore the next step was

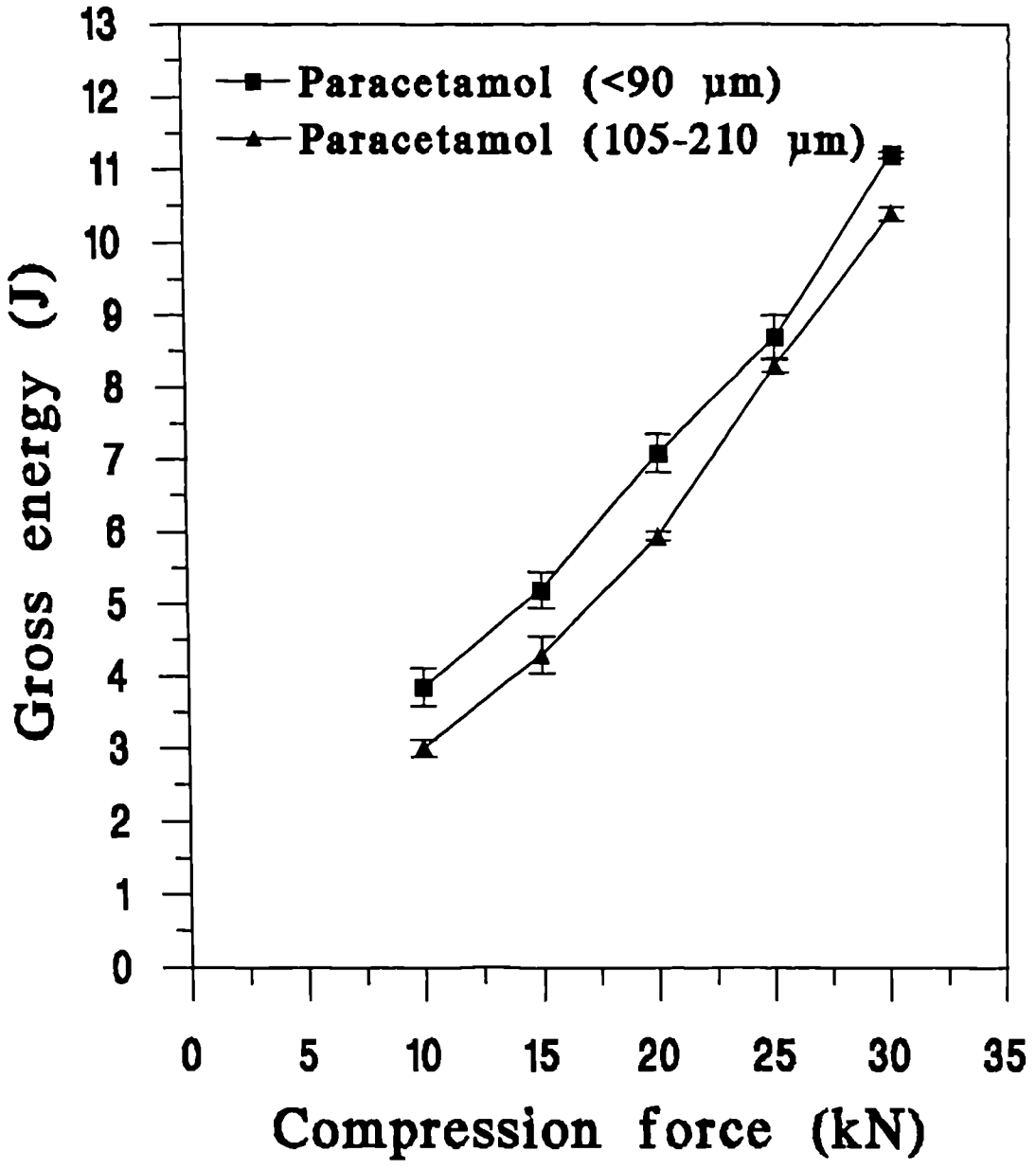


Figure 3.5 Effect of compression force on the gross energies of tablets made from the <90 µm or 105-210 µm fractions of paracetamol, at a compression speed of 10 mm s^{-1}.

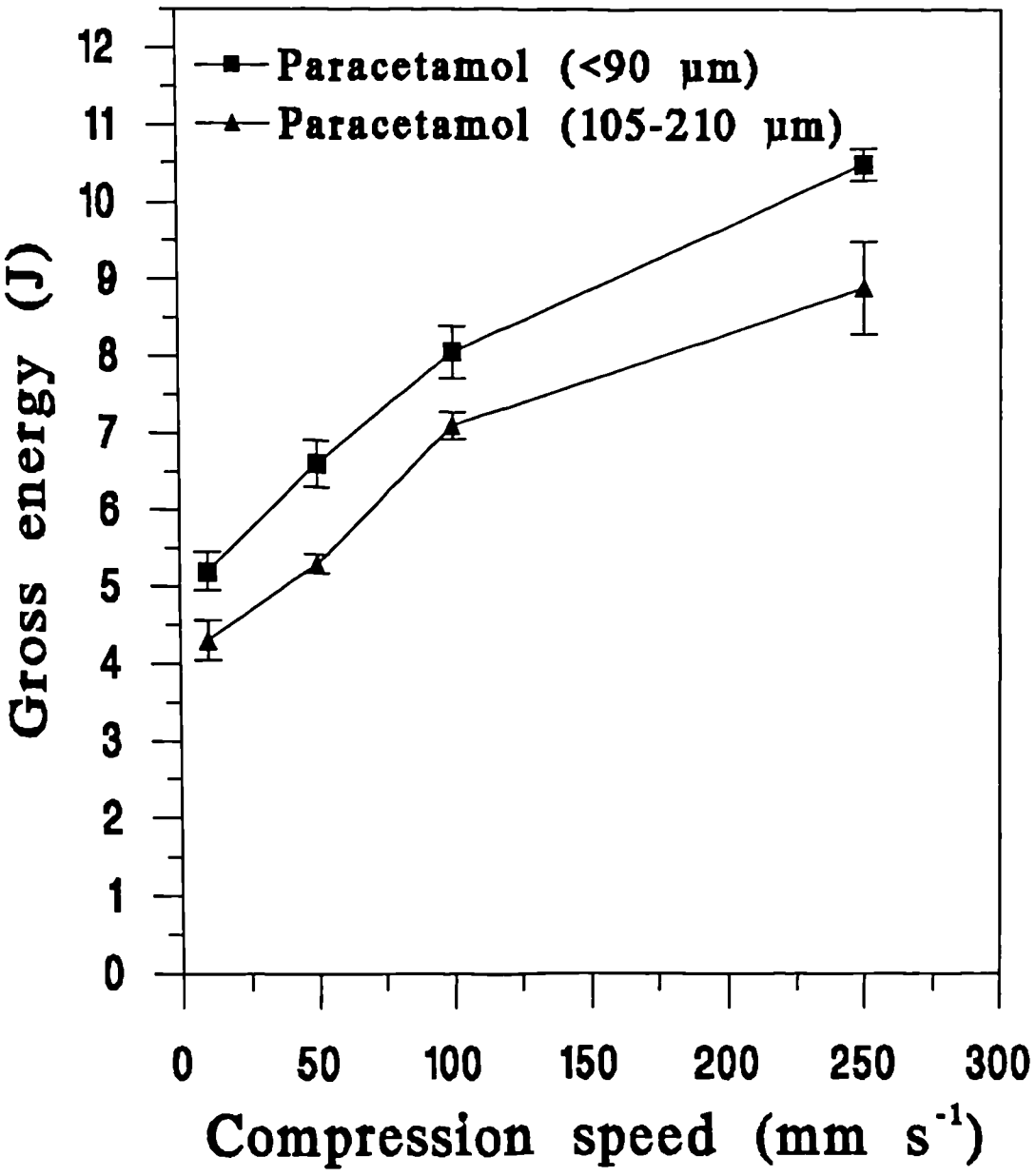


Figure 3.6 Effect of compression speed on the gross energies of paracetamol tablets made from the <90 µm or 105-210 µm fractions of paracetamol, at a compression force of 15 kN.

to distinguish the effect of particle sizes on these energies.

3.3.4.2 Influence of compression force or speed on the elastic energies

The effects of compression force or compression speed on the elastic energies of tablets made from paracetamol are illustrated in figures 3.7 and 3.8, respectively. Increase in the compaction force or compaction speed resulted in an increase in the elastic energies made from two particle fractions.

Figures 3.7 and 3.8 also indicate that at different compaction forces or speeds, the tablets made from the 105-210 μm fraction exhibited lower elastic energies than the <90 μm fraction. However, Tukey's test showed that there was no significant difference ($P>0.05$) between elastic energies for these two fractions (<90 μm and 105-210 μm) at 30 kN compaction forces (figure 3.7), and at 100 mm s^{-1} compaction speed (figure 3.8). Elastic energy is not used for formation of bonds. In fact, this energy is stored in tablets under stress as deformation energy. The release of this stored energy at the end of the compression cycle allows the distorted particles to return to their original shape and so rupture weak particle-particle bonds (Yu et al, 1988). In the present study, the results of elastic recovery were supported by the data of the elastic energies. The elastic energies indicated that the tablets made from smaller particles were relatively more elastic than tablets made from larger particles, resulting in an increase in the elastic recovery of tablets made from the <90 μm fractions (figure 3.4).

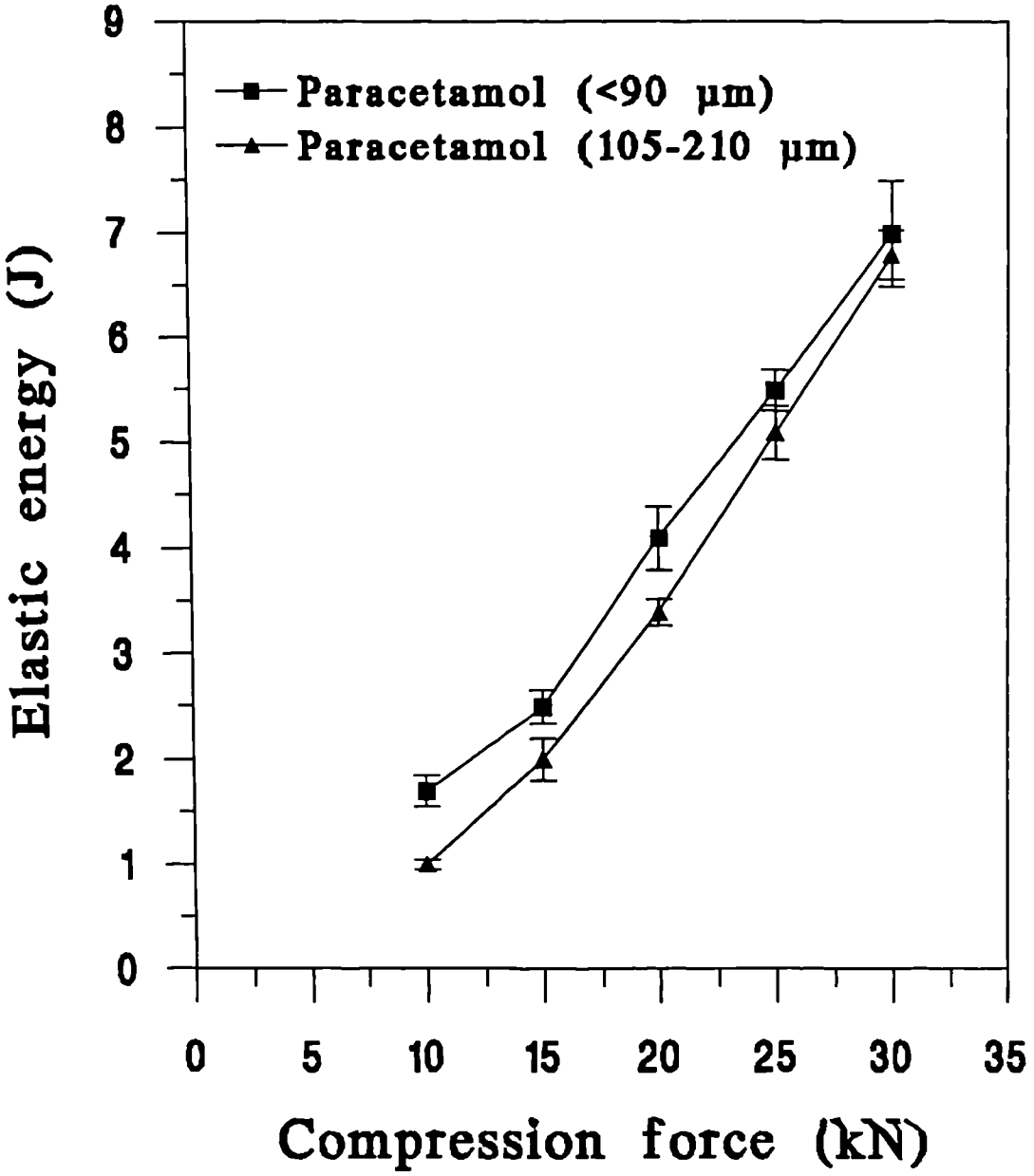


Figure 3.7 Effect of compression force on the elastic energies of tablets made from the <90 µm or 105-210 µm fractions of paracetamol, at a compression speed of 10 mm s^{-1}.

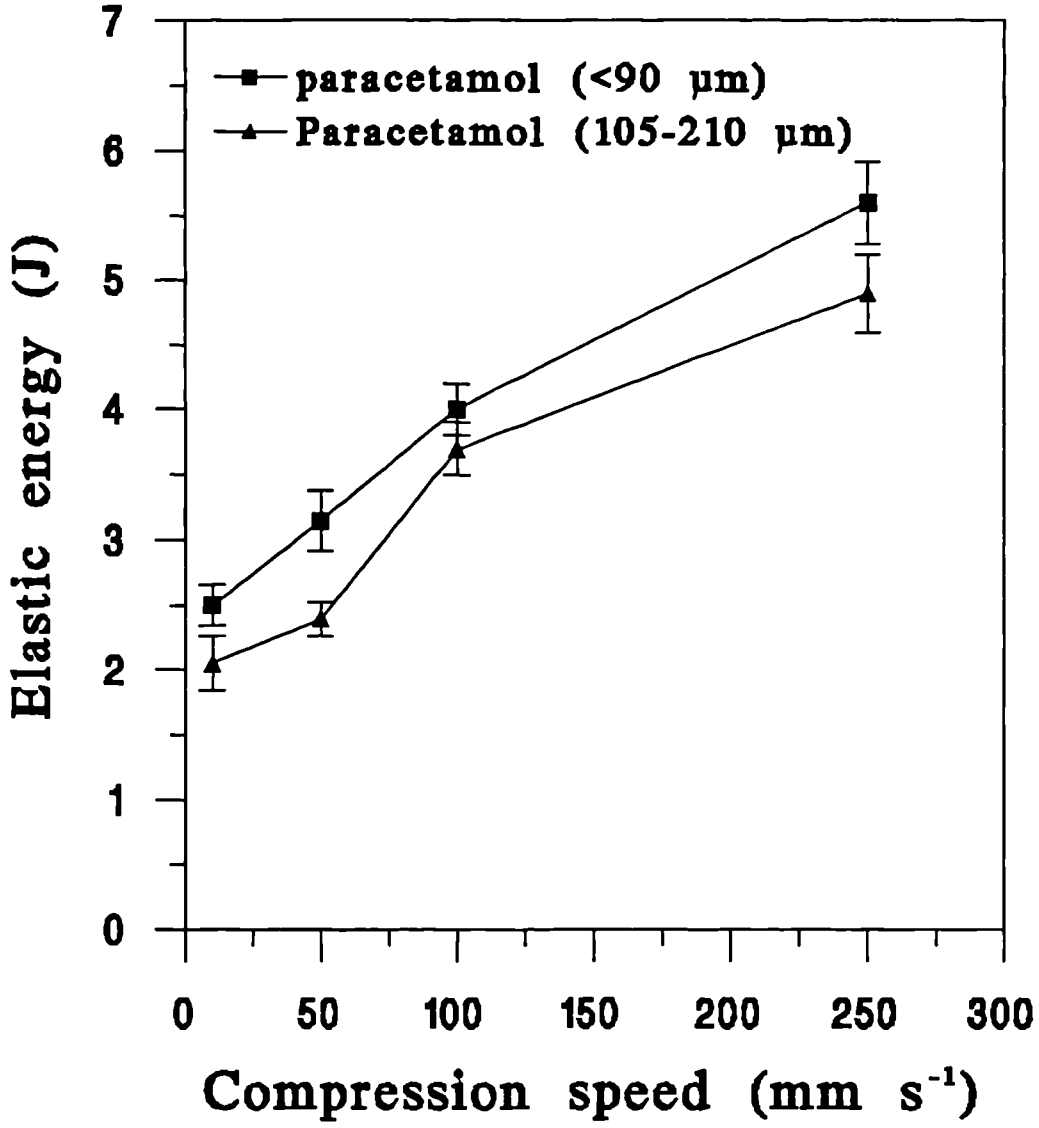


Figure 3.8 Effect of compression speed on the elastic energies of tablets made from the <90 µm or 105-210 µm fractions of paracetamol, at a compression force of 15 kN.

3.3.4.3 Influence of compression force or speed on the plastic (net compaction) energies

Figures 3.9 and 3.10 show the plastic energies of paracetamol tablets at different compaction forces or speeds, respectively. Increase in compression force or compression speed resulted in an increase in the plastic energies for tablets made from each particle fraction of paracetamol.

Plastic or net compaction energy is utilized for die wall friction, interparticle friction, particle slippage and rearrangement, plastic deformation, fragmentation and formation of bonds during compaction. Figures 3.9 and 3.10 indicate that the plastic energies of tablets made from the <90 μm fraction were higher than for tablets made from the 105-210 μm fractions. Tukey's test revealed that at 25 kN compaction force (figure 3.9) and at 250 mm s^{-1} (figure 3.10), there was no significant difference ($P>0.05$) between the plastic energies of tablets made from the <90 μm or 105-210 μm fractions. Increased in plastic energies for smaller particles, may be attributed firstly, to the increased frictional forces between the smaller particles. Secondly, as described in section 3.3.2.1, the mean yield pressures of the smaller particles were higher than those of the larger particles. Therefore, smaller fractions need more energy for fragmentation and deformation.

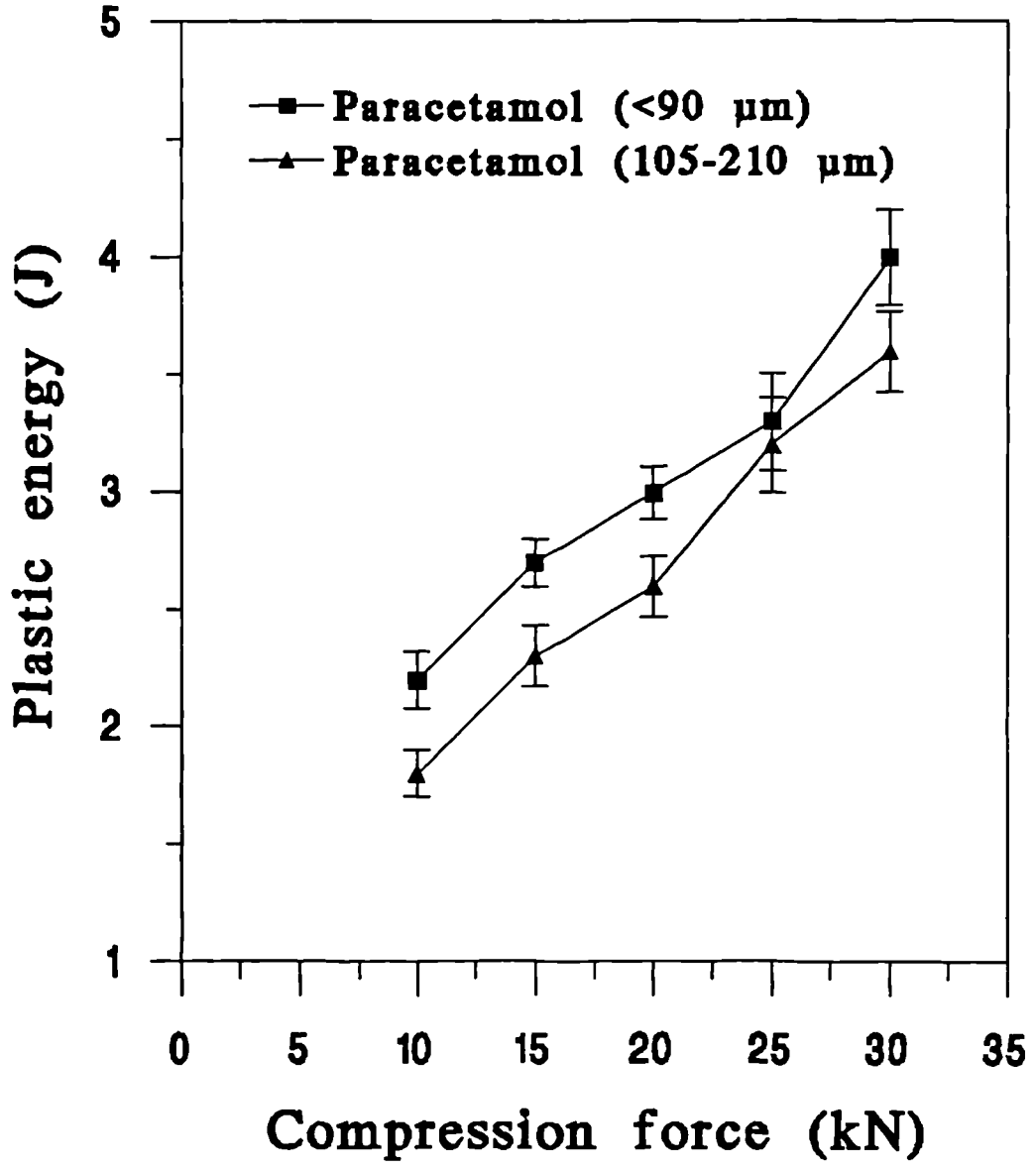


Figure 3.9 Effect of compression force on the plastic energies of tablets made from the <90 μm or 105-210 μm fractions of paracetamol, at a compression speed of 10 mm s^{-1}.

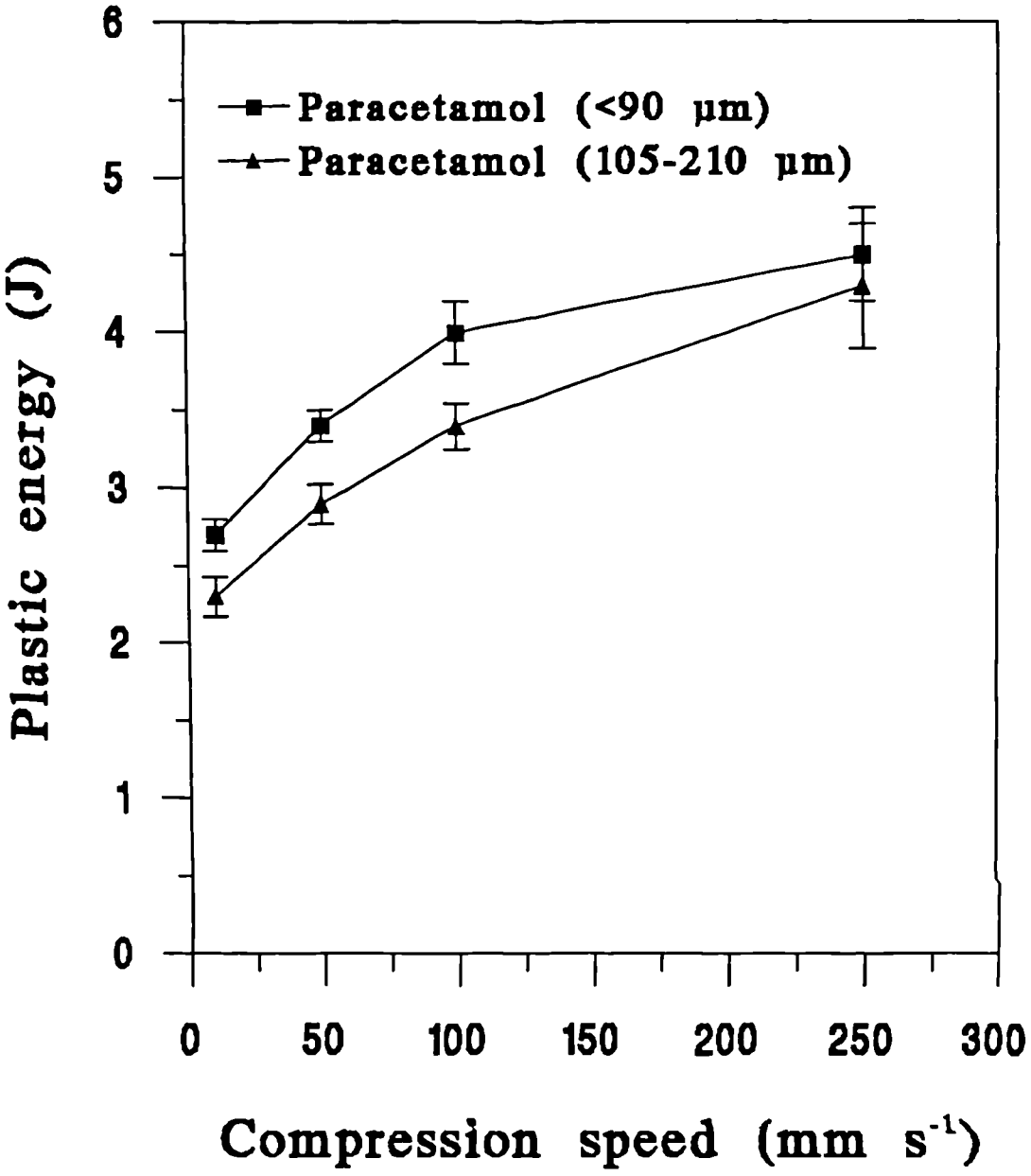


Figure 3.10 Effect of compression speed on the plastic energies of tablets made from the <90 µm or 105-210 µm fractions of paracetamol, at a compression force of 15 kN.

3.3.4.4 Influence of compression force or speed on the ratio of elastic energy/plastic energy

Tables 3.4 and 3.5 show the ratios of elastic energy/plastic energy (EE/PE) at various compaction forces or speeds, respectively. The ratio of EE/PE generally increased, with increase in compression force or speed. Tukey's test showed that there were no significant differences ($P>0.05$) between the EE/PE ratios obtained at 25 and 30 kN for both fractions, and also between 20 and 25 kN only for <90 μm fraction (table 3.4). It was also found (using Tukey's test) that there were no significant differences between the ratios of EE/PE at 10 and 50 mm s^{-1} for both particle sizes, and also at 100 and 250

Table 3.4 Effect of compression force on the ratio of EE/PE of paracetamol tablets made from <90 μm or 105-210 μm fractions, at a compaction speed of 10 mm s^{-1}.

Compression force (kN)	EE/PE ratio±SD	
	105-210 μm	<90 μm
10	0.54±0.05	0.74±0.06
15	0.87±0.09	0.92±0.04
20	1.31±0.11	1.36±0.14
25	1.58±0.18	1.73±0.11
30	1.89±0.16	1.78±0.17

mm s^{-1} only for the 105-210 μm fraction (table 3.5). These results indicated that at higher compression speeds or compression forces the majority of compaction energy was consumed as elastic energy, i.e. the tablets became more elastic. Garr and Rubinstein (1991a) reported that the intensity of capping of paracetamol compacts increased with increasing compaction speed. They observed that the EE/PE ratio increased with compression speed and suggested that the increase in capping tendencies with compaction speed was related to increase in the EE/PE ratio.

Table 3.5 Effect of compression speed on the ratio of EE/PE of paracetamol tablets made from the <90 μm or 105-210 μm fractions, at a compaction force of 15 kN.

Compression speed (mm s^{-1})	EE/PE ratio±SD	
	105-210 μm	<90 μm
10	0.87±0.09	0.92±0.04
50	0.75±0.06	0.92±0.08
100	1.08±0.08	1.00±0.06
250	1.14±0.12	1.24±0.09

At constant compaction force or speed the ratios of EE/PE were apparently higher for the smaller particles. Two way analysis of variance showed that

there were no significant differences (P>0.05) between the EE/PE ratio of the tablets made from the <90 μm or 105-210 μm fractions (table 3.5). However, there were significant differences at different compaction forces (table 3.4). Tukey's test revealed that there was significant differences between the ratio of EE/PE only at 10 kN compaction force, and at other compaction forces the differences between them were not significant.

Although the elastic energies of tablets made from smaller particles were higher than larger particles (figures 3.7 and 3.8), the plastic energies were also higher for the smaller particles (figures 3.9 and 3.10). Consequently there was no large difference between the ratios of EE/PE for these two particle fractions.

3.4 CONCLUSIONS

The results of Heckel analysis indicated that the main mechanism of compression of untreated paracetamol was fragmentation. The larger particle fraction of paracetamol underwent more fragmentation than the smaller particles. Heckel analysis also indicated that for a given applied pressure, the larger particles of paracetamol produced denser compacts than the smaller particles.

The results of elastic recovery, elastic energy and EE/PE ratio, at different compaction force or speed, indicated that paracetamol particles underwent high elastic deformation during compaction, resulting in weak and capped

tablets.

It was found that larger particles exhibited less elastic recovery and elastic energy as compared to smaller particles. This was attributed to increased fragmentation of larger particles resulting in an increase in bonding between particles due to the formation of more new, fresh and clean surfaces.

CHAPTER 4. HABIT MODIFICATION OF PARACETAMOL CRYSTALS

4.1 INTRODUCTION

Crystallization from solution is used widely for the purification of drugs during their final stages of manufacture. The crystallization technique can change the crystal properties such as habit, polymorphism and size. The nature and extent of these changes depend on the crystallization conditions such as presence of impurities, type of solvent and cooling rate as detailed in section 1.2.

Crystallization of paracetamol from a wide range of solvents such as water, alcohols, esters, ketons, dioxane or acetone produced essentially prismatic polyhedral crystals (Fairbrother, 1974; Fachaux et al, 1992b; El-Said, 1995). In fact the prismatic polyhedral habit is the dominant form in paracetamol crystals. However, Fairbrother (1974) demonstrated that crystallization of paracetamol from benzene, toluene and several chlorinated solvents such as dichloroethane produced slender rhombohedral needles.

One common method of crystallization is by the addition of a second substance which reduces the solubility of the solute in the solvent. This method is known as salting-out. The added substance may be a liquid, solid or gas, although liquids (known as diluents) are most frequently used. The diluent must be miscible with the crystallization solvent and the solute

should be relatively insoluble in it. This process is commonly used during crystallization of organic substances from water-miscible organic solvents, by controlled addition of water to the solution. The term "watering-out" is used in this case. The advantages of salting-out method are described in section 1.2.6.2.

The aim of the work presented in this chapter is to modify paracetamol crystals, using a watering-out crystallisation technique. The effect of factors such as solvent type and crystallization temperature on the crystal habit are studied. The solid state characteristics of the modified crystals are also investigated.

4.2 MATERIALS AND METHODS

4.2.1 MATERIALS

Paracetamol and ethanol, as described in section 2.1, were used for this part of the study.

4.2.2 METHODS

4.2.2.1 Crystallization procedures

4.2.2.1.1 Crystallization of paracetamol using a watering-out method at 3°C

Samples of paracetamol (5g) were dissolved in 12 ml of ethanol at 75°C. The

temperature was then reduced to 65°C and the solutions were rapidly added to 50 ml cold water at 3°C. The resultant solutions were mixed by means of a glass rod and the temperature maintained at 3±1°C using an ice-water bath. After 15 min, with no agitation, the precipitated crystals were collected by filtration using a sintered glass funnel No. 3 under vacuum. They were spread on glass petri dishes and dried for 24 h at 55°C. The dried crystals were stored in a desiccator at room temperature before use.

4.2.2.1.2 Alternative crystallization procedures

Crystallization of paracetamol by a watering-out method at 25°C was carried out as explained in section 4.2.2.1.1 but the ethanolic solutions of paracetamol were added to 50 ml water at 25°C and maintained in a water bath at 25±1°C.

Paracetamol was crystallized from an ethanol/water mixture by dissolving 5g paracetamol in a mixture of 12 ml ethanol and 50 ml water (the same amount as used in section 4.2.2.1.1) at 65°C. The solutions were then cooled to 3±1°C or 25±1°C, in an ice-water bath or in a water bath, respectively.

Paracetamol was crystallized directly from ethanol by dissolving 5 g paracetamol in 15 ml ethanol at 65°C. The solutions were then cooled to 3±1°C or 25±1°C, in an ice-water bath or in a water bath, respectively.

Paracetamol was also crystallized directly from water by dissolving 1.5 g

paracetamol in 60 ml water at 65°C. The solutions were then cooled in an ice-water bath at 3±1°C or in a water bath at 25±1°C.

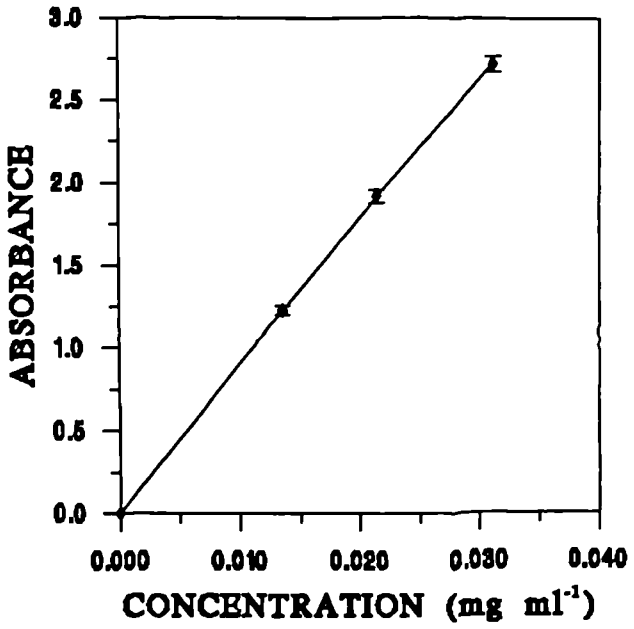
In all cases the precipitated crystals were collected after 15 min by filtration using a sintered glass funnel No. 3 under vacuum. They were spread on glass petri dishes and dried for 24 h at 55°C. The dried crystals were stored in a desiccator at room temperature before use.

4.2.2.2 Determination of paracetamol solubility

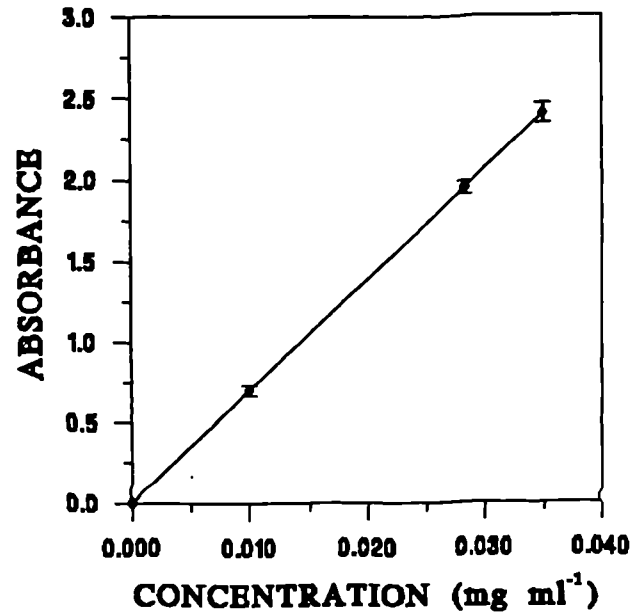
In order to determine the solubility of paracetamol in water, ethanol or their mixture, the following was carried out. First the UV calibration for solutions containing different concentration of paracetamol (0.0 to 0.035 mg ml^{-1}) in ethanol or 19.35% v/v ethanol/water (the same ratio used during crystallization) was determined at 250 or 246 nm, respectively (figures 4.1a and 4.1b). The best fit equations for Beer's law plot of UV absorbance versus paracetamol concentration in ethanol or the ethanol/water mixture are given by equations 4.1 and 4.2, respectively. The UV calibration of paracetamol in water was as described in section 2.2.7.

Y = 0.020 + 87.4 C	(r=0.9995)	Equation 4.1
Y = 0.006 + 68.6 C	(r=0.9999)	Equation 4.2

In these equations, Y is the absorbance of the paracetamol solution and C is the concentration of paracetamol (mg ml^{-1}).



(a)



(b)

Figure 4.1 Ultraviolet absorbance against concentration (mg ml^{-1}) of paracetamol in: (a) ethanol at 250 nm and (b) 19.35% v/v ethanol/water at 246 nm (each point is the mean ±SD of three determinations).

Samples of paracetamol (1, 2 or 8g) were dispersed in 50 ml water, 19.35% v/v ethanol/water or ethanol, in stoppered 100 ml conical flasks. The flasks were shaken in a shaking water bath at 25±1°C or 3±1°C (ice-water) for 8 hours. Then, the paracetamol concentrations in the filtered solutions were determined spectrophotometrically after appropriate dilution, using equations 2.5, 4.1 or 4.2.

4.2.2.3 Determination of the degree of supersaturation of the crystallization systems

The degree of supersaturation, S, of crystallization systems was calculated by equation 4.3, in which c is the concentration of paracetamol in solution and c* is the equilibrium saturation (solubility) of the paracetamol at crystallization temperature (Mullin, 1993).

$$S = c/c^* \qquad \text{Equation 4.3}$$

4.2.2.4 Scanning electron microscopy

Scanning electron micrographs of crystals and particle size measurements were obtained using a scanning electron microscope as described in section 2.2.5.

4.2.2.5 Differential Scanning Calorimetry (DSC), X-ray Powder Diffraction (XPD) and Infrared spectroscopy (IR)

DSC, XPD and IR were carried out, as described in sections 2.2.4.1, 2.2.2 and

2.2.3 respectively.

4.3 RESULTS AND DISCUSSION

4.3.1 MORPHOLOGY OF CRYSTALS

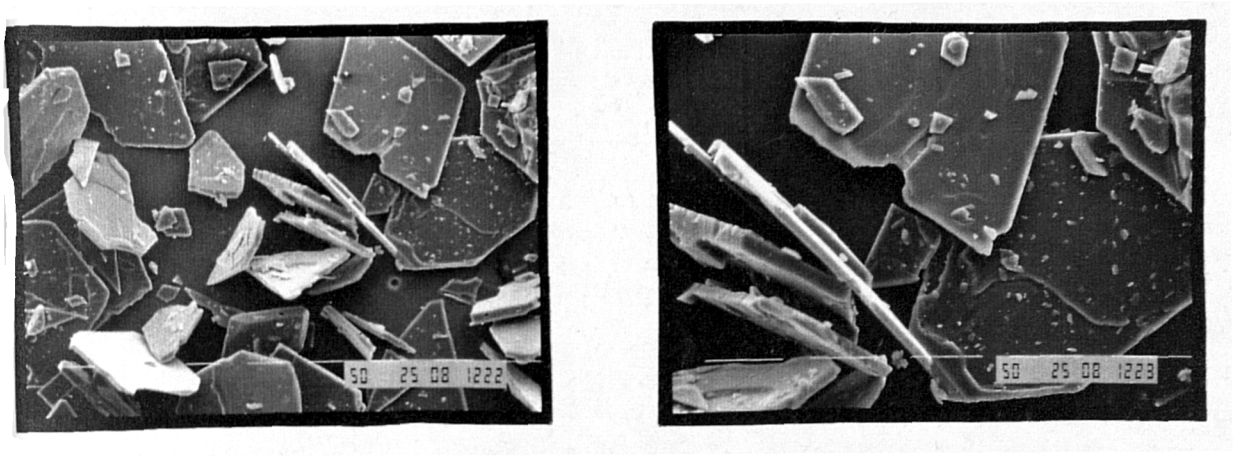
Figure 4.2 exhibits the scanning electron micrographs of paracetamol crystals obtained by the watering-out method at 3°C. These crystals were very thin and flaky. Figure 4.3 shows the scanning electron micrograph of paracetamol crystals obtained by the watering-out method at 25°C. These were prismatic polyhedral crystals.

Crystallization of paracetamol from a mixture of ethanol/water at 3°C produced thin plate-like crystals (figure 4.4a), while at 25°C it produced polyhedral crystals (figure 4.4b).

Crystallization of paracetamol from water or ethanol at 3°C or 25°C, produced prismatic polyhedral crystals (Figures 4.4c, d, e and f).

4.3.2 DEGREE OF SUPERSATURATION OF CRYSTALLIZATION SYSTEMS

The degrees of supersaturation, S, during crystallization of paracetamol in water, ethanol or mixture of ethanol/water at 3°C or 25°C are given in table 4.1. The type of crystals obtained by these methods, including their average length size, are also given in table 4.1.



(a) (b)

Figure 4.2 Scanning electron micrographs of paracetamol particles crystallized by watering-out method at 3°C (magnification of figures a and b are ×100 and ×200, respectively).

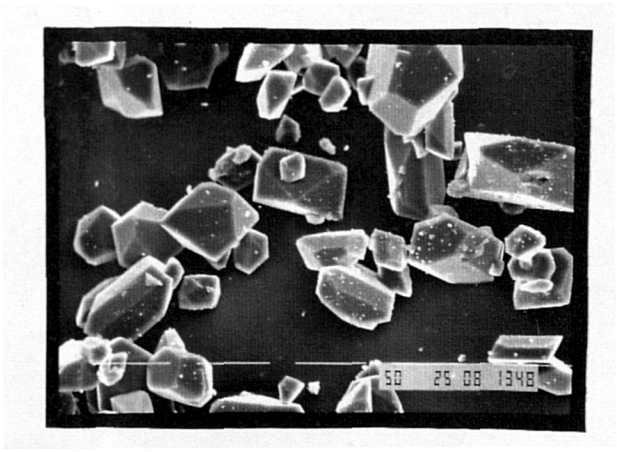


Figure 4.3 Scanning electron micrographs of paracetamol particles crystallized by watering-out method at 25°C (magnification ×200).

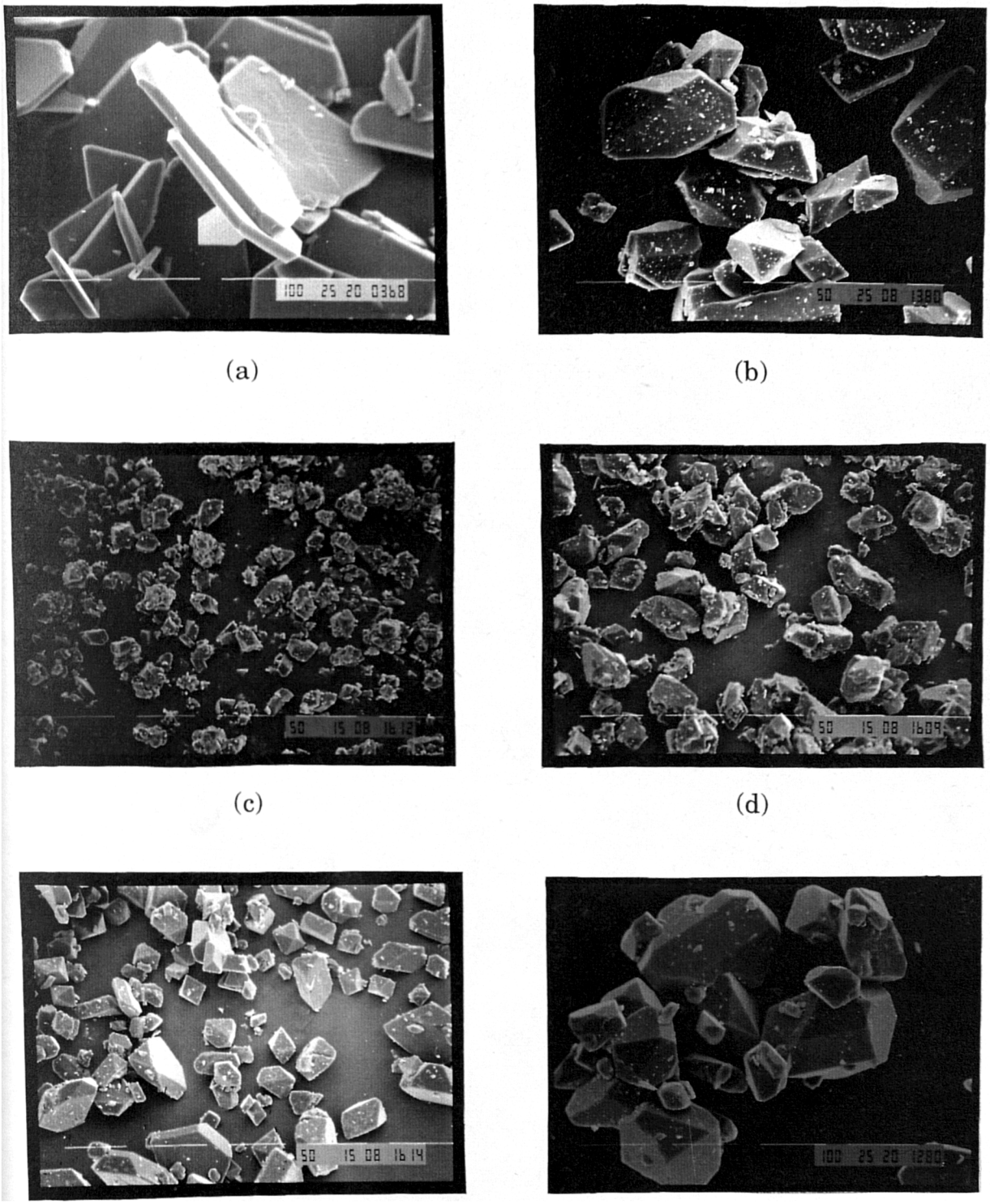


Figure 4.4 Scanning electron micrographs of paracetamol crystallized: a) from mixture of ethanol/water at 3°C and b) at 25°C, c) from ethanol at 3°C and d) at 25°C, e) from water at 3°C and f) at 25°C (all magnification ×200).

Table 4.1 Effect of crystallization solvent and temperature on the degree of supersaturation, type and average length size of paracetamol crystals obtained.

Crystallization solvent	Crystallization temperature (°C)	c (Concentration of paracetamol in system) mg ml^{-1}	c* (Solubility of paracetamol at crystallization temperature) mg ml^{-1}	S, Degree of supersaturation = c/c*	Crystal habit[a]	Average length size (μm)
Water	25	25	12.6	1.98	PP	91
Water	3	25	7.2	3.47	PP	32
Ethanol	25	333.3	149.3	2.23	PP	46
Ethanol	3	333.3	91.2	3.65	PP	20
Ethanol/Water	25	80.6	31.8	2.53	PP	74
Ethanol/Water	3	80.6	12.1	6.66	TPL	157

[a] PP = Prismatic polyhedral, TPL = Thin plate-like

The polyhedral habit is the dominant form of paracetamol crystals and crystallization of paracetamol from different solvents such as water, ethanol or dioxane (Fachaux et al, 1992), isopropanol, dioxane or acetone and their mixtures with water (El-Said, 1995), alcohols, esters, ketons or acetonitrile (Fairbrother, 1974) produced prismatic polyhedral crystals. Table 4.1 clearly indicates that a combination of ethanol and water as crystallization solvent and a low crystallization temperature (3°C), i.e. rapid cooling, were required to produce thin plate-like crystals of paracetamol. In the absence of one of these two factors, polyhedral crystals were produced.

Table 4.1 also indicates that crystallization temperature had a great influence on the degree of supersaturation of the ethanol/water system and produced a high degree of supersaturation at 3°C. It has been reported that a change in the degree of supersaturation may cause preferential growth of crystals in one particular direction, leading to the formation of different crystal habits (Mullin, 1993).

Figure 4.5 shows the cooling curves during crystallization of paracetamol by watering-out method and during crystallization from mixture of ethanol/water at 3°C or 25°C. It is obvious that crystallization temperature had a major effect on cooling rate of crystallization system and crystallization at 3°C caused a rapid cooling of the system.

Some workers have reported the effects of crystallization solvent or cooling

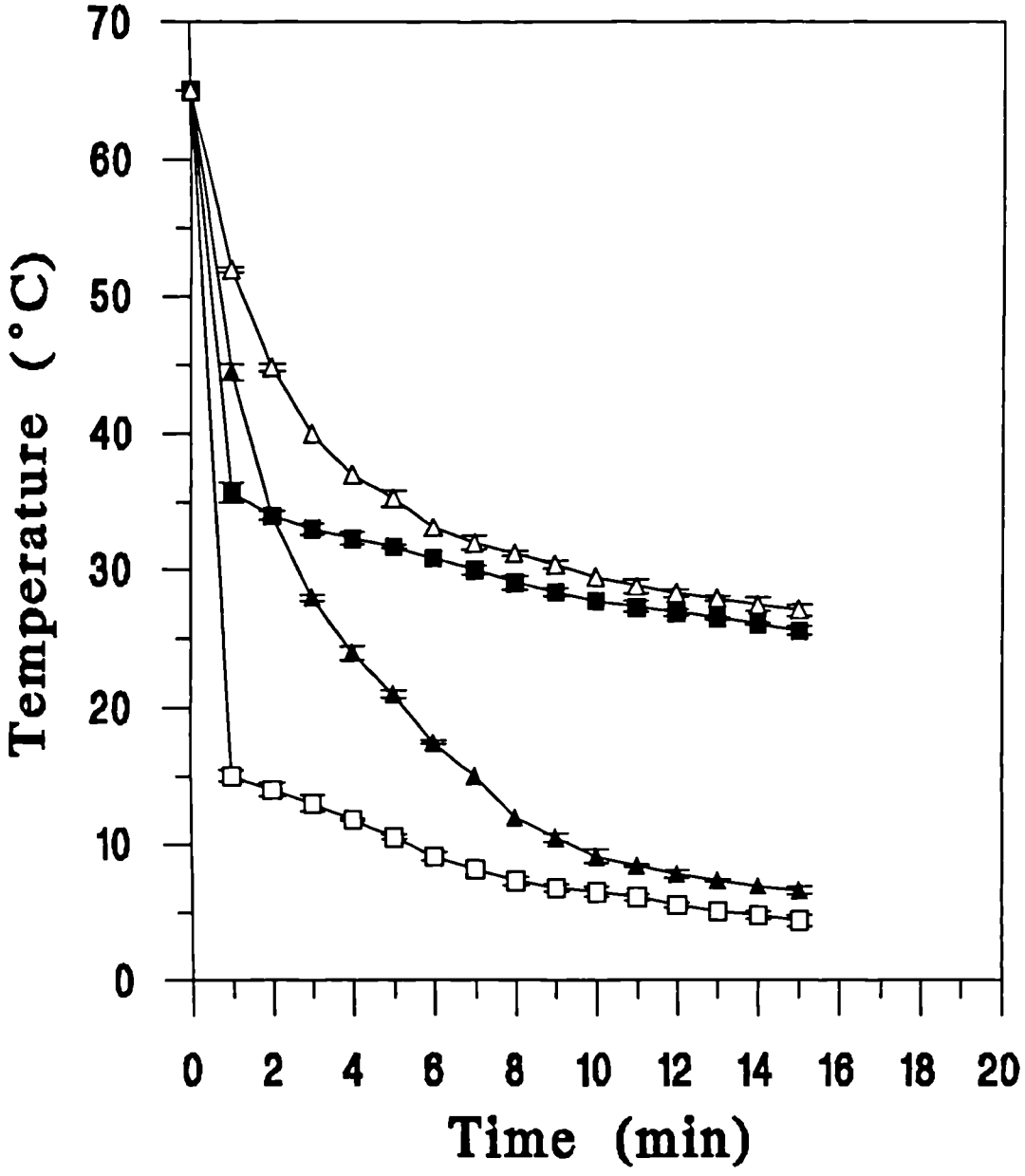
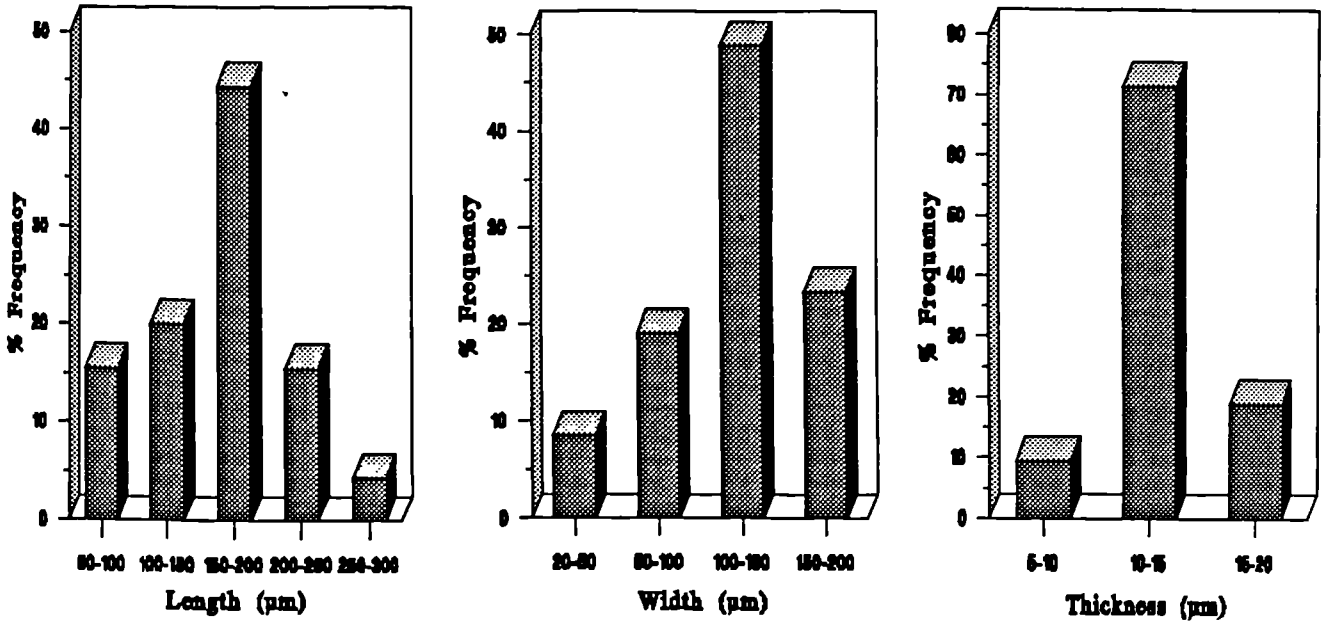


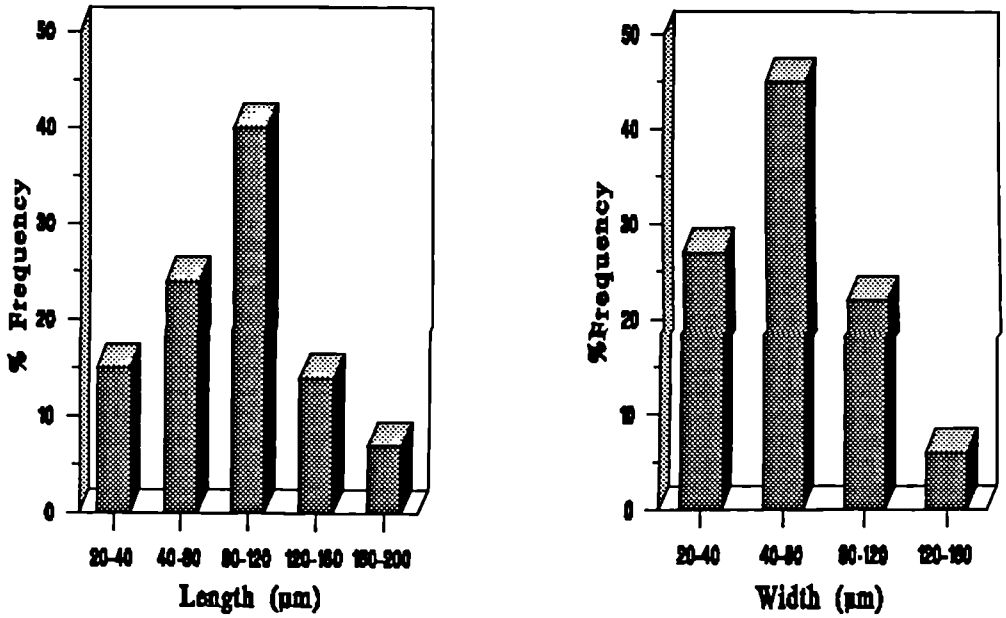
Figure 4.5 Cooling curve of crystallization medium during watering-out method at (□) 3°C and (■) 25°C, and during crystallization from a mixture of ethanol/water at (▲) 3°C and (△) 25°C.

rate on crystal habit. Marshall and York (1989) reported that nitrofurantoin particles crystallized from formic acid were tabular while from a mixture of formic acid/water were needle-like. Ibuprofen crystals obtained from hexane were needle-like, whilst from methanol were grain-like (Gordon & Amin, 1984). Watanabe et al (1982) demonstrated that aspirin was crystallized from water as plate-like crystals but from dioxane or *n*-heptane thin needle crystals were yielded. Cooling rate has also a major influence on the crystal habit. For instance, naphthalene was crystallized as thin plates from methanol by rapid cooling but when it was slowly crystallized, it yielded compact (grain-like) crystals (Wells, 1946). Garti and Tibika (1980) demonstrated that by increasing the cooling rate during crystallization of nitrofurantoin from a formic acid/ethanol mixture, more elongated crystals were collected, i.e. the ratio of length to width increased with increase in cooling rate.

Crystallization temperature or degree of supersaturation may also have a major effect on crystal size. Rapid cooling of a hot and saturated solution yields small crystals whereas a low crystallization rate produces larger particles (Huttenrauch, 1983). Table 4.1 indicates that the paracetamol crystals obtained from water or ethanol at 3°C were smaller than crystals obtained at 25°C.



(a)



(b)

Figure 4.6 Size distributions of a) thin plate-like and b) polyhedral crystals of paracetamol. The thickness of polyhedral crystals were approximately equal to their width.

4.3.3 SOLID STATE CHARACTERISTICS OF POLYHEDRAL AND THIN PLATE-LIKE CRYSTALS

Since the compaction properties of polyhedral crystals of paracetamol obtained from water at 25°C and thin plate-like crystals obtained by watering-out method at 3°C are studied in next chapter, therefore, it is now useful to assess the solid state characteristics of these two forms of paracetamol crystals.

4.3.3.1 Particle size distribution

Figure 4.6 shows the size distributions of polyhedral crystals and thin plate-like crystals of paracetamol. There is a large difference between the size dimensions of these two forms of crystals. This indicates a strong inhibition of crystal growth at some crystal faces and inducement to more growth of other faces for the thin plate-like crystals as compared to the polyhedral crystals.

4.3.3.2 Differential Scanning Calorimetry (DSC)

The DSC scans of the thin plate-like crystals and polyhedral crystals of paracetamol are illustrated in figure 4.7. The mean values of the onsets of the melting point and the enthalpies of fusion for these two forms of crystals are also presented in table 4.2. According to these results, no events such as hydration, solvation or polymorphic modification, had occurred during the crystallization in the particles.

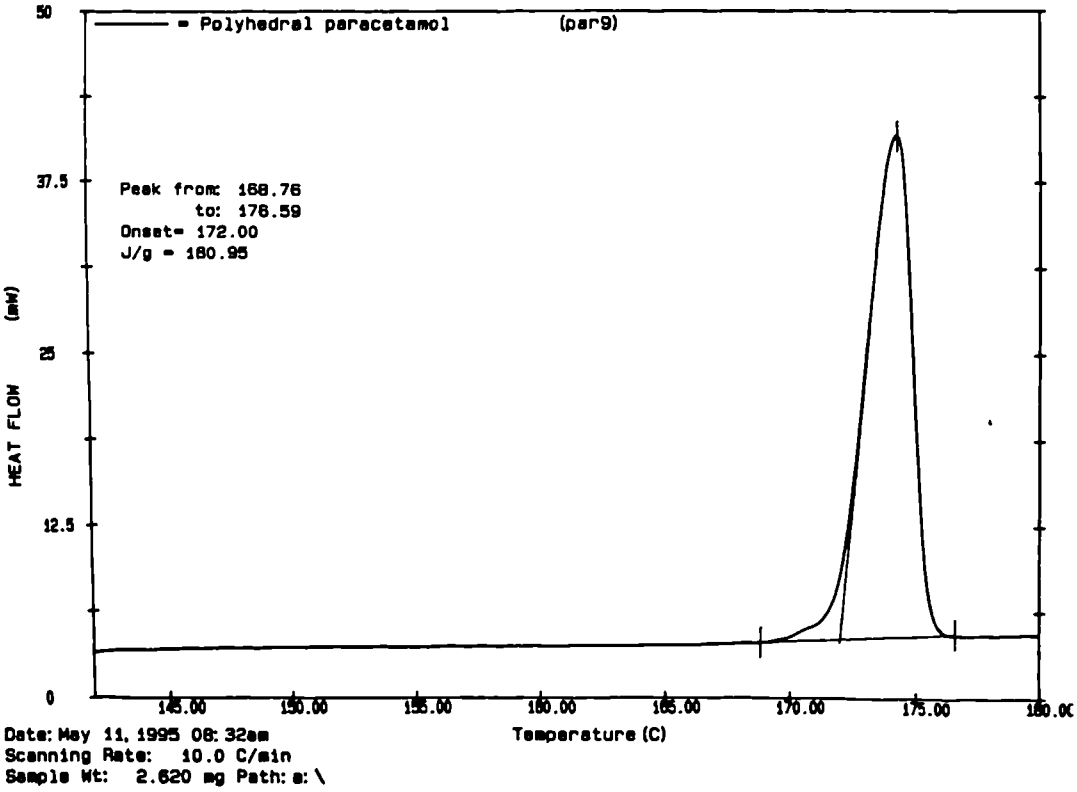
Table 4.2 The onsets of melting point (T_m) and enthalpies of fusion (ΔH_f) for thin plate-like and polyhedral crystals of paracetamol.

Crystal type	Onset of T_m (±SD) (°C)	ΔH_f (±SD) (J/g)
Thin plate-like crystals	171.87±0.14	179.35±10.47
Prismatic polyhedral crystals	171.91±0.21	176.75±4.82

4.3.3.3 X-ray powder diffraction (XPD)

The X-ray powder diffraction spectra for the thin plate-like and polyhedral crystals of paracetamol, are presented in figure 4.8. Both samples exhibited spectra with similar positions of peaks (2θ values). Therefore polymorphism can be ruled out. However, the relative intensities of their peaks were modified. This is may be because the crystals exhibited preferred orientations within the sample holder due to their markedly different crystal habits (Marshall & York, 1989). Therefore the relative abundance of the planes exposed to the X-ray source would have been altered producing the variations in the relative intensities of the peaks (Marshall & York, 1989). El-Said (1995) has also reported that paracetamol crystals obtained from different solvents exhibited similar X-ray diffraction patterns, but different intensities. This was attributed to difference in the crystal size.

(a)



(b)

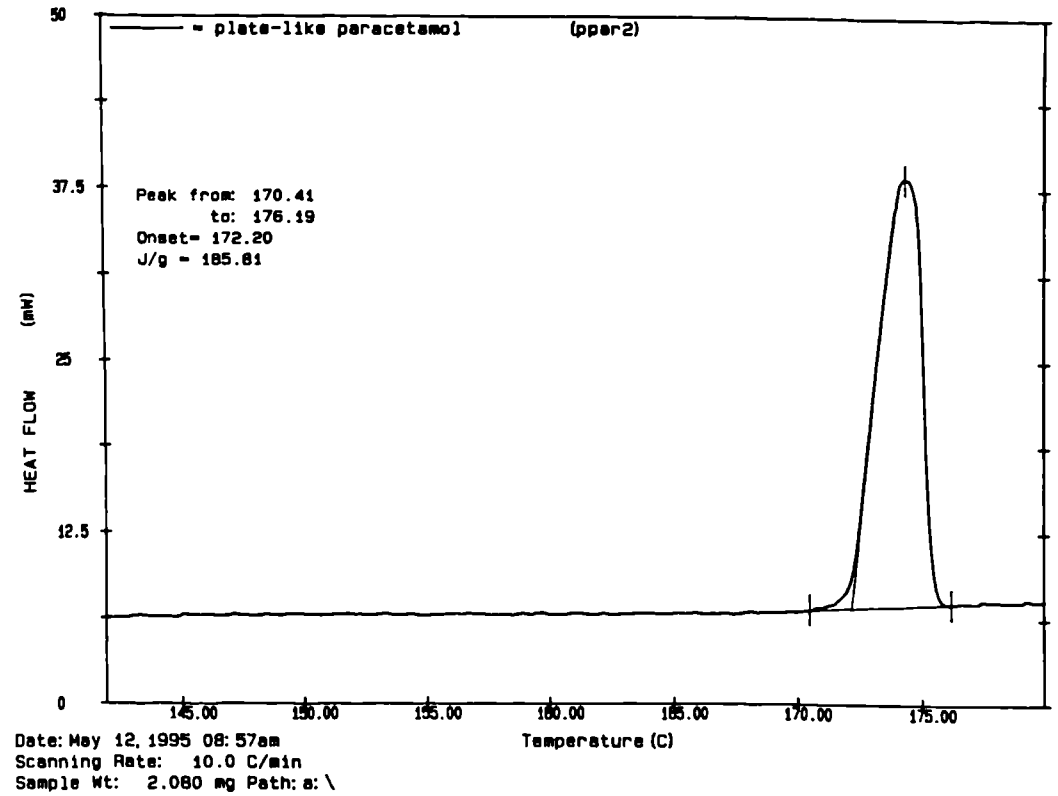
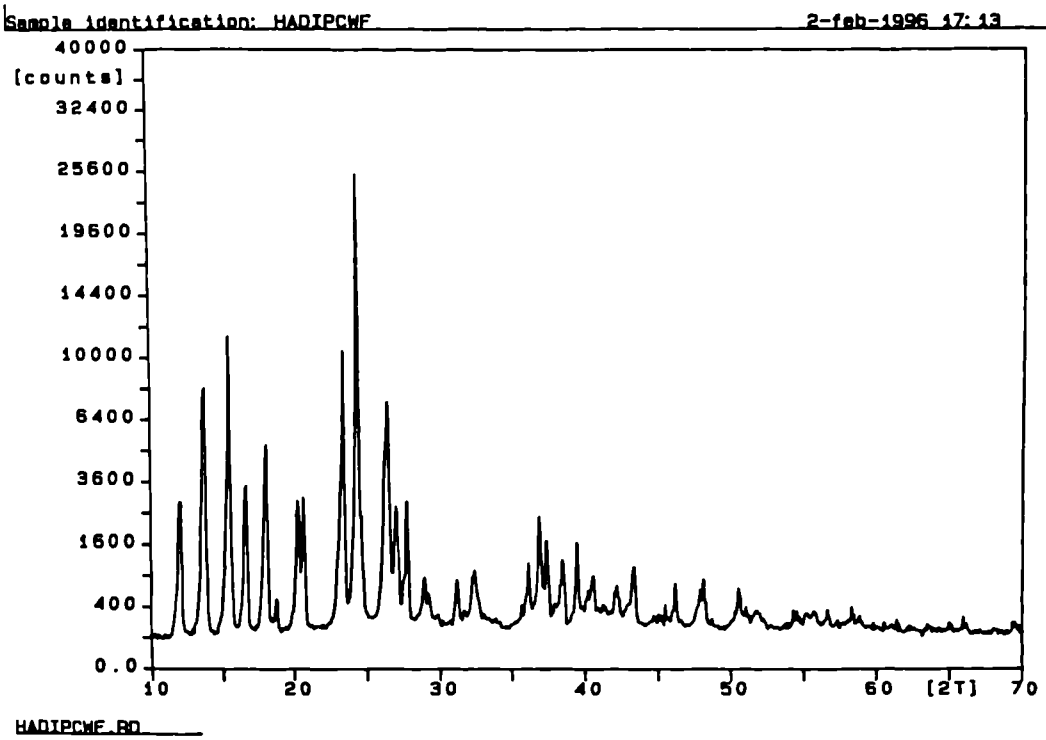


Figure 4.7 DSC scans of a) polyhedral and b) thin plate-like crystals of paracetamol.

(a)



(b)

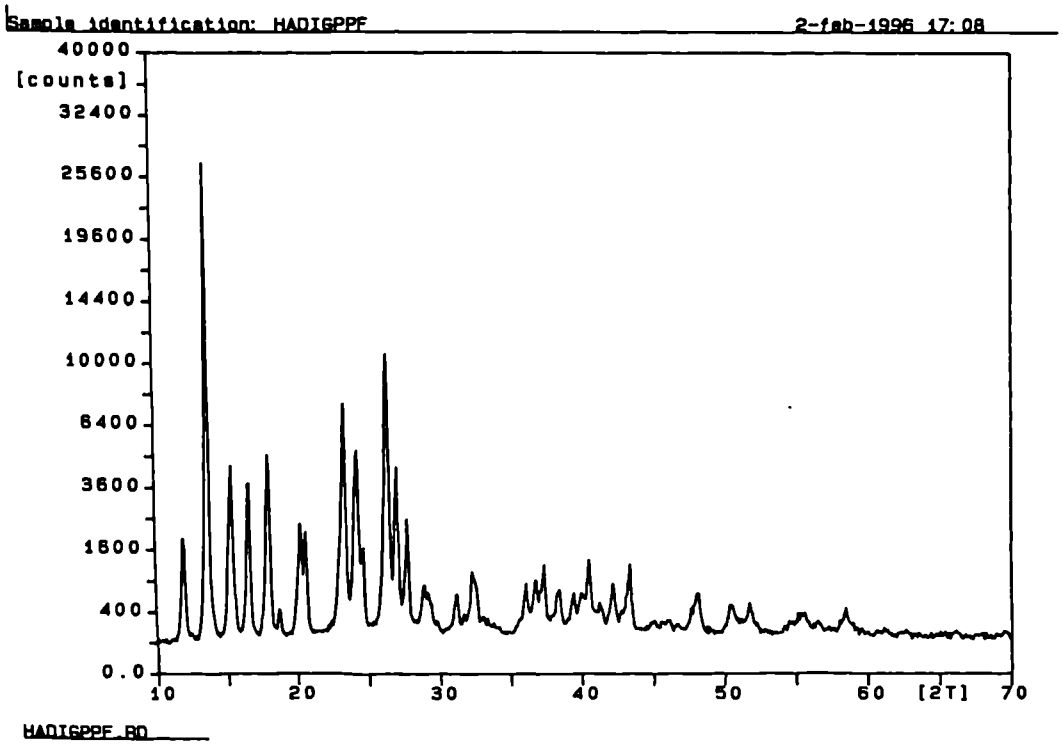
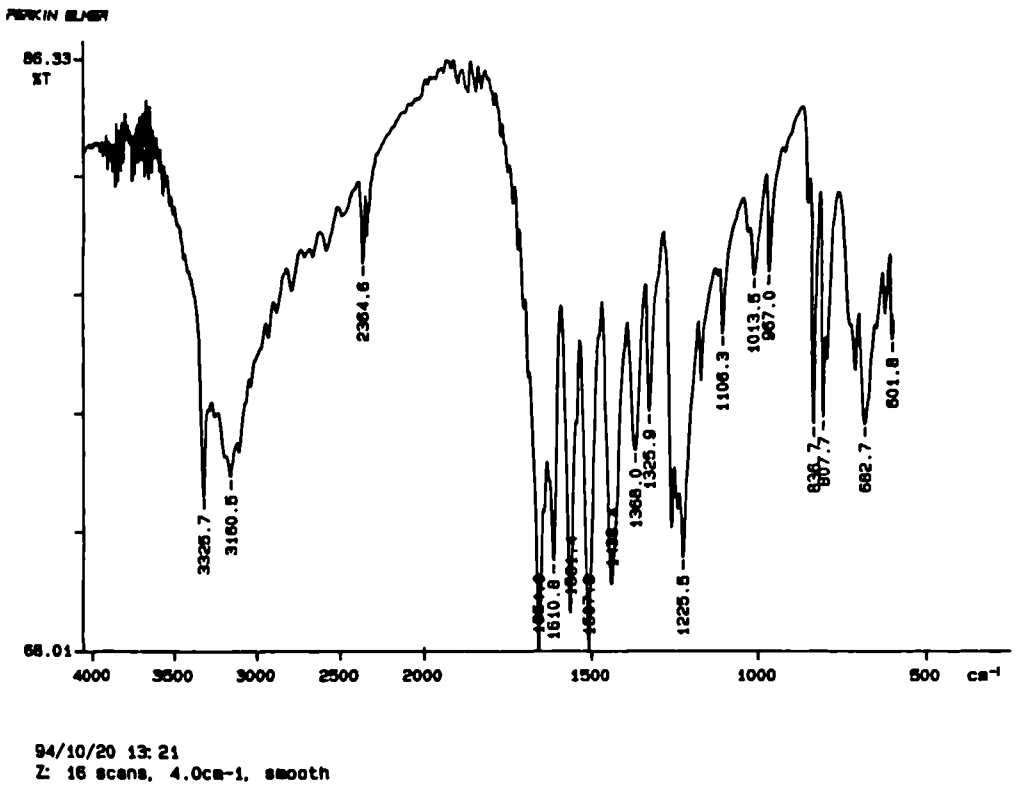


Figure 4.8 The X-ray powder diffraction spectra of a) polyhedral and b) thin plate-like crystals of paracetamol.

(a)



(b)

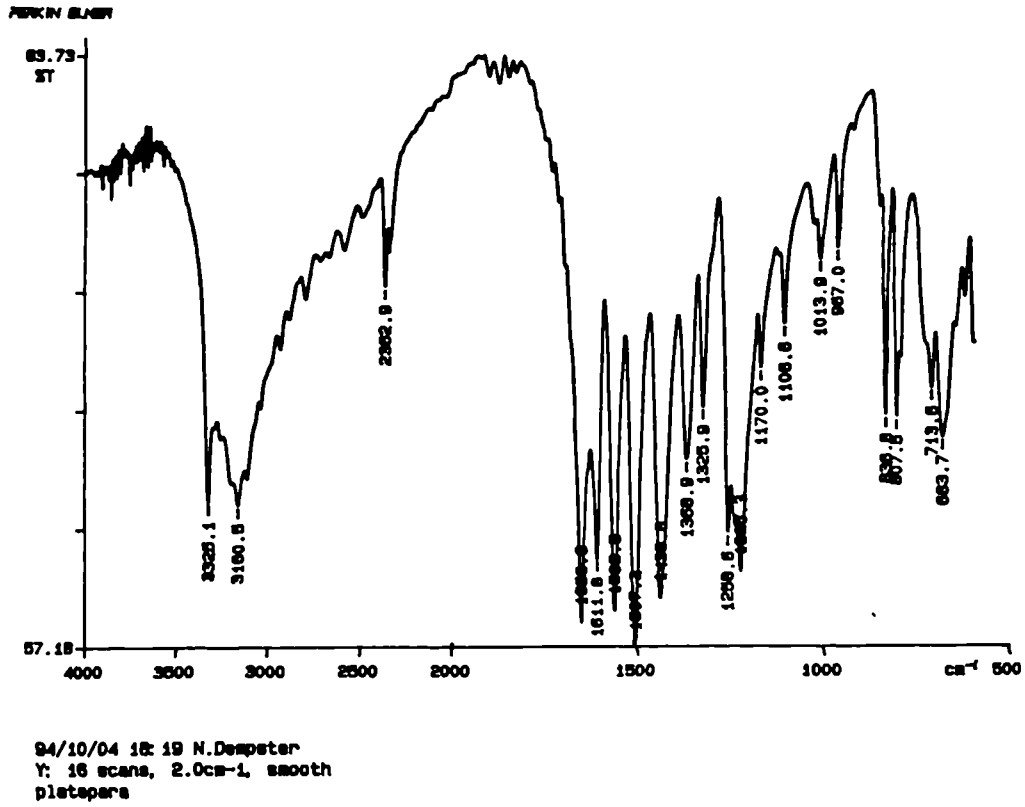


Figure 4.9 The infrared spectra of a) polyhedral and b) thin plate-like crystals of paracetamol.

4.3.3.4 Infrared spectroscopy (IR)

The Infrared spectra of thin plate-like and polyhedral crystals of paracetamol, are presented in figure 4.9. It is obvious that the principal absorption bands for the two samples are similar suggesting that there were no differences between the internal structure and conformation of these samples.

4.4 CONCLUSIONS

Crystallization of paracetamol by a combination of "watering-out" from an ethanolic solution and rapid cooling caused marked modification to the crystal habit and produced thin plate-like crystals which indicate strong inhibition of crystal growth at different crystal faces.

It was found that crystallization solvent (ethanol/water) and crystallization temperature (3°C), i.e. rapid cooling, are both critical in production of thin plate-like crystals. The formation of thin plate-like crystals of paracetamol was attributed to the interaction between paracetamol and binary solvent system during crystallization at 3°C. Elimination of either of these factors inhibited the production of thin plate-like crystals.

It was shown that this modified form of paracetamol crystals (thin plate-like) is a habit modification and not due to polymorphism. It would be interesting to see if the crystal habit has any effect on compaction behaviour of paracetamol. Therefore, the compaction properties of thin plate-like crystals of paracetamol are investigated in chapter 5.

CHAPTER 5. INFLUENCE OF CRYSTAL HABIT ON THE COMPACTION PROPERTIES OF PARACETAMOL

5.1 INTRODUCTION

The crystal habit of a drug is an important variable in pharmaceutical manufacturing. Different crystal forms of a particular drug possess different planes and thus differ not only in their specific surface, but also in their free surface energy. Therefore, they may exhibit different physico-mechanical properties (Huttenrauch, 1983). Properties such as dissolution rate, powder flow and compressibility, which are of pharmaceutical interest, can differ for different habits of the same drug (York, 1983; Marshall & York, 1991). Attempts to change the morphology and the workability of drugs using alternative crystallization procedures include modification of the crystal habits of drugs such as ibuprofen (Gordon & Amin, 1984), hexamethylmelamine (Gonda et al, 1985) and nitrofurantoin (Marshall & York, 1989, 1991).

In this chapter the compaction properties of the two habits of paracetamol crystals, produced by the different crystallization processes, described in the previous chapter, are studied. The aims were firstly, to investigate whether crystal habit had any significant effect on the compaction behaviour of paracetamol and, secondly, whether the modified crystals showed improved compaction properties.

5.2 MATERIALS AND METHODS

5.2.1 MATERIALS

Prismatic polyhedral crystals of paracetamol obtained from water at 25°C (figure 4.4f) and thin plate-like crystals obtained by the watering-out method at 3°C (figure 4.2), as described in chapter 4, were used. Several batches of each crystal type were combined prior to study. For the purpose of convenience, these two crystal forms are expressed as polyhedral and plate crystals throughout this chapter.

5.2.2 METHODS

5.2.2.1 Particle size fractions

Sieved fractions of the polyhedral and plate crystals of paracetamol (105-210 μm) were obtained as detailed in section 2.2.13. The seived fractions were dried in an oven at 55°C for 24 h and stored in tightly closed jars before use.

5.2.2.2. Compression

Compression was carried out using the compaction simulator (section 2.2.11). Four tablets, 400 mg each, were made at compression speeds 10, 50, 100 or 250 mm s^{-1} up to a maximum compaction force of 30 kN.

5.2.2.3 Analyses of compaction data

Analyses of the data according to the Heckel equation were carried out as

detailed in section 2.2.12.2. Mean yield pressures (MYP), the relative densities of powders at zero pressure (D_o) and before appreciable load (D_a), and the extent of particle rearrangement (D_b) were determined.

The plastic and elastic energies were measured using energy analysis on the force-punch separation plots (section 2.2.12.1).

Tablets made from polyhedral or plate crystals of paracetamol were too weak and capped after ejection, and it was impossible to monitor their thickness outside the die. Therefore the percentage of elastic recovery in the die at different compaction forces were determined, as detailed in section 2.2.12.3. The results of analyses of compaction data of untreated paracetamol particles, 105-210 μm (chapter 3), are included in this chapter for comparison.

5.3 RESULTS AND DISCUSSION

5.3.1 CRUSHING STRENGTH OF TABLETS

Compression of the plate and polyhedral crystals at all compression forces, even at lowest compression speed, produced extremely weak tablets which had no measurable strength and a high tendency to cap. The capping and failure increased with increase in either compaction force or compaction speed. These were similar results to untreated crystals (section 3.3.1).

5.3.2 HECKEL ANALYSIS OF PARACETAMOL TABLETS

Figure 5.1 shows typical Heckel plots of the polyhedral and plate crystals of paracetamol, obtained at a compaction speed of 10 mm s^{-1}. This figure indicates that the polyhedral crystals exhibited higher relative densities for a given applied pressure than the plate crystals. Therefore, the degree of densification that occured during compression was greater for the polyhedral crystals. This can be attributed to increased frictional and cohesive forces between the plate crystals, due to their large and flat surfaces (figure 4.2) which would increase the contact points between them, restrict particle sliding and thus reduce densification (York, 1978; Roberts & Rowe, 1986).

The slope of the plot for polyhedral crystals (figure 5.1) was greater than that of the plate crystals. Table 5.1 indicates that the value of slope (K) was greater for the polyhedral crystals and therefore the reciprocal of K, which is the mean yield pressure, was lower.

The values of D_o and D_a (table 5.1) indicate that densification due to die filling and particle rearrangement for the polyhedral crystals was higher than for plate crystals. A high difference between the values of D_o for these two forms of crystals may be indicative of high frictional forces between the plate crystals as compared to polyhedral crystals, which could restrict densification due to die filling.

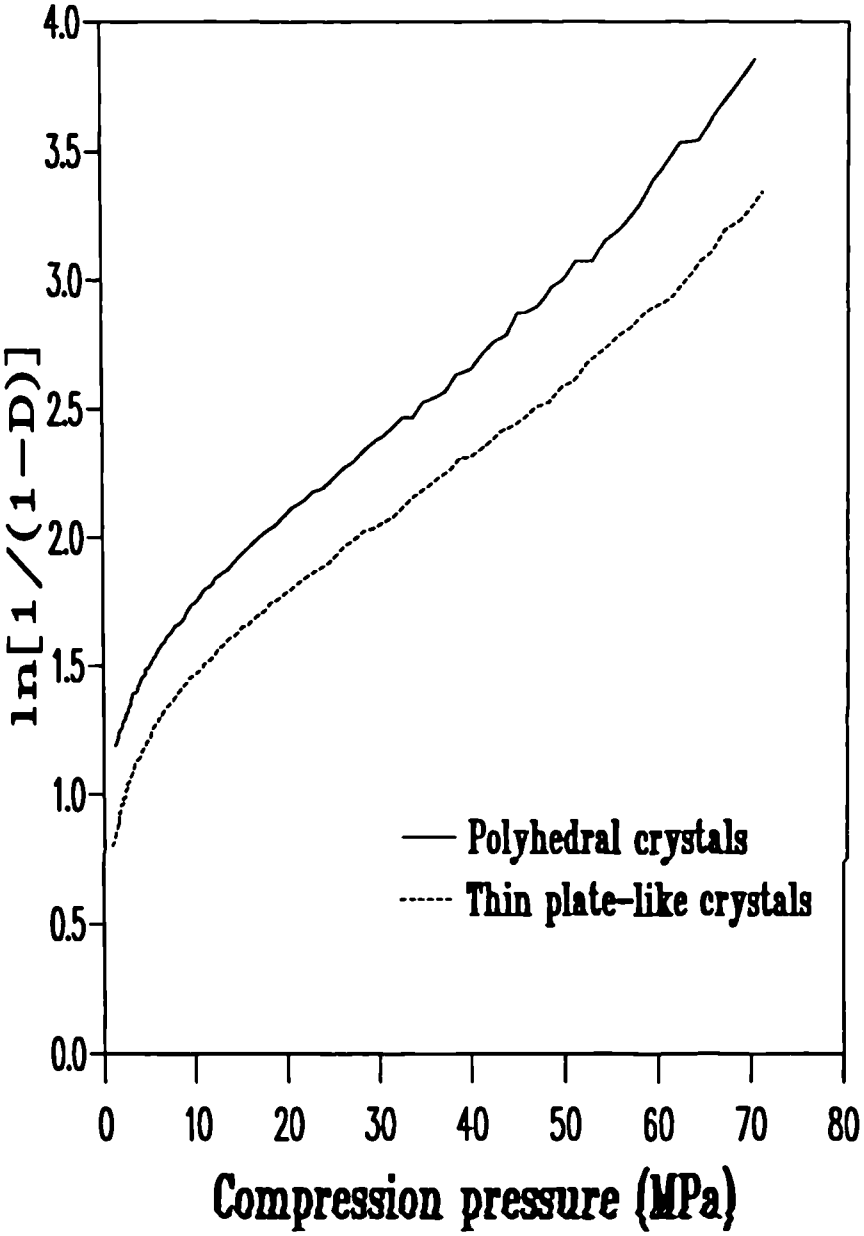


Figure 5.1 Typical Heckel plots of polyhedral or plate crystals of paracetamol obtained at a compaction speed of 10 mm s^{-1}.

Table 5.1 The values derived from the Heckel plots of figure 5.1 of polyhedral and thin plate-like crystals of paracetamol compressed at a compaction speed of 10 mm s^{-1}.

	Polyhedral crystals	Plate crystals
K	0.0367	0.0285
1/K=Mean yield pressure (MPa)	27.5	35.3
D_a	0.71	0.69
D_o	0.66	0.53
r*	0.965	0.925
r**	0.989	0.997

r*=Correlation coefficient of initial portion of Heckel plot (0-20 MPa)

r**=Correlation coefficient of straight line portion of Heckel plot (20-65 MPa)

Table 5.1 indicates that the correlation coefficient of the initial part of Heckel plot (0-20 MPa) was considerably lower for the plate crystals. This is indicative of an extensive fragmentation of the plate crystals as compared to the polyhedral crystals. As described in section 1.4.6, the correlation coefficient of the initial part of Heckel plot can be a useful index in estimating the degree of particle fragmentation. A linear segment (high value of correlation coefficient) is obtained for non-fragmenting materials, while a non-linear curve (low correlation coefficient) corresponds to materials which

consolidate by fragmentation (Duberg & Nystrom, 1986; Humbert-Droz et al, 1983).

Therefore, the Heckel plot and the constants derived from it, were dependent on the crystal habit of paracetamol. Marshall and York (1991) reported that different crystal habits of nitrofurantoin, crystallized from different solvents, similary exhibited different Heckel plots. They reported that the degree of densification that occured during compression was greater for plate like crystals as compared to needle-like crystals. Marshall and York (1991) also demonstrated that the slope of Heckel plots, and thus the mean yield pressures for the two crystal habits of nitrofurantoin were significantly different. Needle like crystals of nitrofurantoin showed higher mean yield pressure than plate like crystals. These observations were attributed to markedly different crystal habits of these samples.

As mentioned in sections 1.4.5.2 and 3.3.2, the value of mean yield pressures derived from the slope of the linear portions of the Heckel plots depend on the elastic and plastic behaviour of the material under applied load. Therefore, for elastic materials a false, low mean yield pressure is obtained (Duberg & Nystrom, 1986; Fell & Newton, 1971). Using phase III of the Heckel plot, it was found that a low mean yield pressure value obtained for untreated paracetamol was due to its elastic behaviour and not plastic deformation (section 3.3.2). Figure 5.2 shows the whole compression cycle (compression and decompression phases) for the plate crystals of paracetamol.

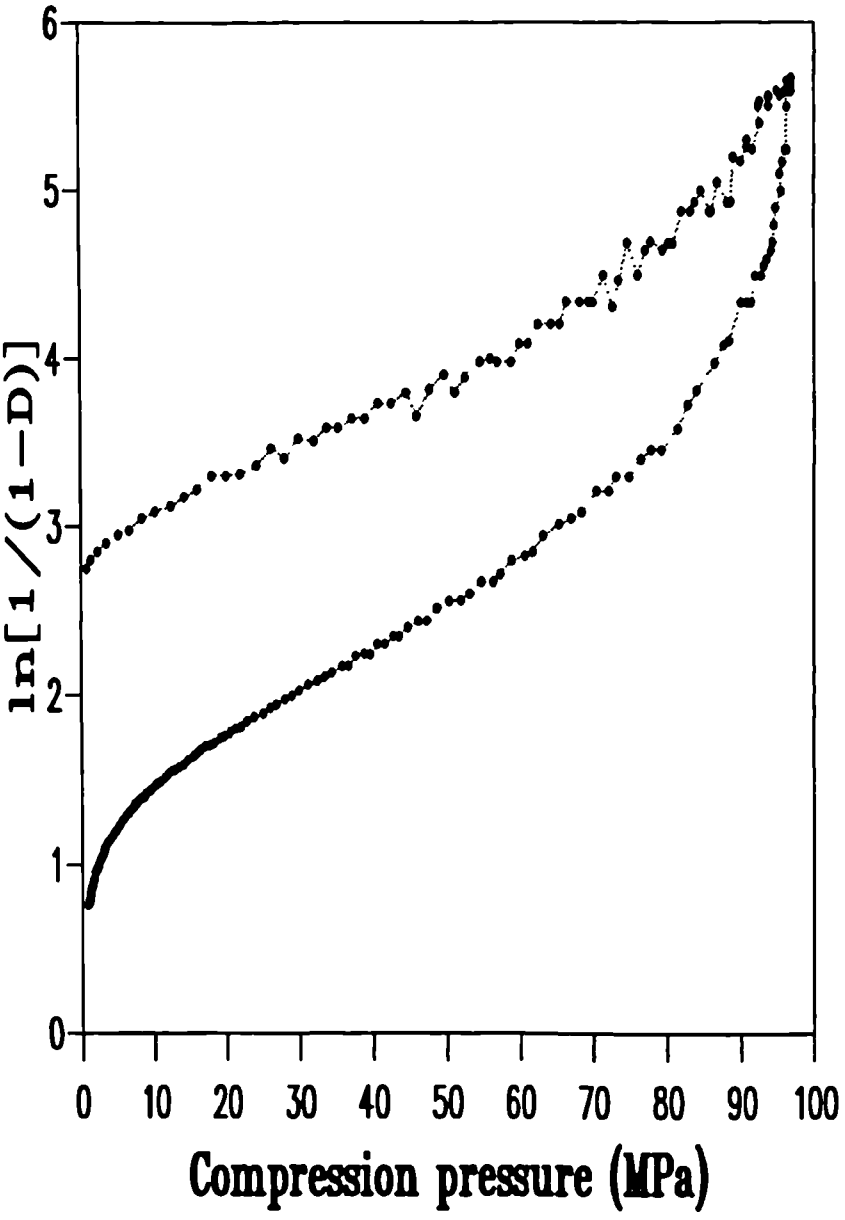


Figure 5.2 Heckel plot, including compression and decompression phases, of the plate crystals of paracetamol, obtained at a compression speed of 10 mm s^{-1}.

The large deviation from the horizontal during decompression (phase III) is indicative of a high degree of elastic behaviour of these particles under pressure.

5.3.2.1 Influence of compression speed on Heckel constants

The effect of compression speed on the constants derived from Heckel plots (mean yield pressure, D_o, D_a and D_b) of the two crystal habits (polyhedral and plate crystals) of paracetamol were investigated and the results are presented in this section.

Two way analysis of variance showed that there were significant differences ($P<0.05$) between the mean yield pressures of polyhedral, plate and untreated crystals (table 5.2). Tukey's test revealed that there were no significant differences ($P>0.05$) between the mean yield pressures obtained at 250 mm s^{-1} for polyhedral and plate crystals. Tukey's test also revealed that there were no significant differences between the mean yield pressures of untreated and plate crystals at 10 or 50 mm s^{-1} compaction speed.

As the compaction speed increased, the mean yield pressure for polyhedral and plate crystals increased. However, Tukey's test revealed that there were no significant differences ($P>0.05$) between the mean yield pressures obtained at 10 and 50 mm s^{-1} and also at 100 and 250 mm s^{-1} for polyhedral crystals. For plate crystals, the mean yield pressures were significantly different only at 10 and 100 or 250 mm s^{-1}.

Table 5.2 The effect of compression speed on mean yield pressures (MYP) of polyhedral, plate and untreated crystals of paracetamol.

Compression speed (mm s^{-1})	MYP±SD (MPa)		
	Polyhedral crystals	Plate crystals	Untreated crystals*
10	28.2±1.6	35.1±1.8	34.4±2.0
50	30.5±1.4	37.3±2.6	35.5±1.2
100	36.9±1.4	41.9±1.3	38.6±0.6
250	38.9±0.8	40.8±1.6	42.3±1.6

* Taken from table 3.2

The changes of mean yield pressure with compaction speeds were calculated as strain rate sensitivity (SRS), using equation 3.1 (section 3.3.2.1). The values of SRS for polyhedral and plate crystals of paracetamol were 27 and 14%, respectively. The SRS value of untreated crystals was 18.7% (section 3.3.2.1). As mentioned in sections 1.4.6 and 3.3.2.1, due to the time dependent nature of plastic flow, the mean yield pressures increase with increasing punch velocity for plastic materials which consequently show higher values of SRS (Roberts & Rowe, 1985; 1986). The results clearly indicate that polyhedral and untreated crystals were more sensitive to compaction speed, suggesting that they were more plastic than the plate crystals which were

more brittle.

The values of D_o, D_a and D_b (table 5.3) for both type of crystals tended to decrease with increasing punch speeds. Tukey's test revealed that there were no significant differences ($P>0.05$) between the values of D_o at all compression speeds except at 10 and 250 mm s^{-1} for plate crystals. For polyhedral crystals, the difference between the values of D_o at 10 and 50, and also at 50 and 100 mm s^{-1} compaction speeds were not significan. The values of D_a at 10 and 50 mm s^{-1} for the polyhedral crystals, and at 50 and 100 mm s^{-1} for plate crystals were not significant ($P>0.05$). Tukey's test also revealed that there were no significant differences ($P>0.05$) between the values of D_b at 10 and 50 mm s^{-1} for plate crystals. The values of D_b for polyhedral crystals at 50 and 100, and also at 100 and 250 were not significantly different.

Table 5.3 The values of D_a, D_o and D_b ($\times 10^{-1}$) (±SD) of polyhedral and plate crystals of paracetamol at different punch speeds.

Compression speed (mm s^{-1})	Polyhedral crystals			Plate crystals		
	D_o	D_a	D_b	D_o	D_a	D_b
10	6.50 ±0.05	7.03 ±0.09	0.50 ±0.05	5.25 ±0.06	6.93 ±0.05	1.65 ±0.13
50	6.50 ±0.07	7.00 ±0.07	0.50 ±0.07	5.15 ±0.05	6.65 ±0.05	1.50 ±0.10
100	6.40 ±0.04	6.80 ±0.05	0.40 ±0.04	5.15 ±0.11	6.57 ±0.04	1.43 ±0.08
250	6.20 ±0.05	6.60 ±0.04	0.37 ±0.04	5.05 ±0.05	5.98 ±0.10	0.88 ±0.08

The decrease of relative densities with increasing compaction speed may be due to an increase in the frictional and cohesive forces between particles and/or restriction of air escape from the powder bed (Roberts & Rowe, 1985).

At each compaction speed, the plate crystals of paracetamol showed lower values of D_o and D_a than the polyhedral crystals (table 5.3). However, Tukey's test revealed that the values of D_a obtained at 10 mm s^{-1} for the two types of crystals were not significantly different ($P>0.05$). The degree of densification that occurs during compression depends on the surface structure, size and shape of particles (York, 1978; McKenna & McCafferty, 1982; Roberts & Rowe 1985; 1986). As discussed earlier (section 5.3.2), the number of contact points between plate crystals, because of their flat and large surfaces, increased, resulting in higher interparticulate cohesive forces which tend to oppose densification. This leads to a decrease in the relative densities of the compacts.

The higher values of D_b shown by the plate crystals (table 5.3) could be attributed to a high degree of fragmentation of the particles at low pressure. Humbert-Droz (1983) demonstrated that brittle materials are characterized by a high value of D_b because of the curvature of the initial part of Heckel plot. Small particles, yielded from fragmentation of bigger crystals would fill the void spaces between the particles, resulting in an increase in particle rearrangement (D_b).

5.3.3 INFLUENCE OF COMPACTION FORCE ON THE ELASTIC RECOVERY OF PARACETAMOL TABLETS

The effect of compression force on the elastic recoveries in the die of tablets made from different crystal habits of paracetamol are shown in figure 5.3. The elastic recoveries of tablets made from untreated paracetamol, 105-210 μm, (section 3.3.3) are also exhibited in this figure.

The elastic recoveries of the tablets increased with increase in compression force. The tablets made from plate crystal exhibited higher elastic recoveries than those made from the polyhedral crystals. However, Tukey's test showed that the differences between the elastic recoveries of tablets made from the two crystal habits at 15 kN were not significant ($P>0.05$). Generally, untreated crystals also exhibited lower elastic recoveries than plate crystals. However, the differences between them was significant only at 20 and 25 kN.

It was shown that tablets made from larger particles of paracetamol exhibited lower elastic recoveries than those made from a smaller fraction (section 3.3.3). This was attributed to a greater fragmentation of the larger particles under pressure which would produce more fresh, clean surfaces and result in an increase in interparticulate bonding. Although the plate crystals underwent more fragmentation than the polyhedral crystals (section 5.3.2), tablets made from the former exhibited higher elastic recoveries. Milosovich (1963) reported that the poor compaction properties of a specific habit of a drug can be attributed to the presence of crystal faces that give poor adhesion

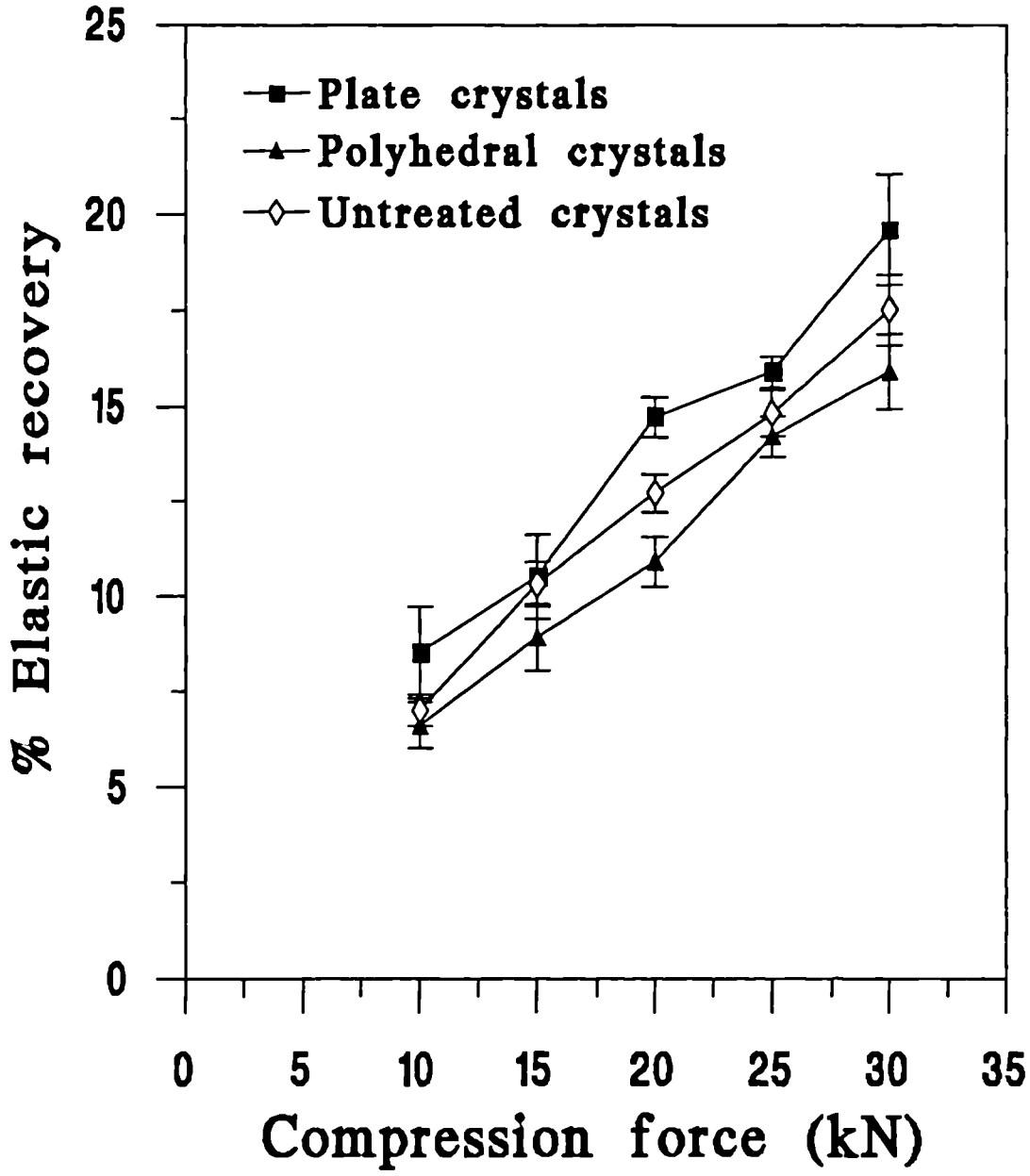


Figure 5.3 Effect of compression force on the elastic recovery in the die of tablets made from polyhedral, plate or untreated crystals of paracetamol, at a compression speed of 10 mm s^{-1}.

to each other and the absence of faces that are required for optimal adhesion. It is obvious that for plate and polyhedral crystals (figure 4.2 and 4.4f) the relative abundance of the different faces within the crystals were modified. This can affect the interparticulate bonding between these crystals resulting in different elastic recoveries for these two habits of paracetamol.

5.3.4 ENERGIES INVOLVED DURING THE COMPACTION PROCESSES

5.3.4.1 Influence of compression force or speed on the gross energies

The effects of compaction force or compaction speed on the gross energies of tablets made from the polyhedral and plate crystals of paracetamol are illustrated in figures 5.4 and 5.5, respectively. Increasing the compaction force or compaction speed, resulted in an increase in gross energies for both types of crystals.

Figures 5.4 and 5.5 also indicate that at all compaction forces or speeds the tablets made from plate crystals consumed more energy during compaction than tablets made from polyhedral or untreated crystals. The gross energies of tablets made from polyhedral and plate crystals were significantly different only at 15 and 20 kN. The increased gross energy for tablets made from plate crystals could be attributed to an increase in plastic (net compaction) energy and/or elastic energy of tablets, which will be studied in the next sections.

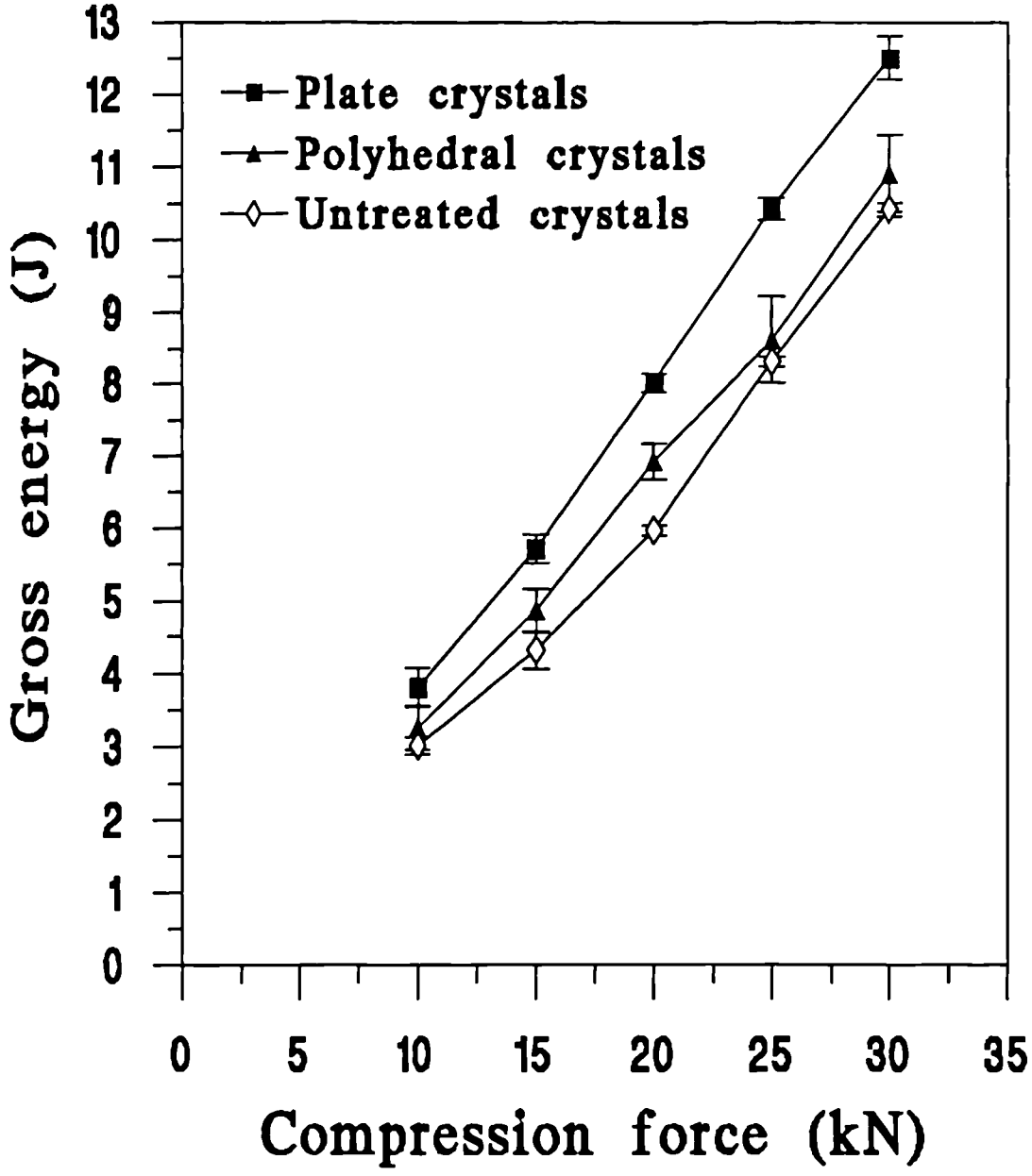


Figure 5.4 Effect of compression force on the gross energies of tablets made from the polyhedral, plate or untreated crystals of paracetamol, at a compaction speed of 10 mm s^{-1}.

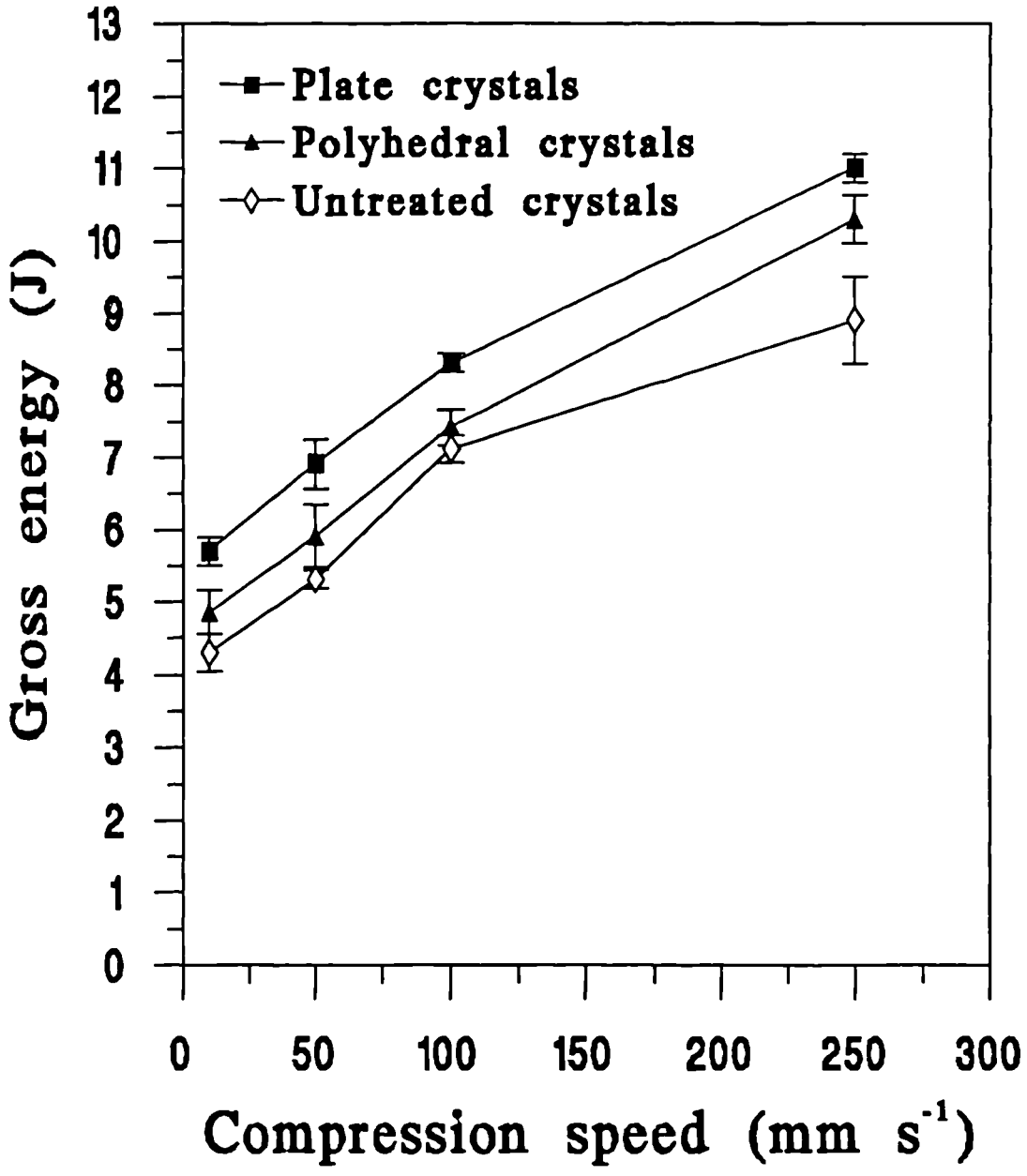


Figure 5.5 Effect of compression speed on the gross energies of paracetamol tablets made from polyhedral, plate or untreated crystals of paracetamol, at a compaction force of 15 kN.

5.3.4.2 Influence of compaction force or speed on the elastic energies

The effect of compaction force or compaction speed on the elastic energies of tablets made from polyhedral or plate crystals of paracetamol are illustrated in figures 5.6 and 5.7. These figures indicate that with increasing the compaction force or compaction speed the elastic energies of paracetamol tablets increased.

Figures 5.6 and 5.7 also indicate that at different compaction forces or speeds, generally the tablets made from polyhedral crystals exhibited lower elastic energies than tablets made from plate crystals. However, Tukey's test revealed that there were no significant differences between the elastic energies of tablets made from polyhedral or plate crystals at 10, and at 15 kN compaction forces (figure 5.6), and also at 50 mm s^{-1} compaction speed (figure 5.7). Tukey's test also revealed that at all compaction forces or speeds, except at 100 mm s^{-1} compaction speed, there were no significant differences between the elastic energies of tablets made from untreated crystals with two other samples (plate and polyhedral crystals). The results of elastic energies (figure 5.6 and 5.7) supported the elastic recoveries (figure 5.3). These results indicated that the plate crystals underwent more elastic deformation during compaction than the polyhedral crystals.

Several studies have reported that crystal shape affects the compaction properties of drugs. Hong-Guang and Ru-Hue (1995) investigated the compaction properties of paracetamol of different crystalline shapes obtained

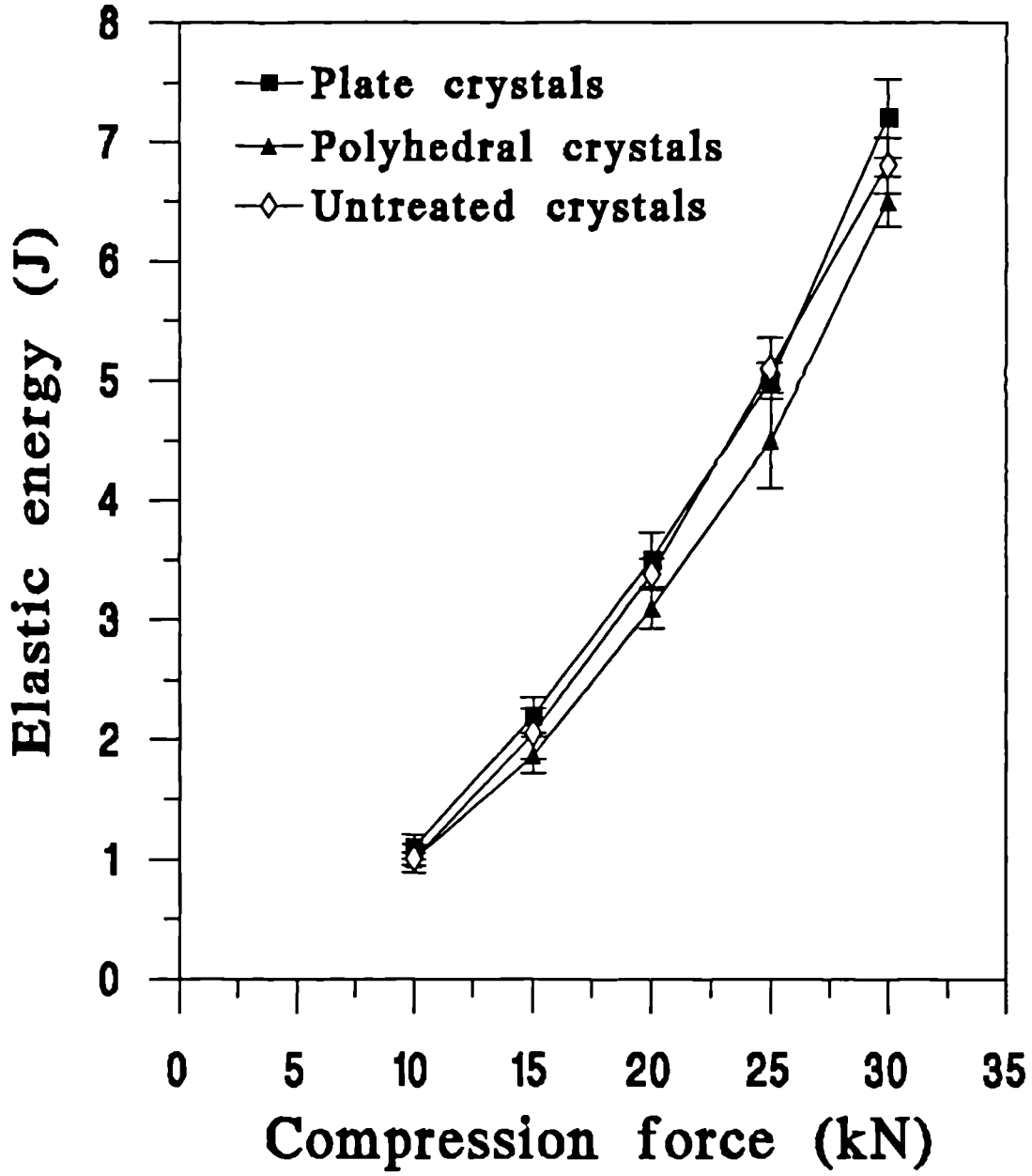


Figure 5.6 Effect of compression force on the elastic energies of tablets made from polyhedral, plate or untreated crystals of paracetamol, at a compression speed of 10 mm s^{-1}.

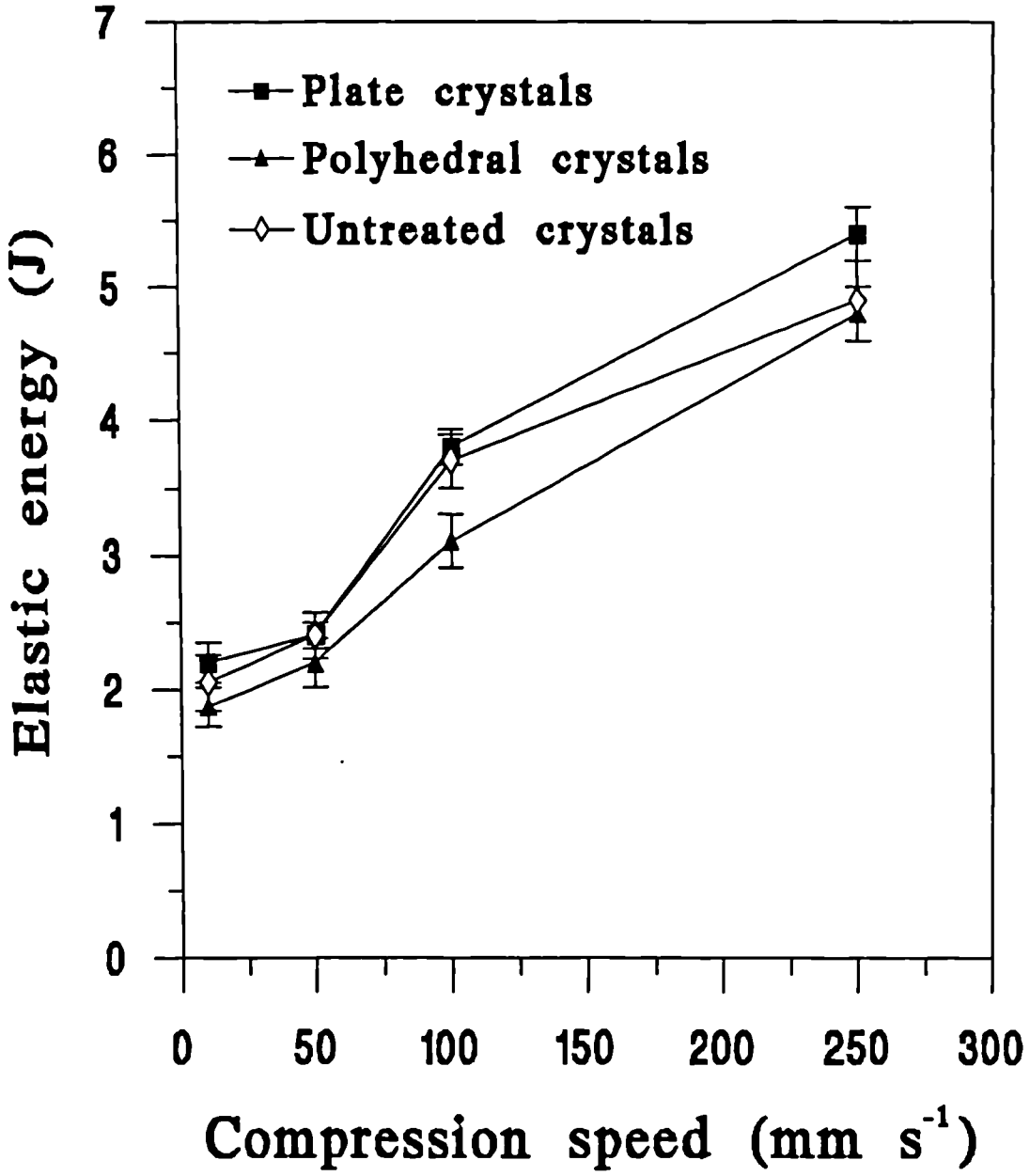


Figure 5.7 Effect of compression speed on the elastic energy of tablets made from polyhedral, plate or untreated crystals of paracetamol, at a compaction force of 15 kN.

from different manufacturers. They reported that needle-like crystals of paracetamol exhibited poorer compressibility and tablets made from them showed a greater extent of capping and lamination compared to tablets made from polyhedral crystals. This was attributed to greater elastic deformation of the needle-like crystals. Marshall and York (1991) reported that needle-like crystals of nitrofurantoin underwent more elastic deformation than plate-like crystals. They showed that the elastic recoveries of tablets made from needle like-crystals of nitrofurantoin were greater than those of plate-like crystals.

5.3.4.3 Influence of compression force or speed on the plastic (net compaction) energies

Figures 5.8 and 5.9 show the effect of compression force or compression speed on the plastic energies of tablets made from polyhedral or plate crystals of paracetamol. According to these figures, increase in compression force or speed resulted in an increase in the plastic energies.

The plastic energies of tablets made from plate crystals were higher than for polyhedral and untreated crystals (figures 5.8 and 5.9). Tukey's test revealed that at 15 kN compaction force (figure 5.8) and also at 10 and 250 mm s^{-1} compression speeds (figure 5.9), there were no significant differences ($P>0.05$) between the plastic energies of tablets made from two types of paracetamol crystals. Increased plastic energies for plate crystals, may be attributed firstly to the increased frictional forces and secondly more fragmentation for plate crystals compared to polyhedral crystals during compaction.

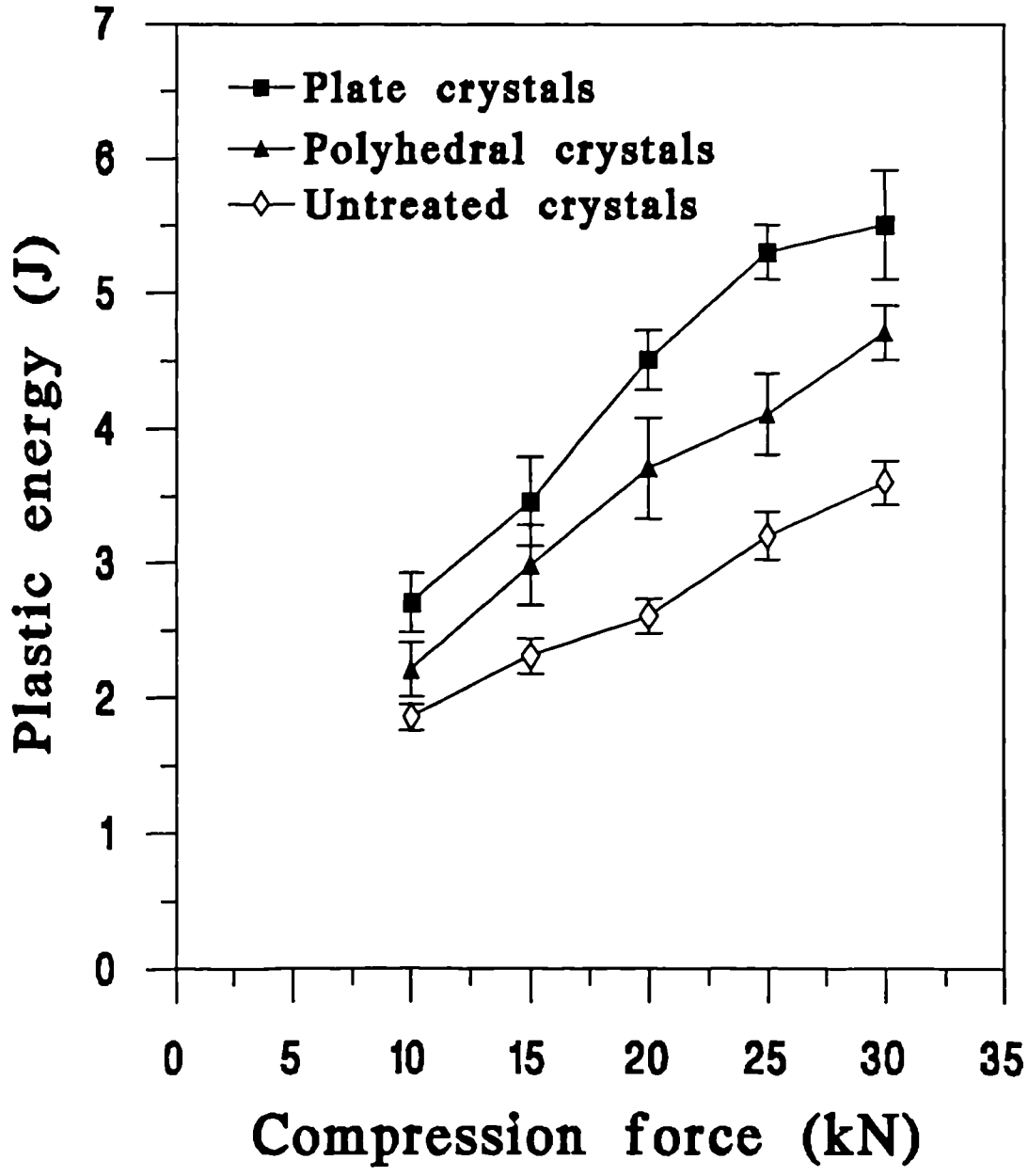


Figure 5.8 Effect of compression force on the plastic energies of tablets made from polyhedral, plate or untreated crystals of paracetamol, at compression speed of 10 mm s^{-1}.

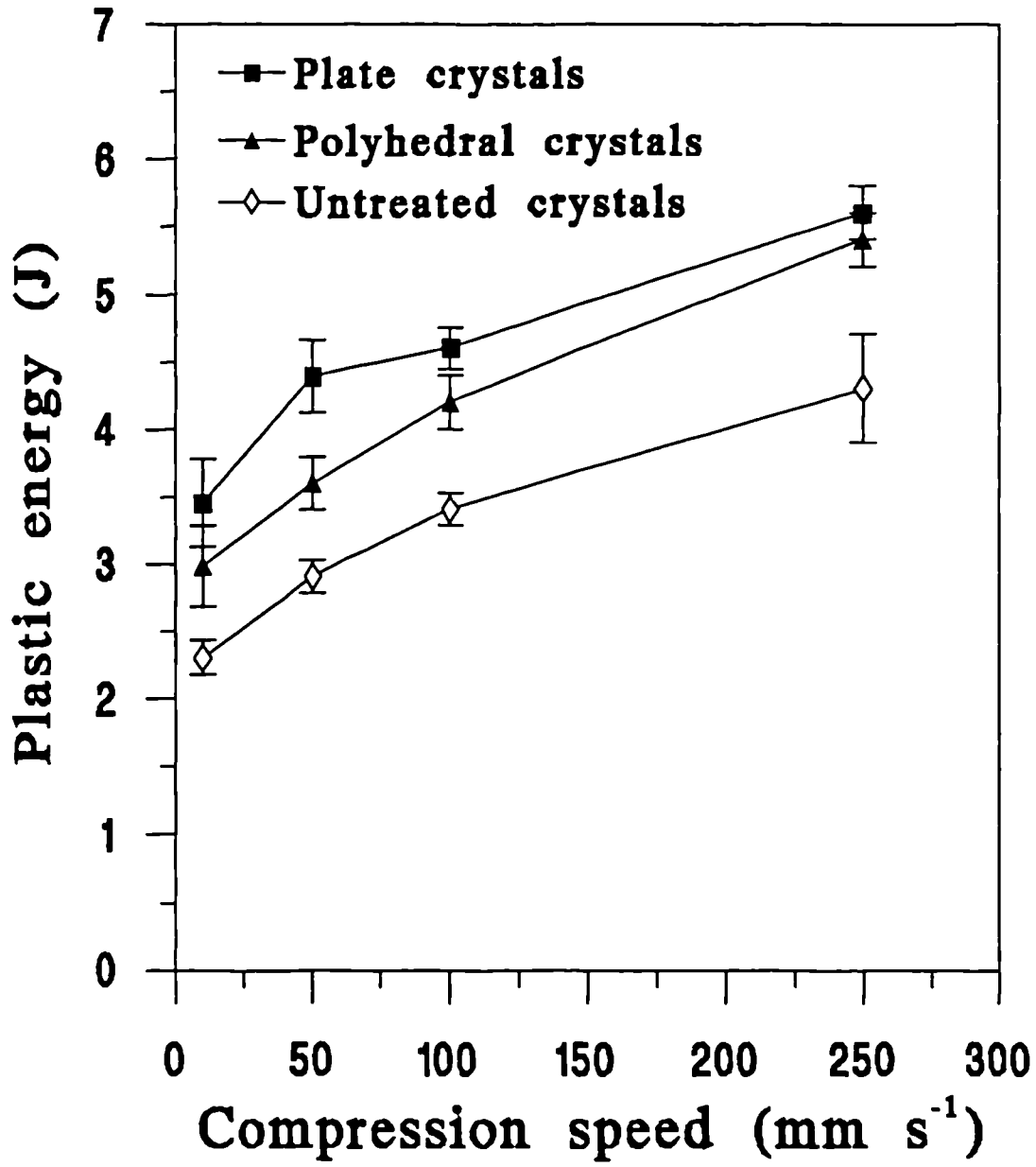


Figure 5.9 Effect of compression speed on the plastic energies of tablets made from polyhedral, plate or untreated crystals of paracetamol, at a compression force of 15 kN.

At all compaction forces or speeds the untreated particles exhibited lower plastic energies than polyhedral or plate crystals of paracetamol. The two crystal habits used in this study (polyhedral and plate crystals) were freshly crystallized with smooth surfaces, sharp edges and with specific habit (figures 4.2 and 4.4f). Untreated crystals, which had probably undergone mechanical processing such as grinding, packaging and handling after crystallization, had no smooth surfaces, sharp edges or specific habit and were grain-like (figure 3.1). Mechanical operations such as grinding have important effects in cleaving different planes of the crystals. This affects the physico-mechanical properties of crystals (Huttenrauch, 1983). The presence of cracks in the crystal structure of untreated paracetamol could cause the ease fracture of these particles during compression, resulting in lower energies required for fragmentation of untreated crystals.

5.3.4.4 Influence of compression force or speed on the ratio of elastic energy/plastic energy

Tables 5.4 and 5.5 show the elastic energy/plastic energy (EE/PE) ratio of tablets made from polyhedral, plate or untreated crystals of paracetamol at various compaction forces or speeds. The ratio of EE/PE generally increased with increase in compression force or speed. Tukey's test showed that there were no significant differences ($P>0.05$), for plate crystals, between the ratios obtained at 15 and 20 kN (table 5.4). The ratios obtained at 100 and 250 mm s^{-1} for polyhedral crystals, and at 10 and 50 mm s^{-1} for plate crystals (table 5.5) were not significantly different.

Table 5.4 Effect of compression force on the ratio of EE/PE of paracetamol tablets made from polyhedral, plate or untreated crystals, at a compaction speed of 10 mm s^{-1}.

Compression force (kN)	EE/PE ratio±SD		
	Polyhedral crystals	Plate crystals	Untreated crystals*
10	0.45±0.04	0.39±0.04	0.54±0.05
15	0.64±0.01	0.66±0.11	0.87±0.09
20	0.85±0.11	0.78±0.08	1.31±0.11
25	1.10±0.08	0.94±0.05	1.58±0.18
30	1.40±0.07	1.37±0.19	1.89±0.16

* Taken from table 3.4

These results indicate that at higher compaction forces or speeds the tablets became more elastic, i.e. at higher forces or speeds, the majority of energy involved during compaction, is utilized as elastic energy, resulting in increased capping and failure (Garr & Rubinstein, 1991).

Although the elastic energies of tablets made from plate crystals were higher than polyhedral crystals (figures 5.6 and 5.7), the plastic energies were also higher for the plate crystals (figures 5.8 and 5.9). Therefore, there were no

Table 5.5 Effect of compression speed on the ratio of EE/PE of paracetamol tablets made from polyhedral, thin plate-like or untreated crystals, at a compaction force of 15 kN.

Compression speed (mm s^{-1})	EE/PE ratio±SD		
	Polyhedral crystals	Plate crystals	Untreated crystals*
10	0.64±0.01	0.66±0.11	0.87±0.09
50	0.57±0.03	0.55±0.05	0.75±0.06
100	0.75±0.09	0.83±0.05	1.08±0.08
250	0.89±0.06	0.96±0.08	1.14±0.12

* Taken from table 3.5

significant differences (using two way analysis of variance) between the EE/PE ratio of tablets made from these two types of crystals at different compaction forces or speeds (tables 5.4 and 5.5).

At all compaction forces or speeds the ratio of EE/PE for untreated crystals of paracetamol is more than that for polyhedral or plate crystals (tables 5.4 and 5.5). Increase in the EE/PE ratio for untreated particles can not be related to poorer compaction properties of these particles as compared to polyhedral or plate crystals. Although, the plastic energies of tablets made

from polyhedral or plate crystals of paracetamol were significantly higher than untreated crystals (figure 5.8 and 5.9), this increased energy was not consumed for formation of bounds or plastic deformation of particles. Figures 5.3, 5.6 and 5.7 indicate that the elastic recoveries and elastic energies of tablets made from untreated crystals of paracetamol were similar to those of polyhedral or plate crystals, or even sometimes less than those for plate crystals.

5.4 CONCLUSIONS

Crystal habit had a great influence on the compaction behaviour of paracetamol. Heckel plots and their constants, strain rate sensitivities, elastic recoveries, elastic energies and plastic energies were affected by the different crystalline habits of paracetamol.

The results of Heckel ananlysis and strain rate sensitivity indicated that polyhedral crystals underwent a greater plasticity during compression than plate crystals which were more brittle in nature during compression.

The results of elastic recoveries and elastic energies indicated that the plate crystals underwent more elastic deformation during compaction than the polyhedral crystals.

The two crystal habits of paracetamol (plate and polyhedral crystals) did not exhibit any major improvement in their compaction properties as compared

to untreated paracetamol. Therefore, the next stage was to investigate a crystallization procedure in which improvemed compaction behaviour was produced.

CHAPTER 6. STUDY OF INTERACTIONS BETWEEN POLYVINYLPYRROLIDONE AND PARACETAMOL

6.1 INTRODUCTION

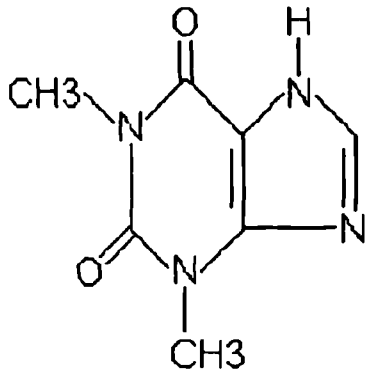
There are many examples in the literature in which interactions between polyvinylpyrrolidone (PVP) and various pharmaceutical agents have been investigated. It has been demonstrated that PVP is a strong crystal growth inhibitor for some drugs such as sulphathiazole, salicylic acid and paracetamol by adsorption on to their crystal surfaces (Simmonelli, 1970; Ziller & Rupprecht, 1988 & 1990). A binding tendency between PVP and various pharmaceutical compounds has been reported by several workers (Higuchi & Kuramoto, 1954; Kahela & Austin, 1971b; Plaizier Vercammen & De Neve, 1980; Horn & Ditter, 1982).

One group of additives used during crystallization processes is long chain polymeric materials (Mullin, 1993). Those additives which influence the crystallization processes are those that can be adsorbed on to the crystal surfaces (Davey, 1982). The degree of adsorption between additives and the crystal surfaces depends on their chemical and structural properties such as the presence of anionic or cationic groups, or the possibility of the formation of hydrogen bonds (Khamski, 1976; Davey, 1982). The aim of the work presented in this chapter is firstly to investigate the possible interactions between PVP and paracetamol, and secondly to predict whether PVP can be used as an effective additive during crystallization of paracetamol.

6.2 MATERIALS AND METHODS

6.2.1 MATERIALS

Paracetamol, different grades of PVP, ethanol and potassium bromide as described in section 2.1 were used. Ethylenediamine tetra-acetic acid disodium (EDTA) and sodium bicarbonate (each general purpose reagent, BDH Chemicals Ltd, Poole, UK), and anhydrous theophylline (obtained from BASF, Cheadle, Cheshire, UK) were also used for this part of study. Theophylline is a white crystalline powder, soluble 1:80 in alcohol, 1:120 in water, very slightly soluble in ether, freely soluble in dilute acids, ammonium and alkali hydroxide solutions. Its maximum UV absorbances in aqueous acid and aqueous alkali are at 270 and 275 nm, respectively (Moffat et al, 1986). The chemical structure of theophylline is shown below:



$C_7H_8N_4O_2$

Mol. Wt=180.2

Figure 6.1 The chemical structure of theophylline.

6.2.2 METHODS

6.2.2.1 Determination of paracetamol solubility in the presence of PVP

In order to determine the aqueous solubility of paracetamol in the presence of PVP the following was carried out. Samples of paracetamol (2.5 g) were dispersed in 100 ml water or aqueous solutions containing 0.1% w/v PVP 10000 in stoppered 100 ml conical flasks. The flasks were shaken in a shaking water bath at 37±1°C for 24 h. Then, using equation 2.5, the paracetamol concentration was determined in the filtered solutions after appropriate dilutions as described in section 2.2.7.1. Aqueous PVP solutions had no absorbance above 240 nm. The presence of PVP in the paracetamol solutions did not interfere with the UV absorbance of paracetamol at 244 nm.

6.2.2.2 Crystallization of paracetamol in the presence of different grades of PVP

Solutions containing 21.75 mg ml^{-1} paracetamol were prepared by dissolving 8.7 g paracetamol in 400 ml of distilled water at 55°C. PVP powders with average molecular weights of 2000, 10000 or 50000 was added to the solutions at 55°C to give concentrations of 5.75, 11.5, 23, 46 or 92 mg/100 ml. After complete dissolution of the PVP, the flasks were immersed into a water bath at 30±1°C and the solutions were occasionally stirred. After 2 h, crystals were observed in some flasks. The solutions with no visible crystals, were then placed into a water bath at 25±1°C with no stirring. After 24 h, the

crystals were observed in further flasks. Subsequently, the flasks containing clear solutions (with no crystals) were stored in a refrigerator at 4±1°C. After 24 h these solutions were examined for crystal growth.

In the case of the high molecular weight PVP 1000000, an opaque (turbid) solution was produced, after adding PVP to the paracetamol solutions, even at lowest concentration of PVP (5.75 mg/100 ml). The degree of turbidity of these solutions increased with increase in the concentration of PVP. Sekikawa et al (1972; 1978) reported that high molecular weight PVP (PVP K90) could be coacervated by the addition of some electrolytes or aromatic compounds such as benzoic acid, paracetamol or phenol. Therefore it was decided not to examine the crystallization of paracetamol in the presence of PVP 1000000.

6.2.2.3 Equilibrium dialysis

The interaction between paracetamol and PVP in aqueous solution was investigated using dialysis. Visking tube No. 5-24/32 (Medicell International, London, UK) with a molecular weight cut-off of 12000 daltons was used.

6.2.2.3.1 Preparation of dialysis tube

Dialysis tubing generally contains glycerin as plasticizer, traces of sulphurous compounds and heavy metal ions (McPhie, 1971). Some of these contaminants may have drastic effects during experiments and obviously must be removed before use. A recommended and successful method for the preparation of

dialysis tubes, is to simmer the dialysis tubing in solutions of sodium bicarbonate, EDTA or distilled water, respectively (McPhie 1971).

Dialysis tubes (25 cm length) were boiled in solutions of 1% w/v sodium bicarbonate, then in 1% w/v EDTA and finally in distilled water, 20 minutes for each. A double knot was tied at one end of each tube and the sample solutions were poured into it. A double knot was then tied at the top. The distance between the two knots was about 11 cm in all experiments. Checks were made to ensure that the tubes did not leak.

6.2.2.3.2 Experimental details

a) Equilibrium dialysis for paracetamol

Solutions containing PVP 50000 (4 or 8% w/v) were prepared by dissolving PVP in distilled water containing 1×10^{-2} M paracetamol. Ten ml of these solutions were poured into the dialysis tubes. These tubes were immersed into the USP XXII dissolution flasks (described in section 2.2.8) containing 1000 ml distilled water at 37°C and the solutions were stirred at 50 rpm using the USP XXII apparatus II. A diagram of set up is illustrated in figure 6.2 . The amounts of paracetamol in the solutions surrounding the dialysis tubes were determined, spectrophotometrically at 244 nm, every hour for up to 15 h. Sekikawa et al (1979) showed that the cellulose membrane did not show any measurable binding or interaction with paracetamol. The experiments were carried out in triplicate for each variable and the mean

values were reported.

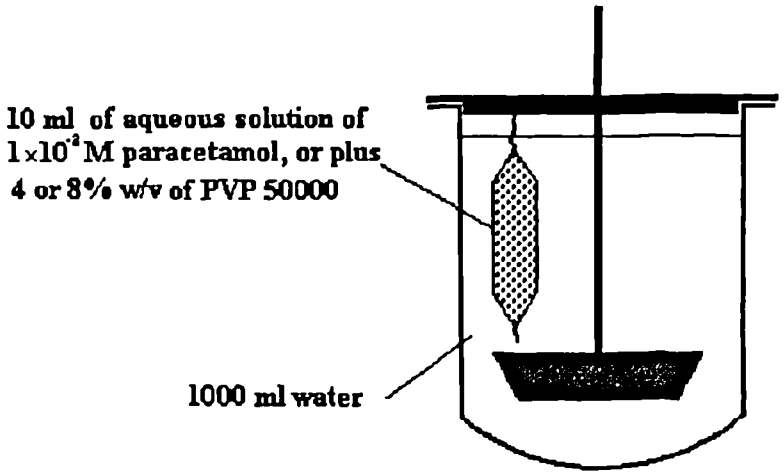


Figure 6.2 Diagram of a dialysis tube in a dissolution flask.

b) Equilibrium dialysis for theophylline

Solution containing 4% w/v PVP of molecular weight 50000 was prepared by dissolving the PVP in distilled water containing 1×10^{-2} M anhydrous theophylline. Ten ml of this solution was poured into each dialysis tube and the amount of theophylline released in the dissolution medium determined as explained for paracetamol, at 272 nm.

6.2.2.4 Preparation of a PVP-paracetamol co-precipitate

A co-precipitate of paracetamol/PVP (1:2), was prepared by dissolving paracetamol (2 g) and PVP of molecular weight 50000 (4g) in 60 ml ethanol. This solution was then heated in a water bath at 60±1°C for 24 h to

evaporate the solvent. The produced crust was scraped off, ground and stored in a desiccator before use.

6.2.2.5 Infrared spectroscopy

The infrared spectra of untreated paracetamol, the 1:2 paracetamol/PVP co-precipitate (see section 6.2.2.4) and PVP 50000 were obtained as described in section 2.2.3.

6.2.2.6 Differential scanning calorimetry (DSC)

The DSC studies were carried out for untreated paracetamol, PVP 50000, the 1:2 co-precipitate of paracetamol/PVP and physical mixtures of paracetamol and PVP 50000 containing 3, 5, 10, 20, 30 or 50% w/w PVP. The mixtures were mixed by mortar and pestle. The mean values of onset temperatures of melting and the enthalpies of fusion of these samples were measured as explained in section 2.2.4.1.

6.2.2.7 Hot stage microscopy

Hot stage microscopy was carried out for untreated paracetamol, *PVP 50000*, the 1:2 co-precipitate of paracetamol/PVP and the physical mixtures of paracetamol and PVP (see section 6.2.2.6), as explained in section 2.2.4.2. The start and end points of melting and the behaviour of these mixtures during heating were examined.

6.3 RESULTS AND DISCUSSION

6.3.1 INFLUENCE OF PVP ON THE AQUEOUS SOLUBILITY OF PARACETAMOL

There are a large number of papers in which the increase in absolute solubility of active substances in solutions of PVP has been described. For example, it has been reported that the aqueous solubility of trimethoprim increased from 0.4 mg/ml in water to more than 4 mg/ml in the aqueous solutions of 70% w/w PVP 40000 (Gupta et al, 1991). Cadwallader and Madan (1981) reported that PVP significantly increased the solubilities of testosterone, progesterone and diethylstilbestrol between 1.5-2 times in solutions of 6% w/v of PVP K30. Collett and Kesteven (1974; 1978), reported that the solubility of allopurinol in PVP solutions increased with increasing concentrations of PVP. The solubility of naproxen increased by more than 6 fold in the presence of 10% w/v PVP 25000 (Bettinetti et al, 1988). In all cases the increase in solubility of active substances in the presence of PVP has been attributed to their ability to form water soluble complexes with PVP (Cadwallader & Madan, 1981).

In the present study, the aqueous solubility of paracetamol in the presence of small amounts of PVP 10000 was investigated and the results are listed in table 6.1. According to these results, PVP at the concentration used in this study (0.1% w/v), did not affect the solubility of paracetamol. Lipman and Summers (1980) reported that there is a 2.3 times increase in paracetamol

solubility in the presence of 10% w/v PVP solution. Sekikawa et al (1979) reported that the solubility of paracetamol increased about 1.15 times in the presence of 1% w/v PVP K30. Table 6.1 shows that the concentration of PVP in this study was below that which produces an increase in the solubility of paracetamol.

Table 6.1 Solubility of paracetamol in absence or presence of 0.1% w/v PVP 10000 in water at 37°C.

Solubility of paracetamol (g/100ml±SD)	
Water	Water with 0.1% w/v PVP 10000
2.02±0.04	2.02±0.09

6.3.2 INFLUENCE OF DIFFERENT GRADES OF PVP ON CRYSTALLIZATION OF PARACETAMOL FROM WATER

During crystallization of paracetamol from water, PVP had a strong inhibitory effect on the precipitation of paracetamol crystals. The precipitation of the solid phase (paracetamol crystals) in the presence of different amounts of various molecular weights of PVP, is summarised in table 6.2. These results clearly indicate that the inhibitory effect of PVP on the crystallization of paracetamol was dependent on the molecular weight and concentration of PVP. The lowest molecular weight of PVP (PVP 2000) had a minor effect while the higher molecular weights of PVP (PVP 10000 or

Table 6.2 Effect of different amounts of various molecular weights of PVP on the precipitation of paracetamol crystals.

Molecular weight of PVP	Concentration of PVP (mg/100ml)	2 h at 30°C	2 h at 30°C + 24 h at 25 °C	2 h at 30°C + 24 h at 25°C + 24 h at 4°C
	0	+	*	*
PVP 2000	5.75	+	*	*
	11.5	-	+	*
	23	-	+	*
	46	-	+	*
	92	-	-	+
PVP 10000	5.75	-	+	*
	11.5	-	-	+
	23	-	-	+
	46	-	-	+
	92	-	-	+
PVP 50000	5.75	-	-	+
	11.5	-	-	+
	23	-	-	+
	46	-	-	+
	92	-	-	+

+ Crystal observed
- No crystal observed
* Test completed at previous stage

PVP 50000) had a marked inhibitory effect, even at very low concentrations. Table 6.2 also indicates that by decreasing the crystallization temperature to 4°C, the paracetamol crystals had precipitated at all concentrations of PVP. This is attributed to an increase in the supersaturation degree of the system,

at low temperature, as shown in table 4.1.

In section 1.2.3, it was mentioned that the presence of impurities in a crystallization system can suppress nucleation. This effect may be caused by changing the equilibrium solubility of the solute in the solution or by adsorption of impurity onto nuclei. Therefore, in the present study, two hypothesis can be given for the inhibitory effect of PVP on the crystallization of paracetamol:

1- By increasing the solubility of paracetamol in the solution.

2- By adsorption onto the surfaces of nuclei (during crystal growth) and by inhibition of the deposition of paracetamol molecules onto the crystal lattice.

Table 6.1 indicates that PVP 10000, at a concentration of 100mg/100ml, had no effect on paracetamol solubility while it was shown that PVP 10000, even at very low concentration (11.5 mg/100 ml), greatly inhibited the precipitation of paracetamol crystals (table 6.2).

It has been long known that the presence of small amounts of high molecular weight substances such as gelatin, sodium carboxymethylcellulose, polyacrylamide or polyacrylic acid can suppress or inhibit the nucleation and subsequently increase the induction time during crystallization of materials from their aqueous solution (Mullin, 1993; Davey, 1982). The probable mode of action of high molecular weight substances is that they render the nuclei inactive by adsorbing onto their surfaces (Mullin, 1993). The inhibitory effect

of PVP on the precipitation of paracetamol is probably via the adsorption of PVP onto the surfaces of nuclei during crystal growth. This inhibits further deposition of paracetamol molecules onto the nuclei and therefore increases the induction time and inhibits the appearance of the solid phase.

A review of the literature, reveals that some workers have reported the inhibition of crystal growth by PVP. Femi-Oyewo and Spring (1994) reported that PVP K30 almost completely inhibited the crystallization of paracetamol from water. Simonelli et al (1970) reported that PVP can completely inhibit the growth of sulphathiazole crystals. This effect was attributed to adsorption of PVP onto the surfaces of the sulphathiazole crystals. Ziller and Rupprecht (1988) demonstrated that in a suspension of paracetamol, crystal growth can occur with a decrease in temperature, but the crystal growth was significantly impeded in the presence of a small amount of PVP 180000 (0.003% w/v). The inhibitory effect exhibited by PVP was molecular weight dependent. Lower molecular weights of PVP had only a minor influence on crystal growth. Ziller and Rupprecht (1990) also reported that PVP is a strong crystal growth inhibitor for hydroxybenzoic acid derivatives, salicylic acid and sulphathiazole. Ziller and Rupprecht (1990) demonstrated that PVP had no effect on the crystal growth of compounds such as phenobarbitone, xanthin derivatives (theophylline monohydrate and caffeine monohydrate), phenacetin and acetanilide.

Simmoneli et al (1970) and Ziller and Rupprecht (1988) suggested that the

inhibitory effect of PVP on the crystal growth of sulphathiazole or paracetamol may be due to the formation of protective adsorption layers on the crystal surfaces. These adsorbates produced a barrier which resisted the diffusion of drug molecules from solutions to the crystal surface. Figure 6.3 shows a schematic diagram of the appearance of crystals at various stages of growth in the absence or presence of PVP.

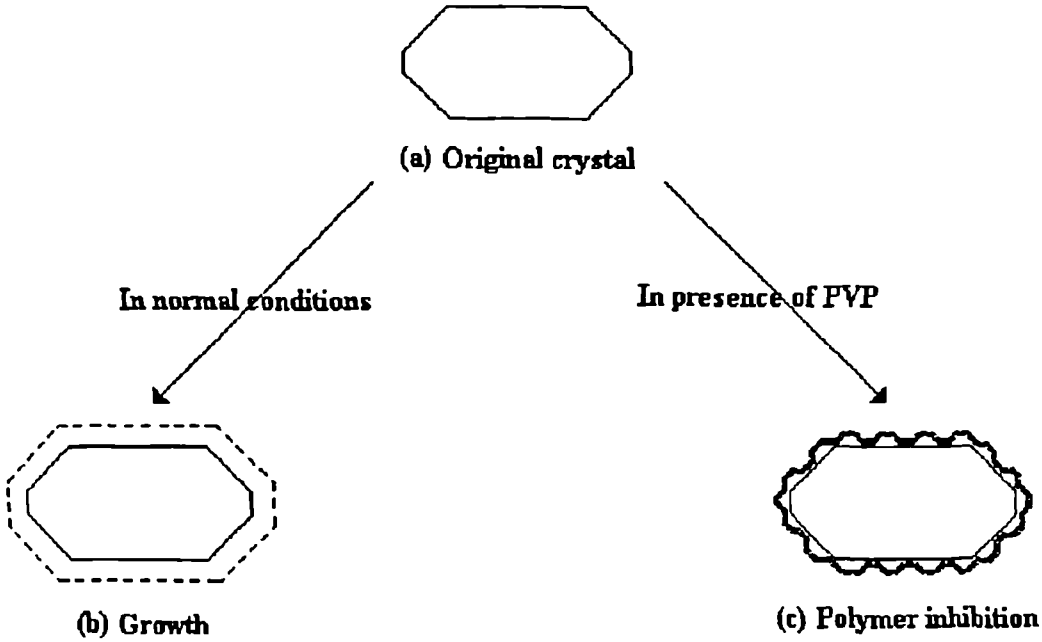


Figure 6.3 Diagram of a crystal or a nuclei at various stages: (a) original crystal; (b) after normal growth; (c) after the addition of PVP, showing polymer inhibition.

6.3.3 DIALYSIS STUDY OF THE BINDING TENDENCY BETWEEN PVP AND PARACETAMOL

Dialysis membranes are thin films of highly polymerized substances such as cellulose which in the presence of solvents, swell to form a molecular sieve, where pores will retain polymer molecules with large molecular weights but allow the diffusion of small molecules. Therefore, the drug molecules bound to the polymer do not pass through the tube membrane and remain inside the tube; only the unbound drug molecules pass through the membrane. This method was used to determine the binding between paracetamol and PVP (see section 6.2.2.3). The results of this study are presented in figure 6.4. It is obvious that PVP had a retardant action on the diffusion of paracetamol. This effect increased with increasing the concentration of PVP in the solution. The slower release of paracetamol in presence of PVP may be attributed to a binding propensity between PVP and paracetamol. Siguier et al (1948) showed that PVP had a retarding action on the diffusion of morphine through a dialysis membrane. This was attributed to the physicochemical combinations of PVP with this drug.

As a control study, the dialysis test was carried out using theophylline in place of paracetamol. It has been reported that there is no binding affinity between xanthin derivatives such as theophylline or caffeine and PVP (Ziller & Rupprecht, 1990; Higuchi & Kuramoto, 1954; Horn & Ditter, 1982). The release of theophylline through the dialysis tube in absence or presence of 4% w/v PVP 50000 is illustrated in figure 6.5.

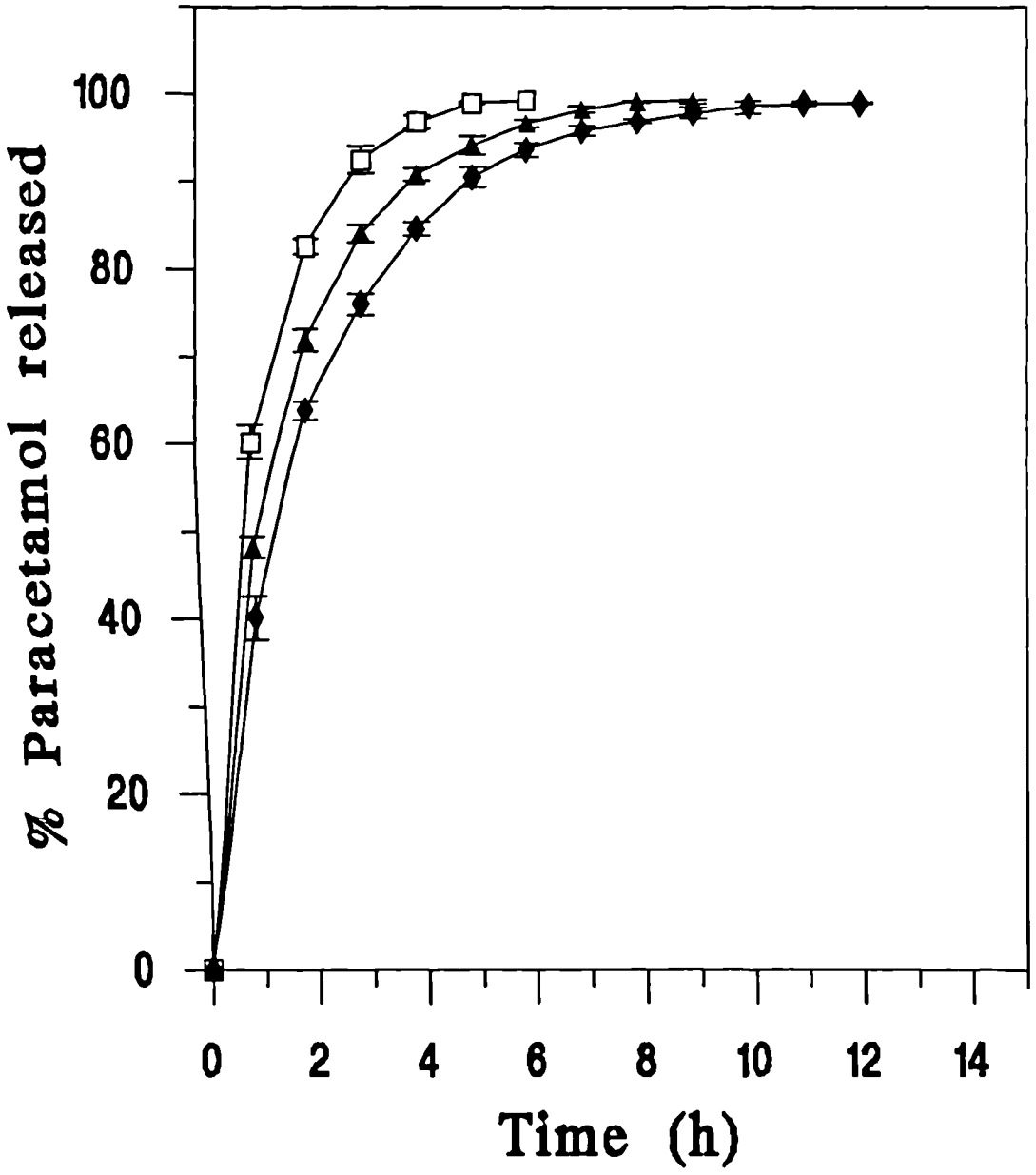


Figure 6.4 The passage of paracetamol through dialysis tube in the absence (□), or in the presence of (▲) 4% or (♦) 8% w/v of PVP 50000.

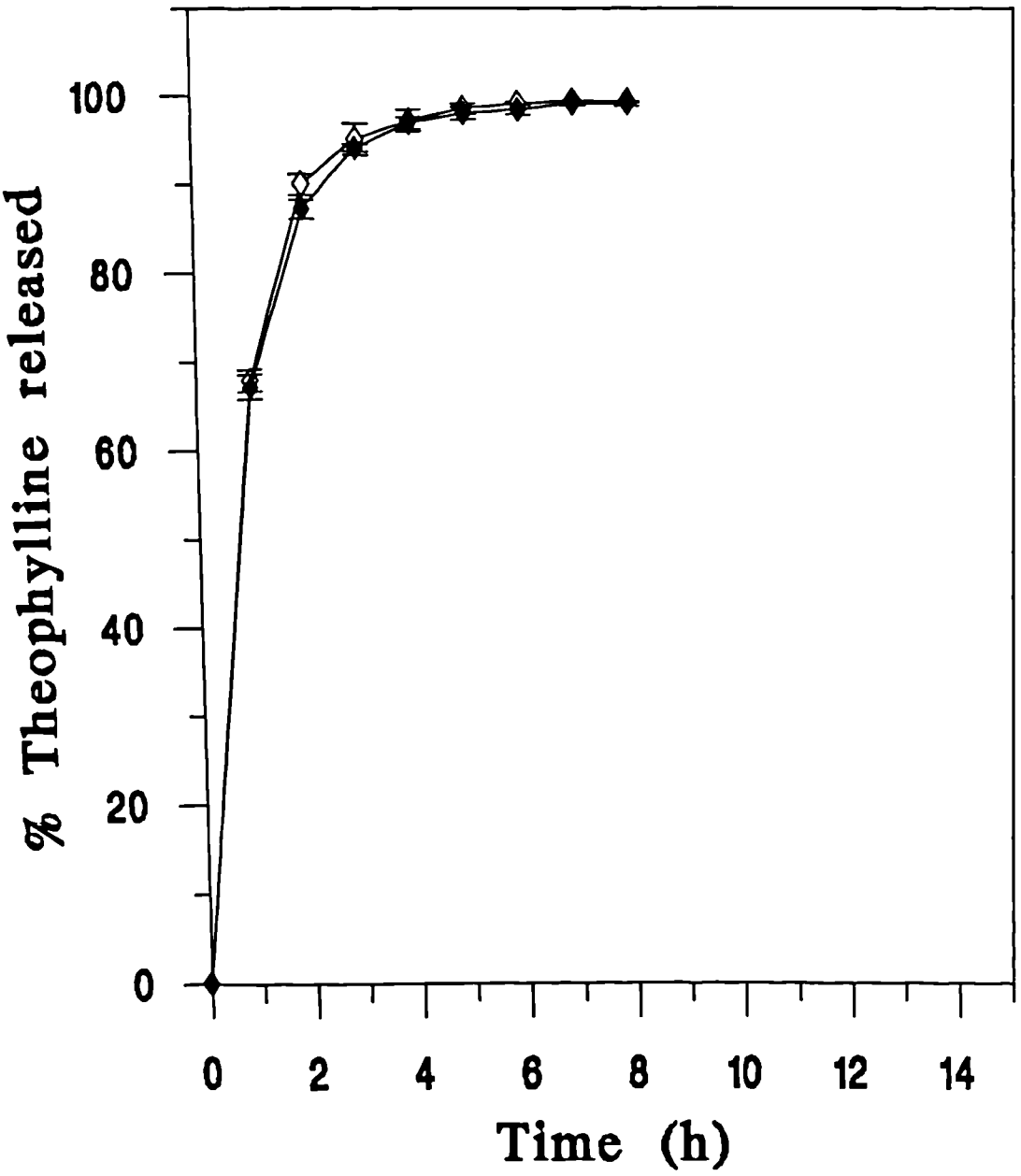


Figure 6.5 The passage of theophylline through dialysis tube in the absence (◊) or in the presence of 4% w/v of PVP 50000 (♦).

It clearly shows that the presence of PVP had no effect on the release of theophylline. Therefore, since there was no influence of PVP on the passage of theophylline compared to paracetamol, the results indicate that there is a potential for bonding between PVP and paracetamol.

The interaction of PVP in aqueous solution with various pharmaceutical agents has been investigated extensively during the past years and it was found that PVP has a great tendency to bind with some drugs and preservatives. One of the most widely methods to examine this kind of interaction is the equilibrium dialysis. In one earlier study, Higuchi and Kuramoto (1954), investigated the complex formation between PVP K30 and some drugs using equilibrium dialysis. They showed that PVP can bind to sulphathiazole, sodium salicylate, mandelic acid and chloramphenicol. No evidence of complex formation was detected with procaine hydrochloride, bezylpenicilline, caffeine, theophylline and cortisone. Molyneux and Frank (1961) and Plaizier Vercammen and De Neve (1980, 1981, 1983) showed that there was an interaction between PVP with some aromatic compounds such as benzoic acid and its derivatives, phenol and salicylic acid, in aqueous solutions using equilibrium dialysis or ultrafiltration. Kahela and Austin (1972), using the gel filtration, demonstrated that there was an interaction between salicylic acid and PVP. All these workers reported that by increasing the concentration of PVP in solution, the percentage of drug bound to PVP increased.

Horn and Ditter (1982) demonstrated that there is a binding affinity between PVP 49000 and several drugs including paracetamol, using chromatographic techniques and equilibrium dialysis. Sekikawa et al (1979) also showed a binding tendency between PVP and paracetamol in their aqueous solution, using dialysis. They showed that in the presence of 5% PVP K30, 12% of paracetamol in a 1×10^{-2} M solution was bound to PVP. However, the results of equilibrium dialysis in the present study (figure 6.4) indicated that after a long period (12 hours) almost all of the paracetamol passed through the dialysis tube. This clearly shows that there was no strong binding between PVP and paracetamol.

Since dialysis is a diffusion-controlled process, in order to maintain an outward free flow and complete removal of dialysable substances through a membrane, it is essential to decrease the concentration of diffusible substances outside the membrane. This can be achieved by using a large volume of solvent outside the dialysis membrane (McPhie, 1971). Horn and Ditter (1982) and Sekikawa et al (1979) used a very low volume of solvent outside dialysis membrane (2 or 20 ml), which was also equal to the volume inside of dialysis membrane. Possibly, under these conditions a complete removal of the dialysable substance (paracetamol) through the membrane would not be achieved.

The present study revealed that the nature of interaction between PVP and paracetamol is physical and reversible. There is probably an equilibrium state

between the amount of bound paracetamol and free paracetamol in the presence of PVP inside the dialysis tube as shown by equation 6.1.

Paracetamol + PVP $\rightleftharpoons$ paracetamol-PVP Equation 6.1

By using a large volume of solvent outside the dialysis tube (100 times more than inside), it allowed equation 6.1 to proceed towards the left hand side and almost all of paracetamol was released through the membrane irrespective of PVP concentration (figure 6.4).

6.3.4 MECHANISM OF INTERACTION BETWEEN PVP AND PARACETAMOL

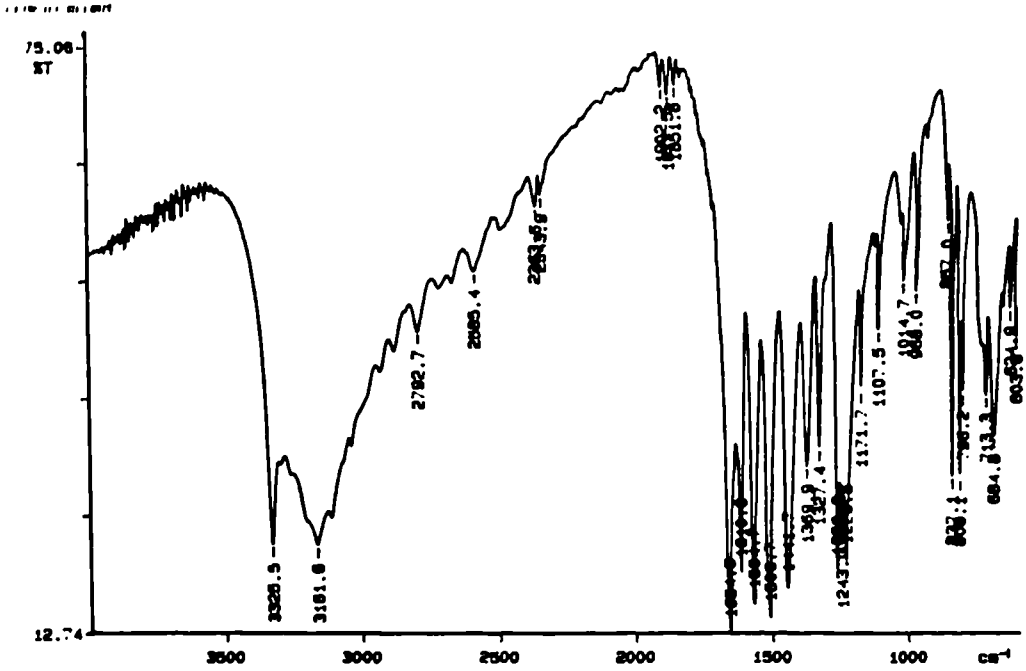
Several studies have been reported that the mechanism of interaction between PVP and some drugs in their solution or co-precipitate is by the formation of hydrogen bonds between the drug and PVP. Jurgensen Eide and Speiser (1967) studied the interaction of some aromatic compounds with PVP in their aqueous solution using equilibrium dialysis. They demonstrated that aromatic compounds containing an -OH, -NH_2 or -COOH group exhibited a higher degree of interaction than compounds without such groups. This indicated that hydrogen bonding plays an important role in such interactions. Similar results were found by Horn and Ditter (1982) who studied the interaction between PVP and some drugs in their aqueous solution using equilibrium dialysis or chromatographic techniques. Molyneux and Frank

(1961) studied the IR spectra of dry PVP films containing varying concentrations of aromatic compounds. For compounds which were capable of hydrogen bonding, there were generally shifts in O-H stretching bands to lower wave numbers, indicating hydrogen bond formation. Matsumaru et al (1977) demonstrated a weak hydrogen bond between the C(21)-hydroxyl group of ajmaline and the carboxyl group of PVP, in their co-precipitate, using NMR spectroscopy. Said et al (1974a,b) studied the interactions between PVP and tolbutamide, succinyl sulphathiazole and chlorpropamide in their co-precipitate using IR spectroscopy. The spectral data showed that a broad peak for the co-precipitate formed due to O-H stretching which confirmed that the interaction between PVP and these drugs was via hydrogen bonding. Doherty and York (1987) investigated the interactions between fursemide and PVP in a solid dispersion system using IR spectroscopy. They showed the existence of hydrogen bonding between the sulphonamide group in frusemide and PVP. NMR data confirmed the IR results.

6.3.4.1 IR studies of paracetamol/PVP co-precipitate

The IR spectra for paracetamol, PVP, and for the 1:2 paracetamol/PVP co-precipitate are illustrated in figures 6.6a, 6.6b and 6.7a, respectively. The IR spectrum of untreated paracetamol (figure 6.6a) shows a sharp band at 3325 cm^{-1} due to O-H stretching but this sharp peak has changed to a broad band in the co-precipitate (figure 6.7a). This may be attributed to the hydrogen bonding between the hydroxyl group of paracetamol and the carboxyl group of PVP.

(a)



(b)

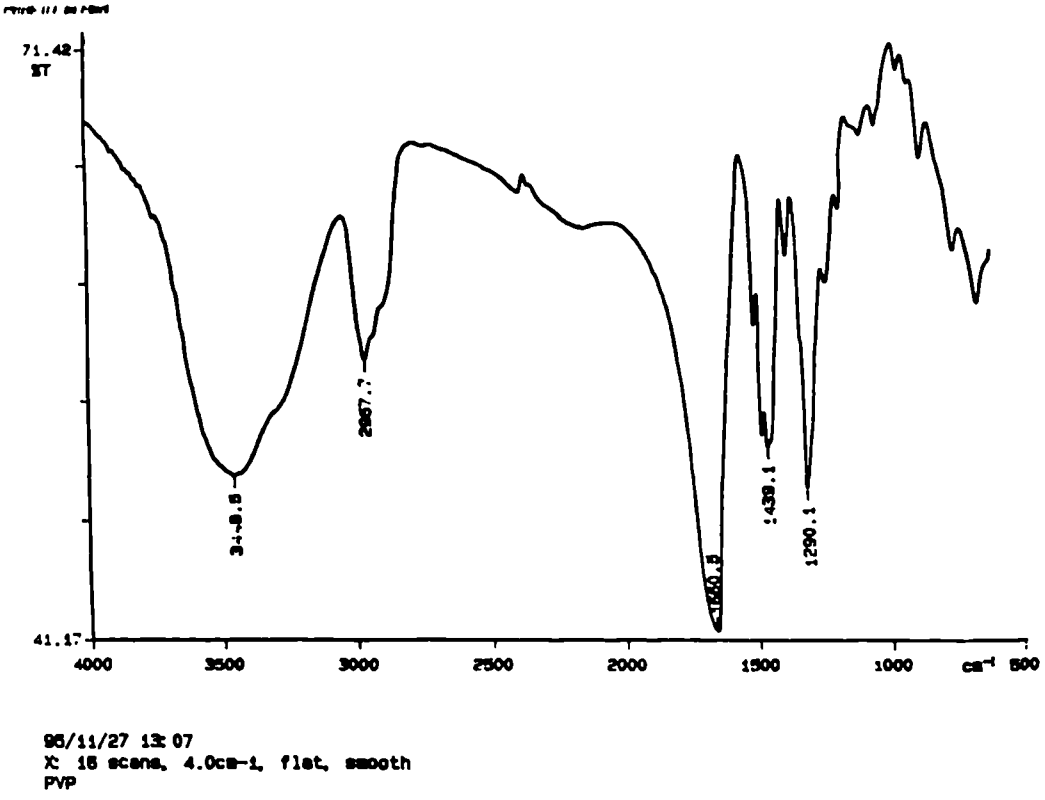
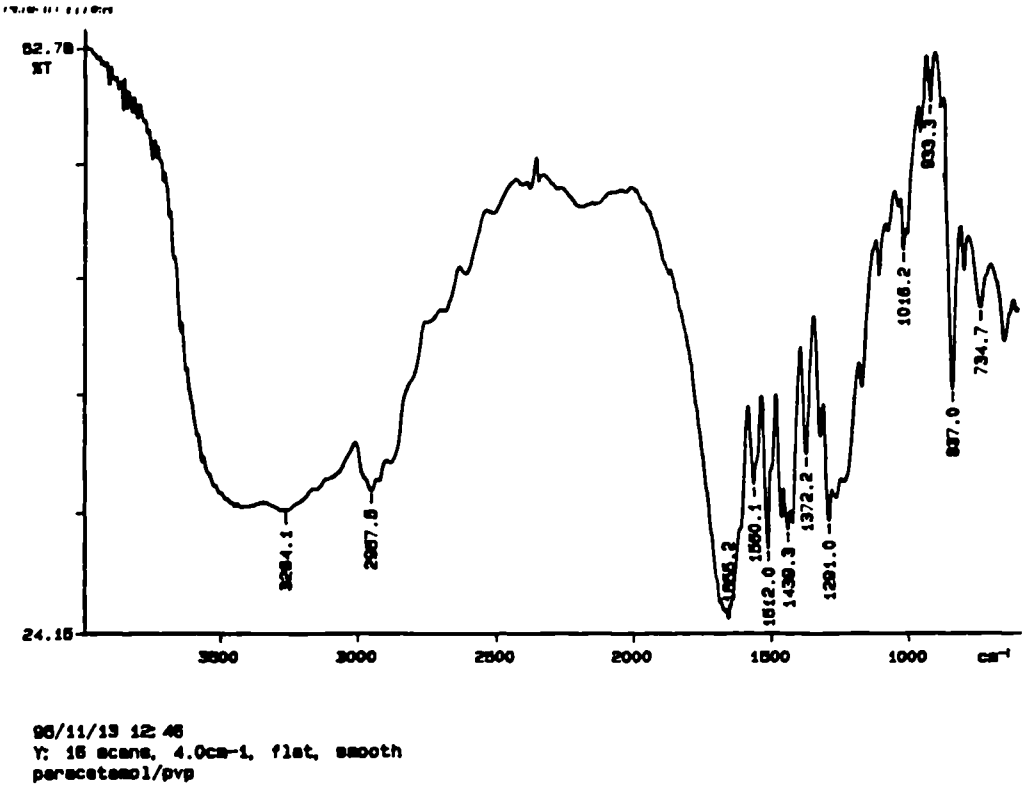


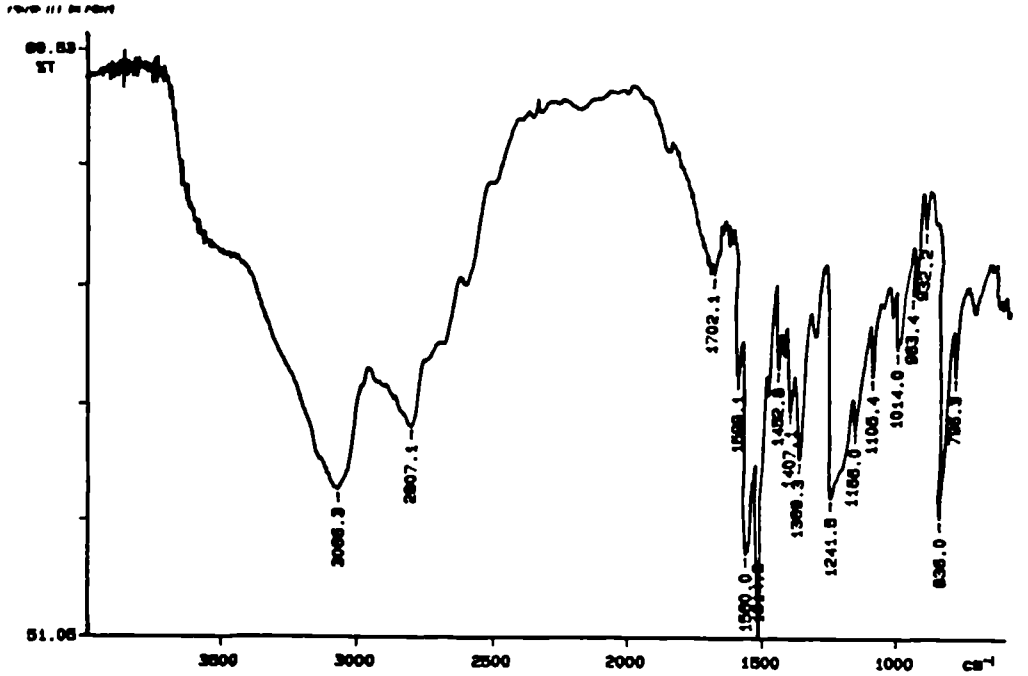
Figure 6.6 The IR spectra of: (a) untreated paracetamol crystals and (b) PVP 50000.

(a)



96/11/13 12:46
Y: 16 scans, 4.0cm-1, flat, smooth
paracetamol/pvp

(b)



96/11/07 17:52
had1/3a2: 16 scans, 4.0cm-1, diff
paracetamol/pvp -pvp 2nd

Figure 6.7 a) Infrared spectrum for the 1:2 co-precipitate of paracetamol and PVP 50000, b) Infrared spectrum of 1:2 PVP-paracetamol co-precipitate, following subtraction of the PVP vibrations, using FTIR computer.

To enhance the resolution of the vibrations in the IR spectrum of the PVP-paracetamol co-precipitate, the vibrations due to PVP were removed by spectral subtraction using the FTIR computer and the resultant spectrum is shown in figure 6.7b. This analysis shows that the O-H vibrations in paracetamol had been significantly shifted to lower frequencies.

This study demonstrated that paracetamol and PVP interact via hydrogen bonding. This is expected as PVP contains a recurring carboxyl group which allows it to hydrogen bond with the hydroxyl group of paracetamol as illustrated in figure 6.8.

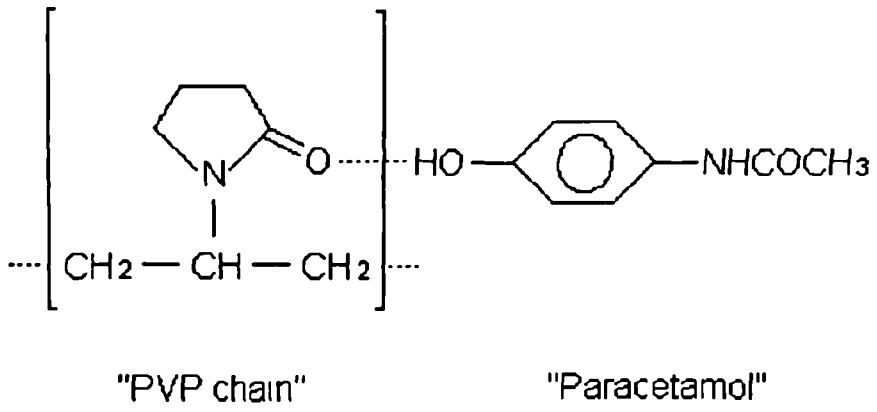


Figure 6.8 A diagram of a possible hydrogen bond formation between the hydroxyl group of paracetamol and the carboxyl group of PVP

6.3.5 THERMAL ANALYSIS OF THE 1:2 PARACETAMOL/PVP CO-PRECIPITATE AND THEIR PHYSICAL MIXTURES

6.3.5.1 DSC studies of paracetamol/PVP co-precipitate

Figure 6.9 shows the DSC scans of paracetamol, PVP 50000 and their co-precipitate (1:2 drug to PVP). The scan of paracetamol shows a sharp melting point with an onset of 171.6°C. The scan of PVP does not show any peaks. Bettenetti et al (1988) showed that PVP has broad peak between 50-120°C related to vaporization of adsorbed water. Degradation of PVP happens above 250°C. Figure 6.9 clearly shows that the fusion peak of paracetamol has disappeared in the co-precipitate system of paracetamol/PVP.

Disappearance of the fusion peak of naproxen in co-precipitates of naproxen/PVP with less than 50% w/w of naproxen in the system has been reported by Bettineti et al (1988). This was attributed to an interaction between naproxen and PVP.

6.3.5.2 DSC studies of paracetamol/PVP physical mixtures

The DSC scans for physical mixtures of paracetamol and PVP with different ratios of paracetamol in the mixtures, are exhibited in figure 6.10. The onsets of melting point and enthalpies of fusion of paracetamol in the mixtures are given in table 6.3.

Table 6.3 The onset of melting point (T_m) and enthalpy of fusion (ΔH_f) for physical mixtures of paracetamol and PVP of molecular weight 50000.

Concentration of PVP (%w/w)	Onset of T_m (±SD) (°C)	ΔH_f (±SD) (J/g)
(Pure paracetamol)	171.6±0.2	176.1±2.2
3	171.5±0.2	150.0±2.4
5	170.9±0.1	134.6±4.5
7	170.8±0.7	126.1±3.2
10	170.5±0.3	104.7±3.6
20	*	62.4±3.1
30	*	30.8±0.6
50	*	0

(* Onset difficult to determine)

These data clearly indicate that the enthalpies of fusion of paracetamol decreased as the proportion of PVP in the physical mixtures increased. In figure 6.10, when the ratio of paracetamol was 50% w/w in the mixture, the DSC scan with a flat baseline with no evidence for the fusion of paracetamol or any eutectic temperature, was obtained. This behaviour is similar to that of co-precipitate of paracetamol/PVP (figure 6.9).

Ford and Rubinstein (1981) reported that when the DSC scan of a mixture of a drug and excipient displays the elements characteristic of each component, without alterations to the position of endotherms, a lack of interaction is indicated. The absence of the characteristic melting points of some drugs such as naproxen, ketoprofen and atenolol in their physical

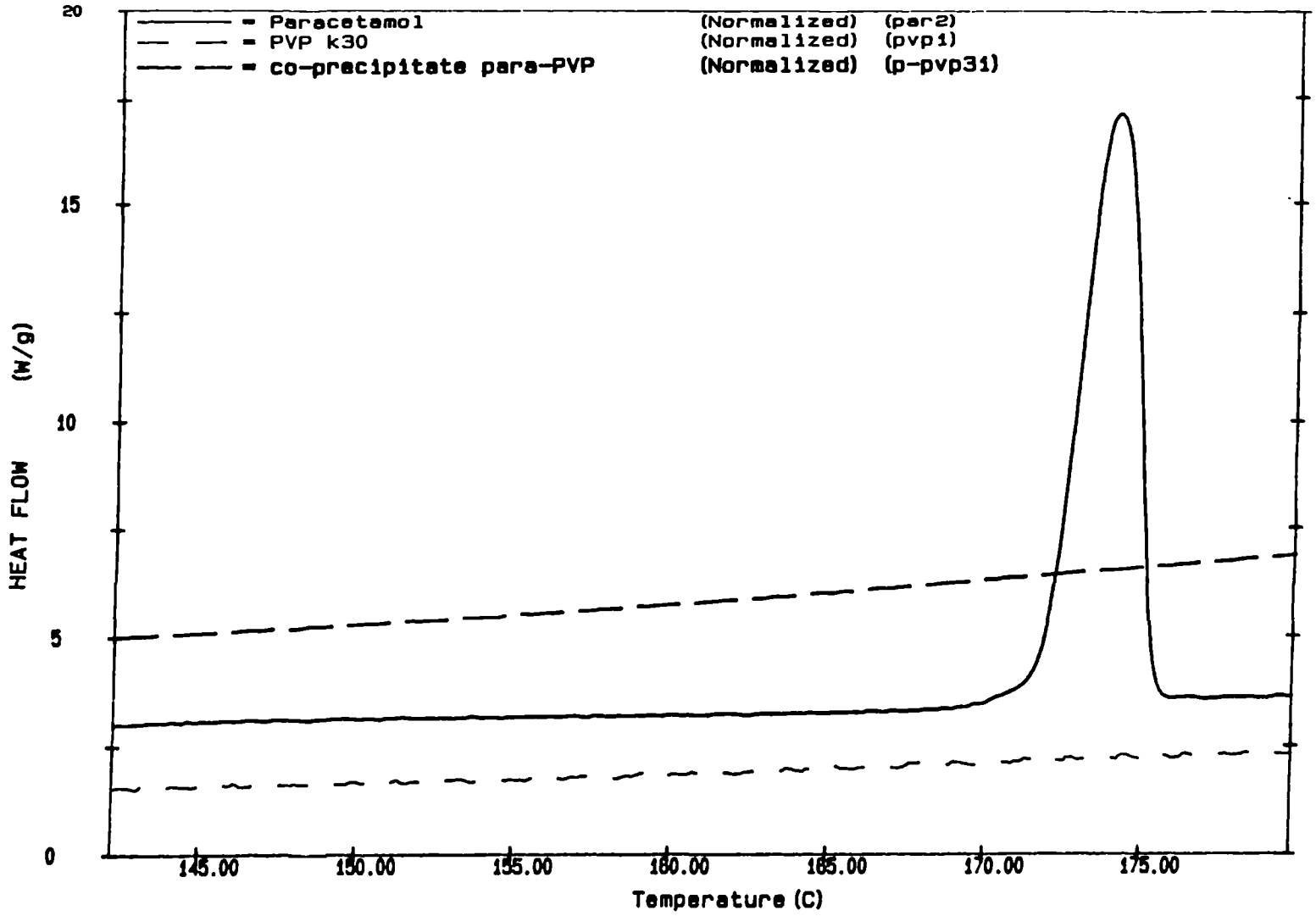


Figure 6.9 DSC scans of paracetamol, PVP 50000 and their co-precipitate with 1:2 ratio of paracetamol to PVP.

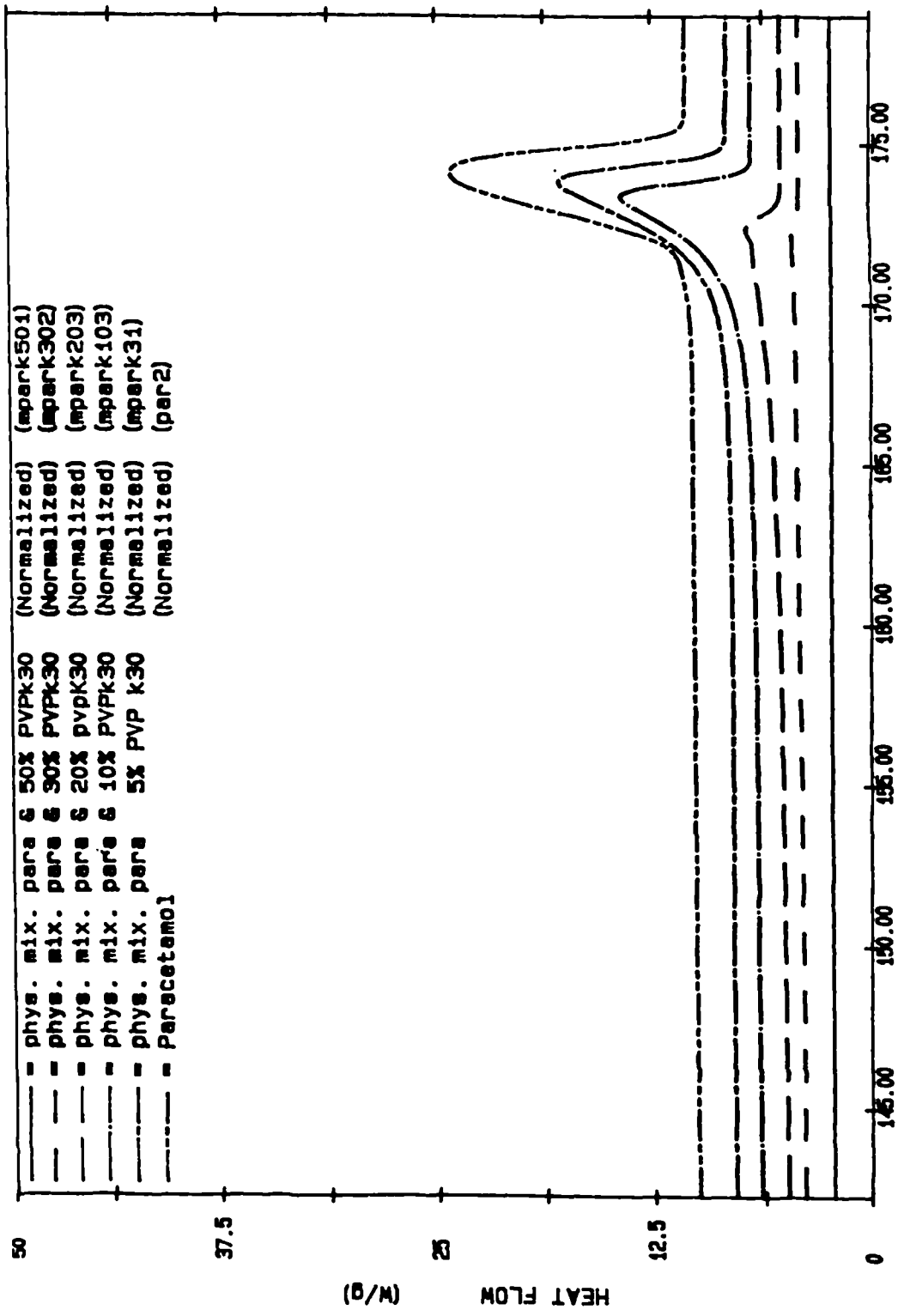


Figure 6.10 DSC scans of physical mixtures of paracetamol and PVP 50000.

mixtures with PVP has been reported by Botha and Lotter (1989, 1990a, b). In all cases, this behaviour was attributed to an interaction between drug and PVP.

6.3.5.3 Hot stage microscopy of paracetamol/PVP co-precipitate and their physical mixtures

The behaviour of paracetamol, PVP or the 1:2 co-precipitate of paracetamol/PVP with increasing temperature was observed using hot stage microscopy. The paracetamol particles exhibited an initial melting at 171°C which was complete at 174°C. The PVP particles did not show any events such as melting with increasing temperature, except their colour became yellowish above 250°C, possibly indicative of degradation. The paracetamol/PVP co-precipitate particles started to soften and melt from 140°C and their melting was complete at about 165°C. The melted particles were very viscous and they could not flow.

Observation of the physical mixtures of paracetamol/PVP with increasing temperature showed that some particles started to melt at 140-143°C. when the percentage of PVP in the mixtures was increased, the number of melted particles at this temperature increased. The majority of particles started to melt at 140°C, in the mixture containing 50% w/w PVP. The melting of these mixtures was complete at 169-172°C, which indicates of presence of free paracetamol.

In paracetamol/PVP co-precipitate, the paracetamol molecules are in intimate contact with PVP, therefore all the particles exhibited the same behaviour with increasing temperature. While, in physical mixtures the contacts between paracetamol and PVP are at the edges and surfaces of particles, therefore they exhibited behaviour corresponding to both paracetamol/PVP and free paracetamol.

The paracetamol crystals under microscope were near shiny and grain-like, while PVP particles were dark with no specific shape, and therefore it was easy to distinguish them from each other. It was observed that during the melting of paracetamol, the PVP particles dissolved in the melted paracetamol. For this reason, by increasing the percentage of PVP in the mixtures, the viscosity of the melted liquid increased. When the content of PVP in the mixtures was more than 50% w/w, all of the PVP particles were unable to be dissolve in the melted paracetamol and they remained solid even till 200°C. Apparently the melted paracetamol was saturated with PVP and it was impossible to dissolve further PVP in the melt. These results can be indicative of an interaction between PVP and paracetamol.

6.4 CONCLUSION

PVP had a significant inhibitory effect on the crystallization of paracetamol from water. The inhibitory effect of PVP on the precipitation of paracetamol crystals was dependent to its molecular weight. The higher molecular weights of PVP were more effective crystal growth inhibitors. It was shown that this

effect was not due to a change in solubility of the paracetamol. This effect of PVP was attributed to the adsorption of PVP onto the paracetamol nuclei (during crystal growth) which inhibited the deposition of paracetamol molecules from solution onto the developing crystal lattices.

There is a potential of binding between PVP and paracetamol in their aqueous solution. Infrared spectroscopy of paracetamol/PVP co-precipitate indicated that the mechanism of the interaction between PVP and paracetamol is by hydrogen bonding. Thermal analysis studies also showed that there was an interaction between PVP and paracetamol.

The results of this study showed potential application of PVP as an additive during crystallization of paracetamol. Therefore, in next chapter the effect of different grades of PVP as additives during crystallization of paracetamol, will be studied.

CHAPTER 7. CRYSTALLIZATION OF PARACETAMOL IN THE PRESENCE OF DIFFERENT GRADES OF POLYVINYLPYRROLIDONE

7.1 INTRODUCTION

One of the most common causes of habit modification is the presence of impurities in the crystallizing solution. The presence of a low amount of an effective additive in the crystallization medium can change the crystal size and shape. The additives used in crystallization procedures may be classified into several groups: surface active agents (surfactants), low molecular weight of organic or inorganic substances, long chain polymeric materials and proteinaceous substances (Mullin 1993).

There are several reports of attempts to change the crystal habit of a particular substance in the presence of additives during crystallization process. For example, the crystal habit of adipic acid was modified in the presence of anionic or cationic surfactants (Michael & Colville, 1960), or in the presence of alkanols or alkanoic acids (Fairbrother & Grant, 1978, 1979). Habit modification of paracetamol crystals in the presence of *p*-acetoxy-acetanillide, or in the presence of agar or gelatin was reported by Chow et al (1985) and Femi-Oyewo and Spring (1994), respectively. Mackaellar et al (1994a,b) demonstrated that the use of poloxamer 188 (a surfactant) during crystallization of ethyl *p*-hydroxybenzene, modified the size and habit of the obtained crystals.

In chapter 6, it was shown that polyvinylpyrrolidone (PVP) has potential as an additive during crystallization of paracetamol. It was demonstrated that in the presence of small amounts of PVP (<0.1% w/v), the crystal growth of paracetamol from water at 25°C was inhibited. In section 4.3.2, it was shown that crystallization of paracetamol by watering-out from its ethanolic solution at low temperature (3°C), produced a high degree of supersaturation. Therefore, this crystallization process is probably a suitable method for crystallization of paracetamol in the presence of PVP.

The aim of the work presented in this chapter was to study the effects of small amounts of different grades of PVP during crystallization of paracetamol by the watering-out method. Furthermore, the properties and solid state characteristics of the obtained crystals were investigated.

7.2 MATERIALS AND METHODS

7.2.1 MATERIALS

Paracetamol, different grades of PVP, ethanol, potassium iodide, iodine, citric acid and potassium bromide as described in section 2.1, were used.

7.2.2 METHODS

7.2.2.1 Crystallization procedures

The crystallization process used was similar to the method which was

introduced in section 4.2.2.1.1 as the watering-out crystallization method. Samples of paracetamol (5g) were dissolved in 12 ml of ethanol at 75°C. The temperature of the solutions were allowed to fall to 65°C. Then the solutions were added rapidly to 50 ml quantities of cold water at 3°C containing 0, 0.1, 0.3 or 0.5% w/v PVP of molecular weights of 2000, 10000 or 50000. The resultant solutions were thoroughly mixed with a glass rod and maintained at about 3±1°C in an ice-water bath with no agitation for five minutes. Then the solutions were gently stirred by means of a glass rod. After 10 minutes, the precipitated crystals were collected by filtration, using a sintered glass funnel No.3 under vacuum. The crystals were spread on glass petri dishes and dried for 24 h at 55°C. The dried crystals were stored in a desiccator, over silica gel, at room temperature before use.

7.2.2.2 Quantitative determination of PVP in the particles

The amount of PVP adsorbed onto the paracetamol particles crystallized from media containing PVP was determined by the photometric analysis of the PVP-iodide complex as described in section 2.2.6.3. Each test was carried out three times and the mean values are reported.

7.2.2.3 Scanning electron microscopy

Scanning electron micrographs of crystals and particle size measurements were obtained using a scanning electron microscope as described in section 2.2.5.

7.2.2.4 Differential scanning calorimetry (DSC), X-ray powder diffraction (XPD) and Infrared spectroscopy (IR)

DSC, XPD and IR studies were carried out, as described in sections 2.2.4.1, 2.2.2 and 2.2.3, respectively.

7.3 RESULTS AND DISCUSSION

7.3.1 INFLUENCE OF PVP ON INDUCTION TIME (TIME REQUIRED FOR APPEARANCE OF CRYSTALS)

Following the addition of the ethanolic solution of paracetamol to cold water containing different concentration of PVP, the time taken for appearance of the first visible particles (induction time) depended on the molecular weight and/or concentration of PVP in the solution (figure 7.1). With increasing molecular weight and/or concentration of PVP, the induction time increased. In the absence of PVP, crystals were observed within 15-20 s, whilst in the presence of 0.5% w/v of PVP 50000 this time was 115 s.

7.3.2 INFLUENCE OF PVP ON CRYSTAL RECOVERY

The recovery of paracetamol during crystallization in the presence of PVP is illustrated in figure 7.2. The recovery of paracetamol decreased as the molecular weight and/or the concentration of PVP in the crystallization medium increased. The recovery in the absence of PVP was 83.5% whilst in the presence of 0.5% w/v of PVP 50000 was 67.5%.

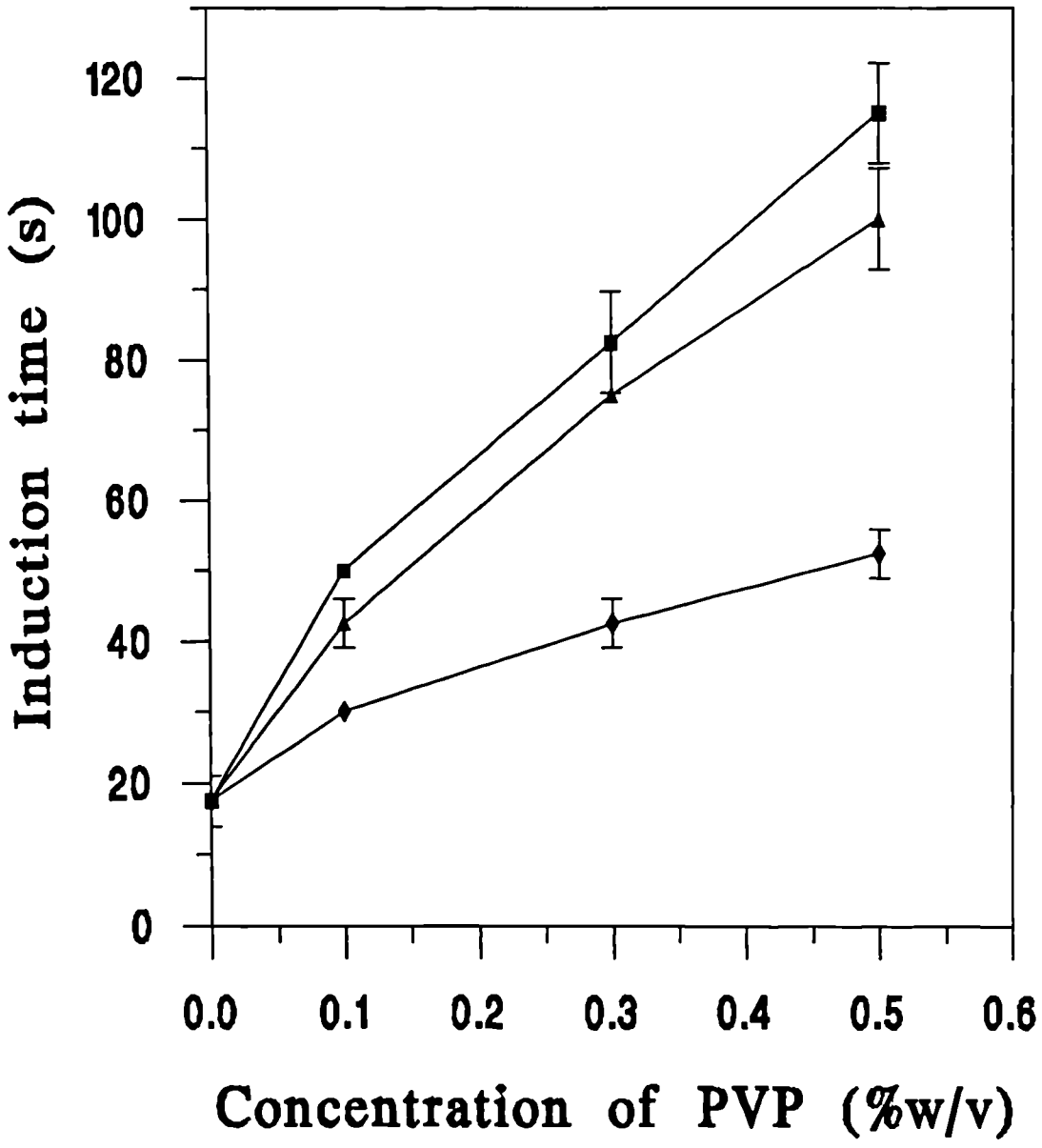


Figure 7.1 Induction time of crystallization as a function of concentration of: (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000.

7.3.3 AMOUNT OF PVP IN THE PARTICLES

The amount of PVP taken up by paracetamol particles crystallized from media containing different concentrations of various grades of PVP is presented in table 7.1. According to these results, by increasing the molecular weight and/or the concentration of PVP in the crystallization medium, the amount of PVP adsorbed onto the particles increased.

Table 7.1 The percentage (%w/w) of PVP adsorbed onto paracetamol particles crystallized in the presence of different concentrations of various grades of PVP.

	Concentration of PVP in crystallization medium (%w/v)		
	(0.1)	(0.3)	(0.5)
Molecular weight of PVP	AP[a]	AP[a]	AP[a]
2000	0.55±0.05	2.13±0.09	3.23±0.14
10000	0.89±0.05	3.21±0.07	3.96±0.06
50000	0.98±0.04	3.48±0.07	4.32±0.19

[a]AP=Amount of adsorbed PVP (%w/w)

7.3.4 INFLUENCE OF PVP ON THE MORPHOLOGY OF PARACETAMOL PARTICLES

Figures 7.3, 7.4 and 7.5 illustrate paracetamol particles crystallized from media containing different amounts of PVP 2000, PVP 10000 or PVP 50000, respectively. These figures clearly indicate that the use of PVP in the crystallization media, had a major effect on the morphology of paracetamol crystals as compared to particles obtained in the absence of PVP (figure 4.2).

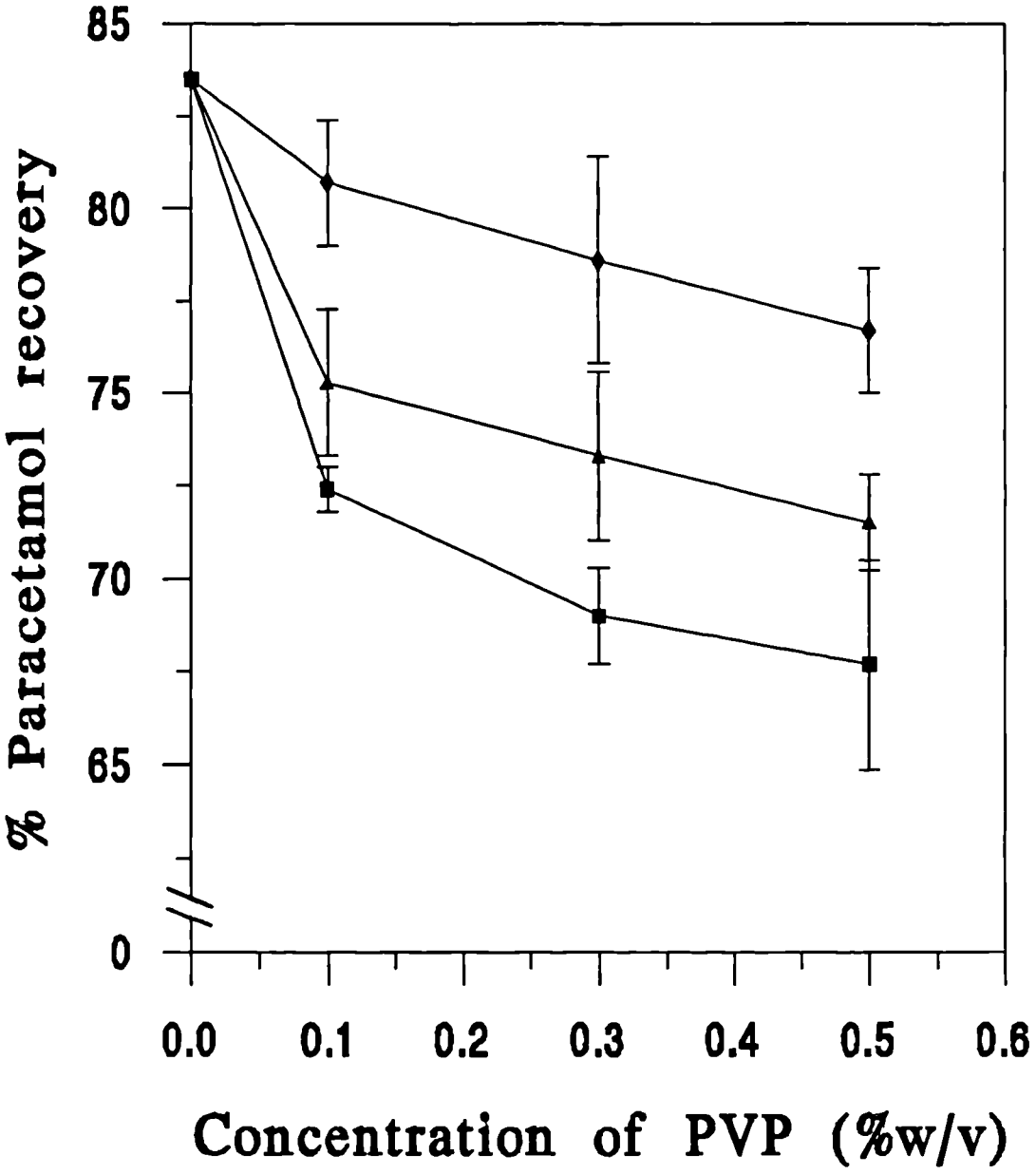


Figure 7.2 Paracetamol recovery as a function of concentration of: (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000.

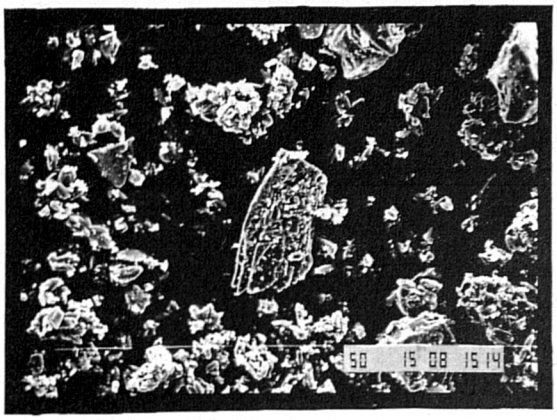
Paracetamol crystals obtained in absence of PVP were very thin and flaky, whereas those obtained in the presence of ≥0.3% w/v of PVP 10000 or PVP 50000 were near spherical in structure (figures 7.4b,c and 7.5b,c). With higher magnification, the spherical particles obtained in the presence of 0.5% w/v of PVP 10000 or PVP 50000 (figures 7.6b and c) seem to be agglomerates (clusters) of numerous fine finger-like (rod-shape) microcrystals which had stuck together. The particles obtained in the presence of PVP 2000 even at highest concentration of PVP (0.5% w/v) consisted of a fewer microcrystals which had stuck together (figure 7.6a).

7.3.5 ASSESSMENT OF PVP AS AN ADDITIVE DURING CRYSTALLIZATION OF PARACETAMOL

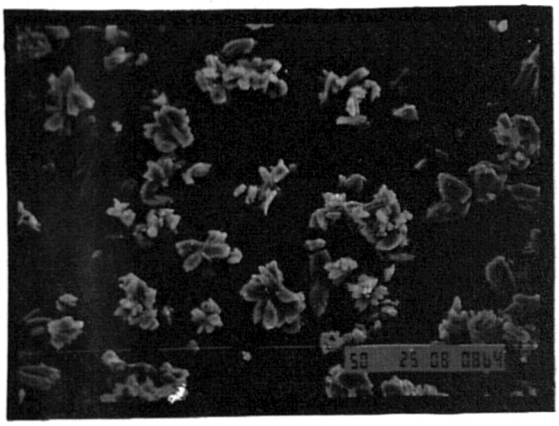
As described in section 1.2.5.1.1, active additives influence the crystallization process and produce crystals of a different shape to those formed from a pure solution. Furthermore, the active additives increase the induction time and also reduce the crystal growth and yield. These effects are attributed to the adsorption of additives onto the crystal surfaces (Davey, 1982).

Chow and Hsia (1991), Gordon and Chow (1992) and Chow et al (1995) reported that crystallization of phenytoin in the presence of three different ester homologues of diphenylhydantoin changed the crystal habit and caused a drastic reduction in crystal yield. These effects were attributed to the adsorption of additive onto the crystal faces of phenytoin. It was also suggested that the most active additive was the one which changed the crystal

(a)

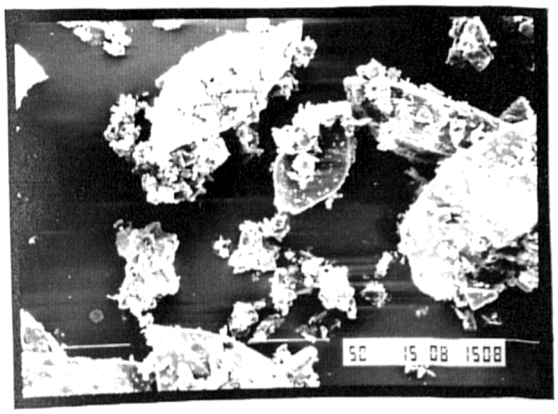


(b)

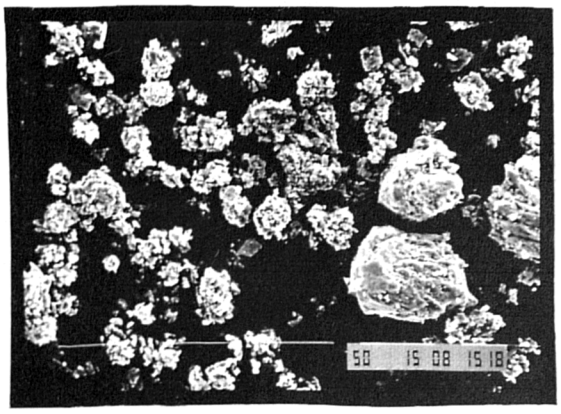


(c)

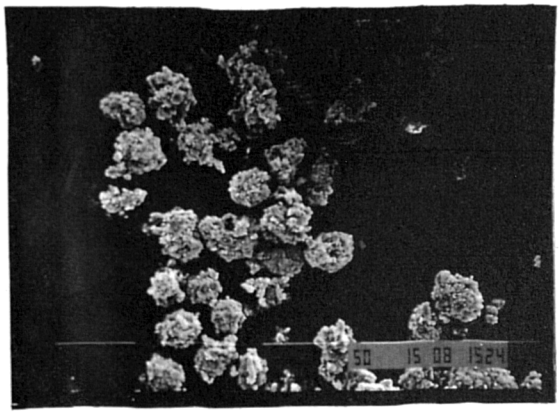
Figure 7.3 Micrographs of paracetamol particles crystallized in the presence of: a) 0.1, b) 0.3 or c) 0.5 %w/v of PVP 2000 (magnification ×200).



(a)

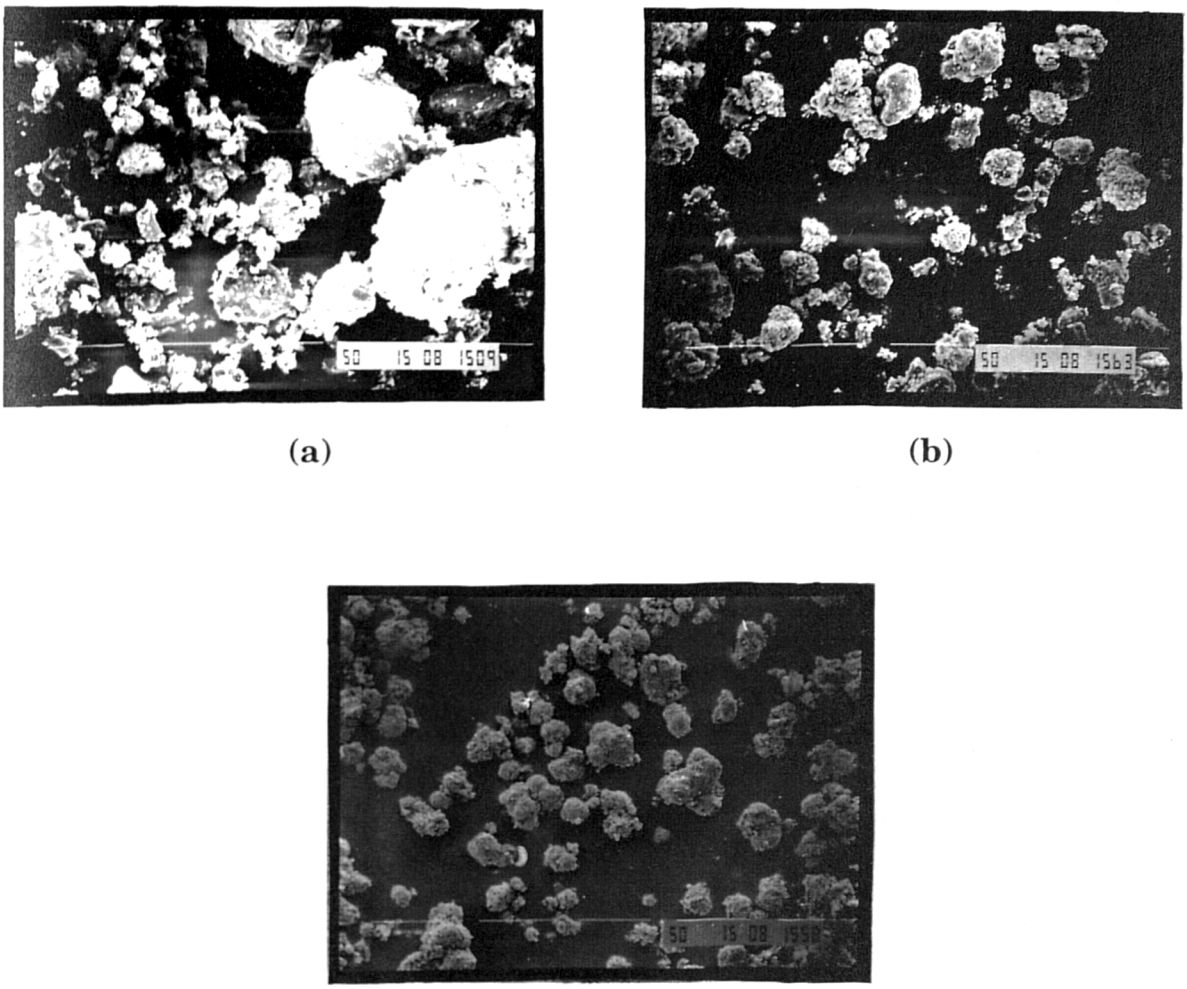


(b)



(c)

Figure 7.4 Micrographs of paracetamol particles crystallized in the presence of: a) 0.1, b) 0.3 or c) 0.5% w/v of PVP 10000 (magnification ×200).



(a) (b)

(c)

Figure 7.5 Micrographs of paracetamol particles crystallized in the presence of: a) 0.1, b) 0.3 or c) 0.5% w/v of PVP 50000 (magnification ×200).

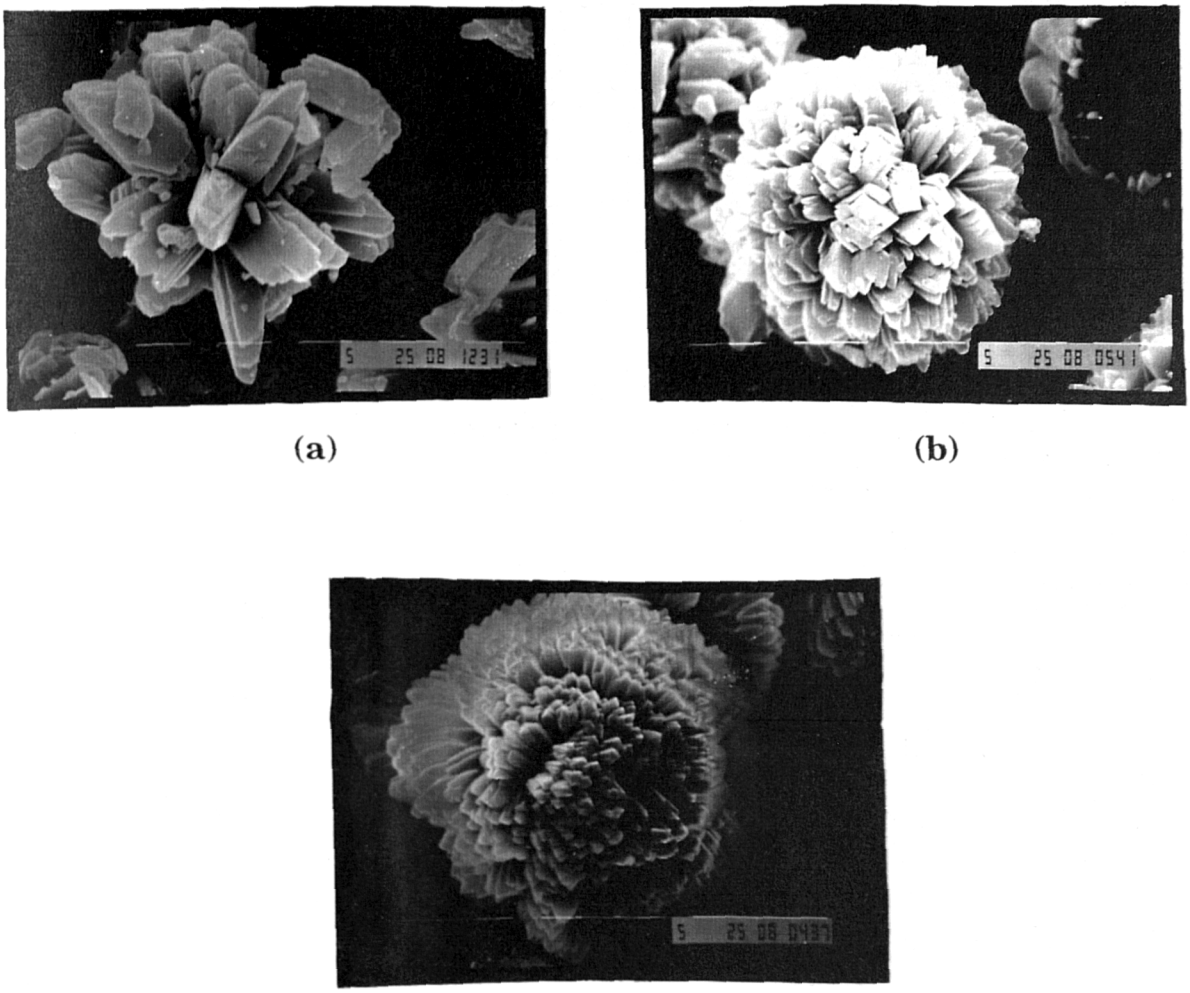


Figure 7.6 Micrographs of paracetamol particles crystallized from media containing 0.5% w/v of: a) PVP 2000, b) PVP 10000 or c) PVP 50000 (magnification ×1500).

habit at the lowest concentration and caused the most reduction in crystal yield. It has been reported that crystallization of paracetamol from water in the presence of agar or gelatin, changed the crystal habit of paracetamol and caused a decrease in crystal yield (Femi-Oyewo & Spring, 1994).

In the present study the observed changes in crystal habit of paracetamol (figures 7.3, 7.4 and 7.5), the delay in the appearance of crystals (figure 7.1), reduction in crystal yield (figure 7.2) and sorption of PVP by paracetamol particles (table 7.1), are indicative that PVP is an effective additive during the crystallization of paracetamol. It appeared that the highest molecular weight of PVP was the most effective additive. The relative effectiveness of the three grades of PVP, as considered by the parameters mentioned above, followed the order PVP 50000>PVP 10000>PVP 2000. In section 6.3.2, it was shown that higher molecular weights of PVP were more effective crystal growth inhibitor for paracetamol than lower molecular weights of PVP.

7.3.6 MECHANISM OF ACTION OF PVP DURING CRYSTALLIZATION OF PARACETAMOL

Impurities can influence a crystallization process by adsorption onto the surfaces of growing crystals and/or by changing the equilibrium solubility of solute and therefore the degree of supersaturation of system (Mullin, 1993). Increase in solution viscosity can also affect the crystallization process and so reduce the crystal growth rate and therefore change the crystal properties (El-Bary et al, 1990; Mackellar et al, 1994a).

In section 6.3.1, it was shown that PVP 10000 of concentration of 0.1% w/v had no significant effect on solubility of paracetamol. The viscosities of 0.1-0.5% w/v solutions of PVP 2000, PVP 10000 or PVP 50000 do not show any significant difference to pure water (Kollidon, Technical information, 1992). Therefore, the observed effects of PVP during crystallization of paracetamol may be attributed to the adsorption of PVP onto the surfaces of growing crystals. Uptake of PVP by paracetamol particles (table 7.1) is also indicative of adsorption of PVP onto the paracetamol particles. In section 6.3.2, it was shown that PVP had a strong inhibitory effect on the precipitation of paracetamol crystals. This effect was attributed to adsorption of PVP onto the paracetamol nuclei.

Simonelli et al (1970) reported that PVP is a strong crystal growth inhibitor for sulphathiazole. This inhibitory effect was attributed to adsorption of PVP onto the surfaces of paracetamol crystals. Mackellar et al (1994a, b) reported that crystallization of ethyl *p*-hydroxybenzene in the presence of small amounts of a series of poloxamers, caused a decrease in the crystal size and changed the crystal habit from plate to prismatic. It was found that poloxamers exerted their effects through adsorption at crystal faces causing a subsequent inhibition of crystal growth.

7.3.7 SOLID STATE CHARACTERISTICS OF PARACETAMOL PARTICLES CRYSTALLIZED IN THE PRESENCE OF 0.5% W/V DIFFERENT GRADES OF PVP

7.3.7.1 Particle size distribution

The size distribution of diameter of agglomerated particles crystallized in the presence of 0.5% w/v of different grades of PVP is illustrated in figure 7.7. In general, the diameter of these particles was between 10-40 μm. Figures 7.6b and c indicate that each agglomerated particle crystallized in the presence of 0.5% w/v of PVP 10000 or 50000 consisted of hundreds of rod-shape microcrystals which had stuck together. The thickness of these microcrystals was about 1-2 μm.

7.3.7.2 X-ray powder diffraction

The X-ray powder diffraction spectra of untreated paracetamol and samples crystallized from media containing 0.5% w/v of different grades of PVP (figure 7.8) exhibited essentially similar diffraction patterns (2θ values), suggesting that particles crystallized in the presence of PVP did not undergo structural modifications. However, the differences in the relative intensities of their peaks, may be attributed to differences in the crystal sizes and habits of the samples (El-Said, 1995; Marshall & York, 1989).

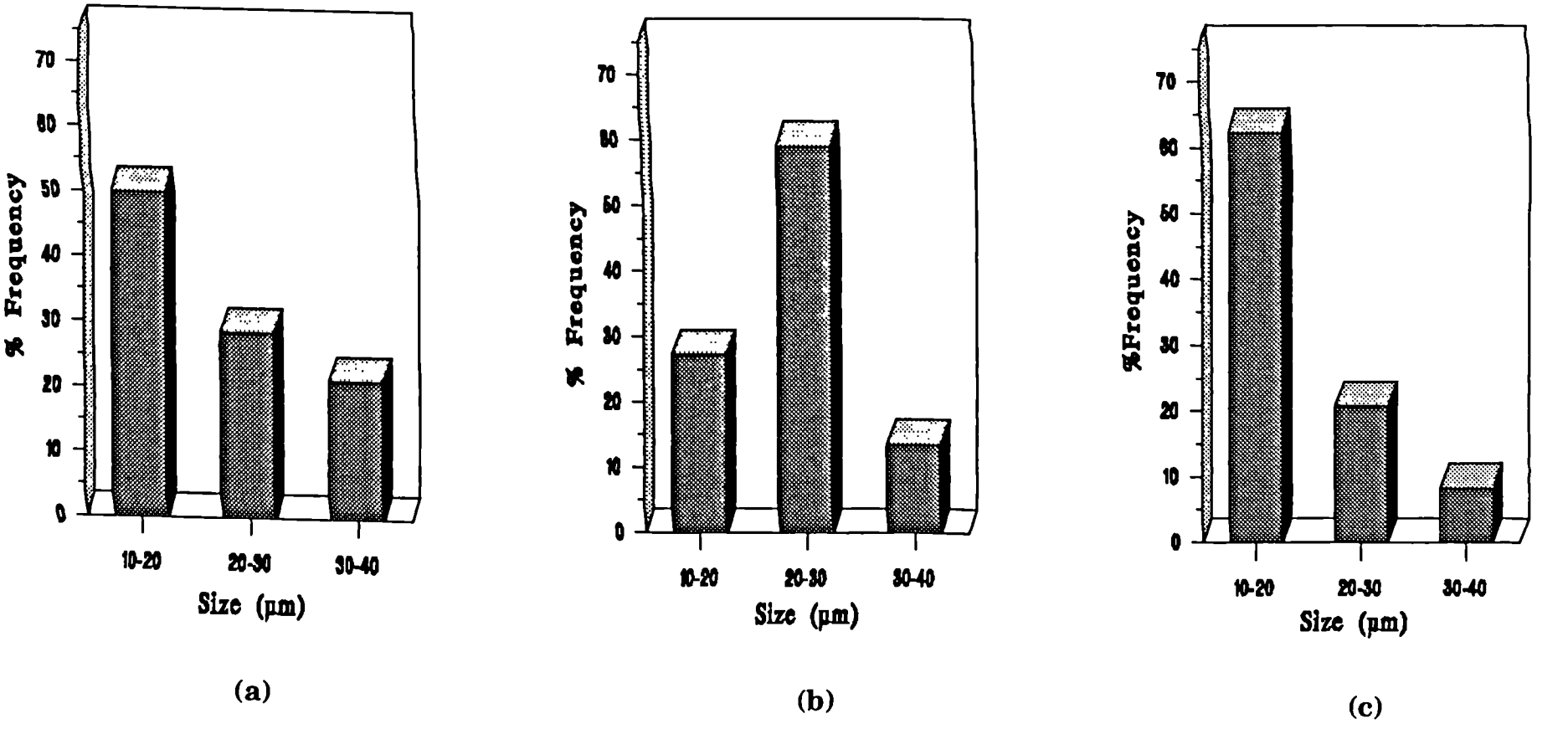


Figure 7.7 The size distribution of diameter of agglomerated particles crystallized in the presence of 0.5% w/v of: a) PVP 2000, b) PVP 10000 or c) PVP 50000.

7.3.7.3 Infrared spectroscopy

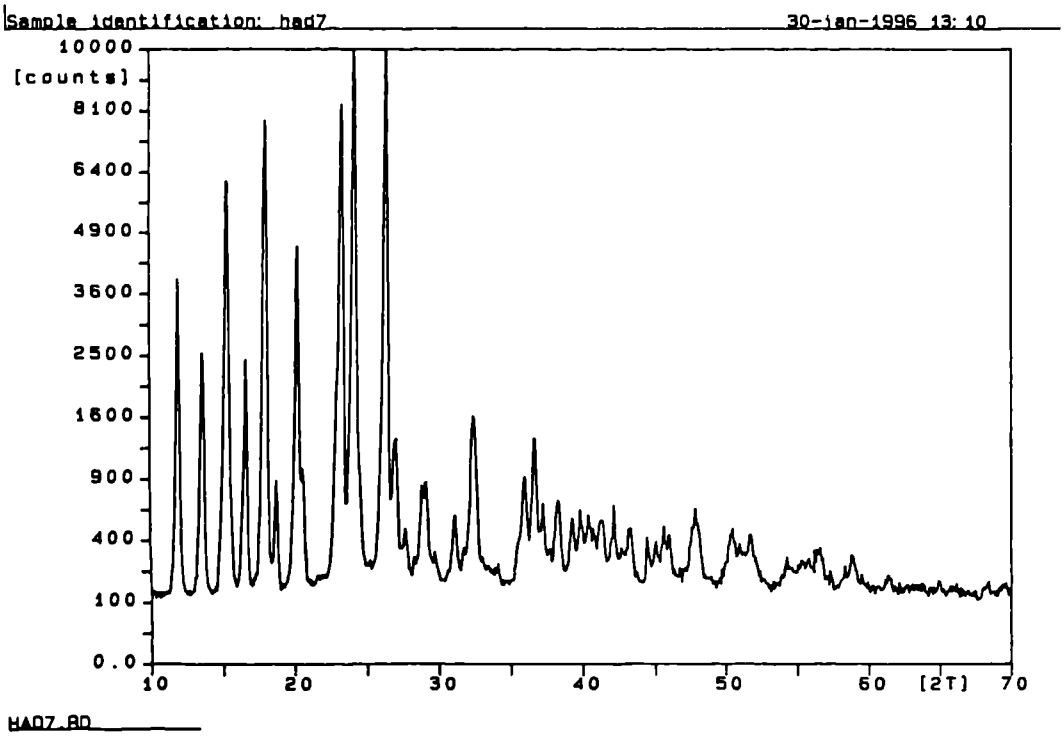
The principal absorption bands of infrared spectra of untreated paracetamol and particles obtained in the presence of 0.5% w/v different grades of PVP (figure 7.9), were similar, suggesting that their structure and conformation were similar.

7.3.7.4 Differential scanning calorimetry

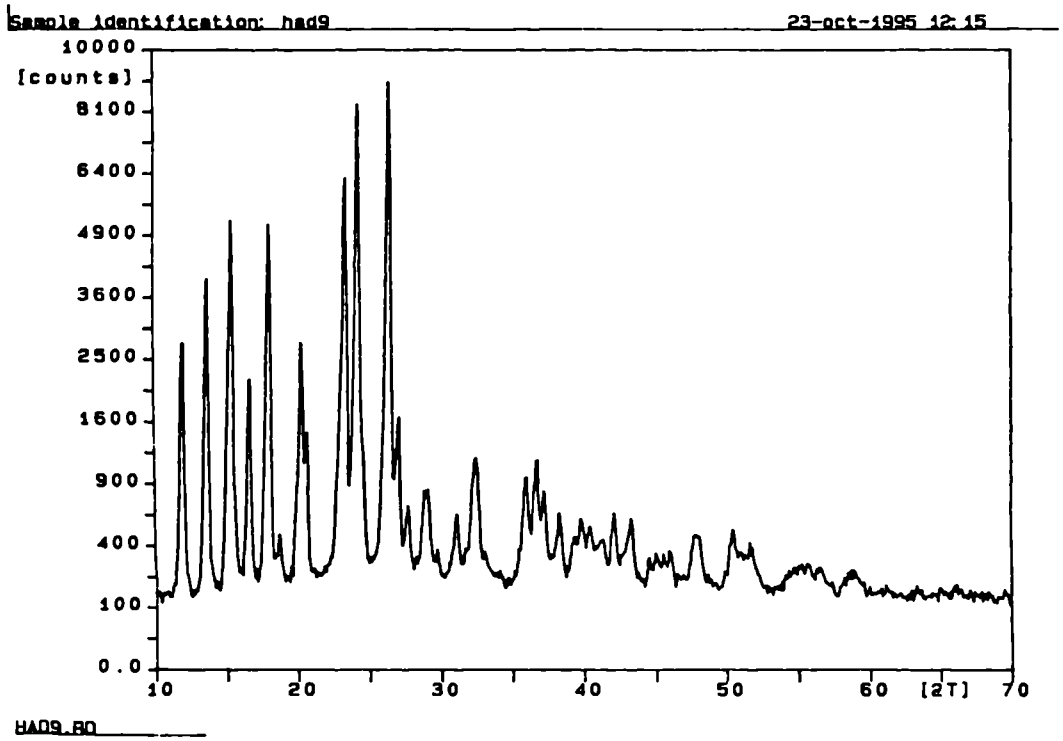
Differential scanning calorimetry of untreated paracetamol and samples crystallized from media containing 0.5% w/v of different grades of PVP are shown in figure 7.10. All samples showed a sharp melting point with flat baseline which indicated that no events such as hydration, solvation or polymorphic transition had occurred during crystallization of the particles.

However, the DSC scans (figures 7.10c,d) show that particles crystallized in the presence of PVP started to melt at lower temperature as compared to untreated paracetamol (figure 7.10a). The mean values of the onsets of melting points and enthalpies of fusion for untreated paracetamol and samples obtained from media containing different grades of PVP are presented in table 7.2.

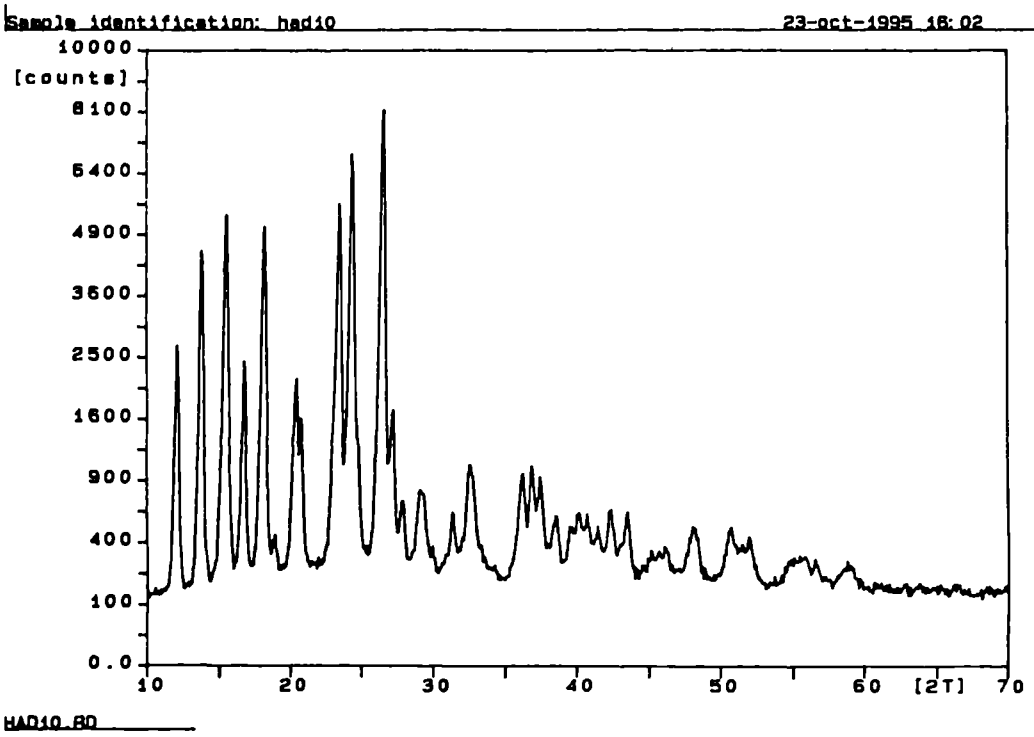
(a)


Sample identification: had7
30-jan-1996 13:10
[counts]
10000
8100
6400
4900
3600
2500
1600
900
400
100
0.0
10
20
30
40
50
60
[2T]
70
HAD7.RD

(b)


Sample identification: had9
23-oct-1995 12:15
[counts]
10000
8100
6400
4900
3600
2500
1600
900
400
100
0.0
10
20
30
40
50
60
[2T]
70
HAD9.RD

(c)



(d)

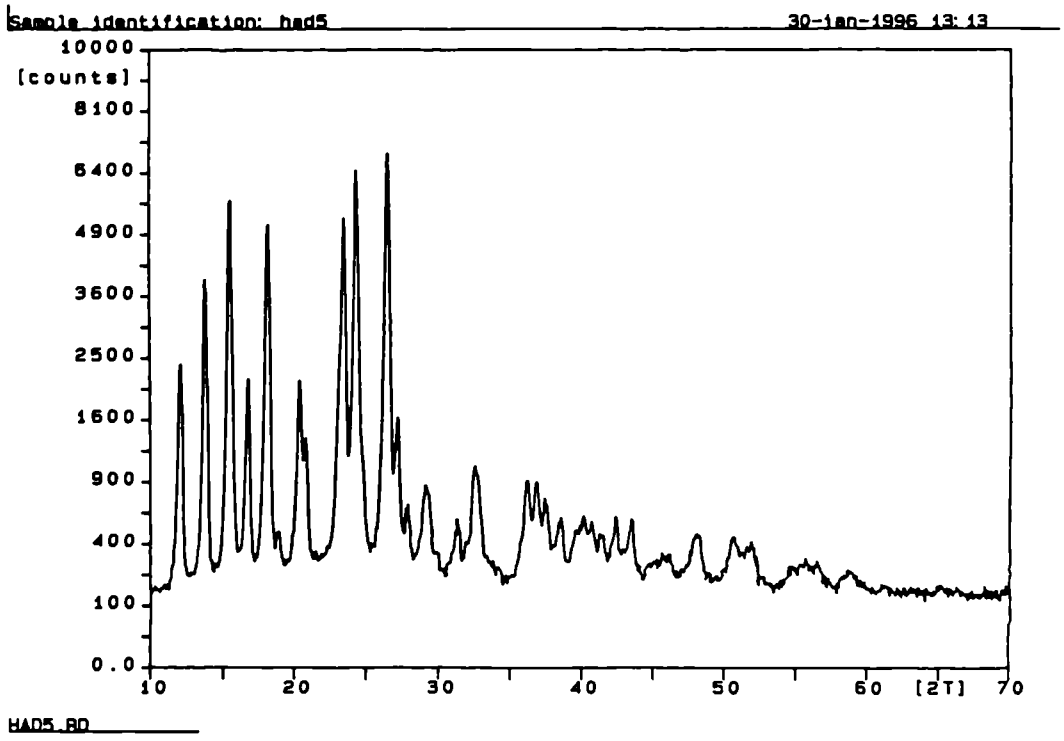
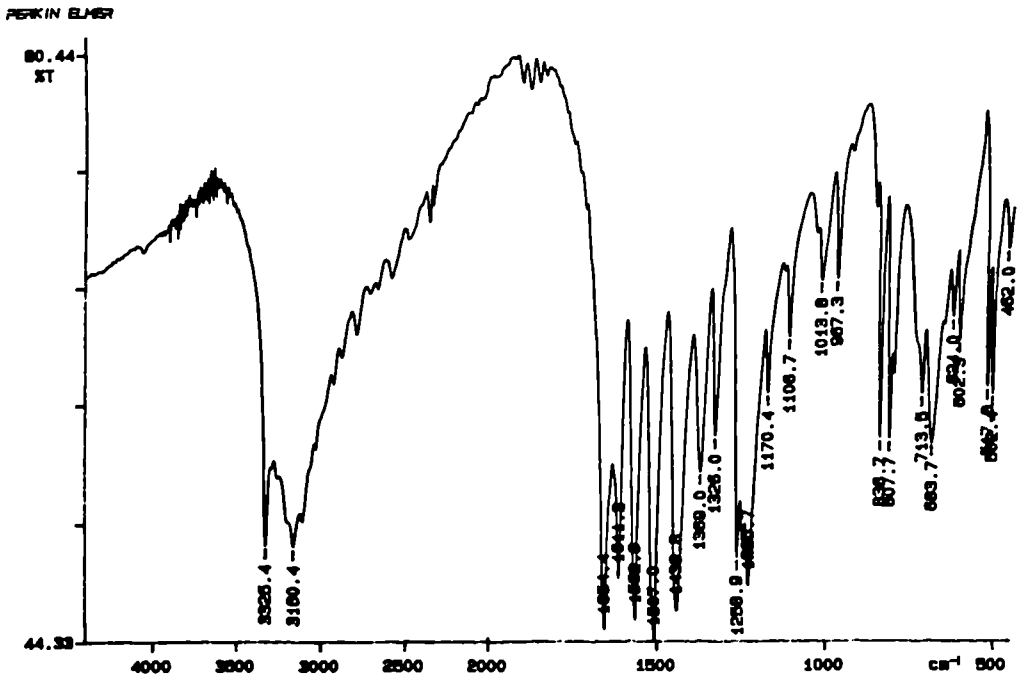


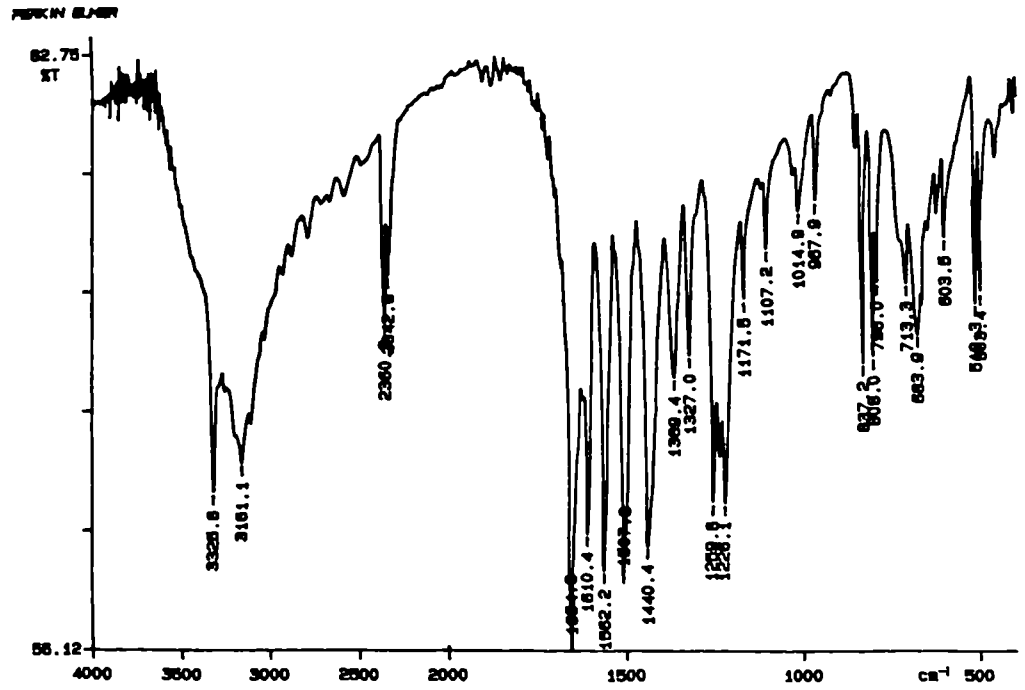
Figure 7.8 The XPD spectra of: a) untreated paracetamol particles, and paracetamol crystallized in the presence of 0.5% w/v of (b) PVP 2000, (c) PVP 10000 or (d) PVP 50000.

(a)



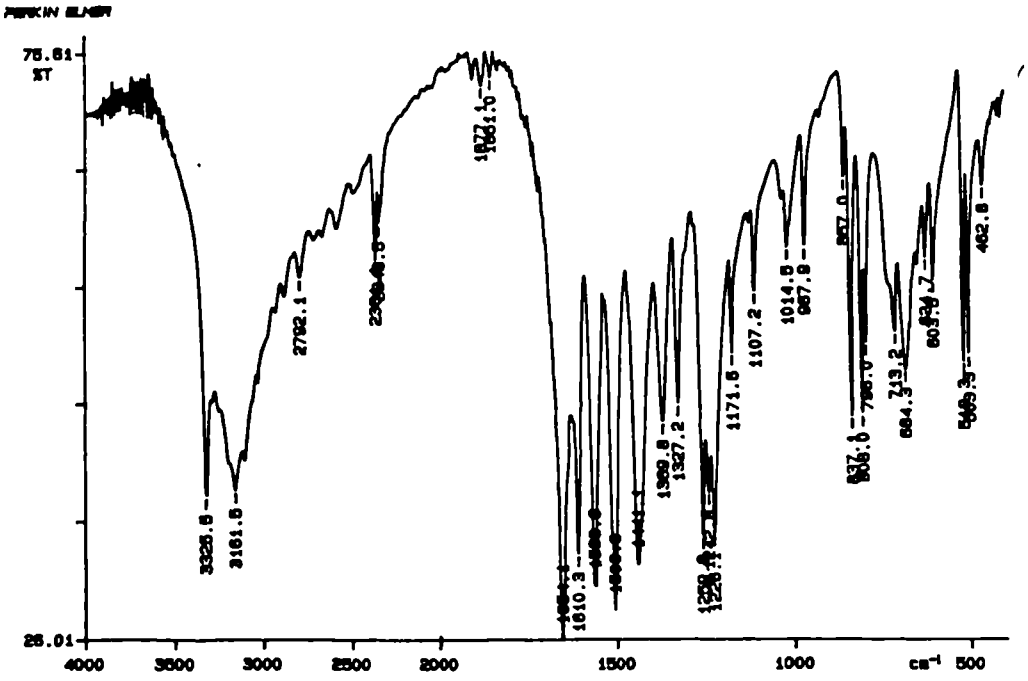
94/10/20 12:42
X: 16 scans, 4.0cm-1, smooth

(b)



94/07/27 12:06 R Edwards
Y: 64 scans, 4.0cm-1, flat, smooth
K2

(c)



(d)

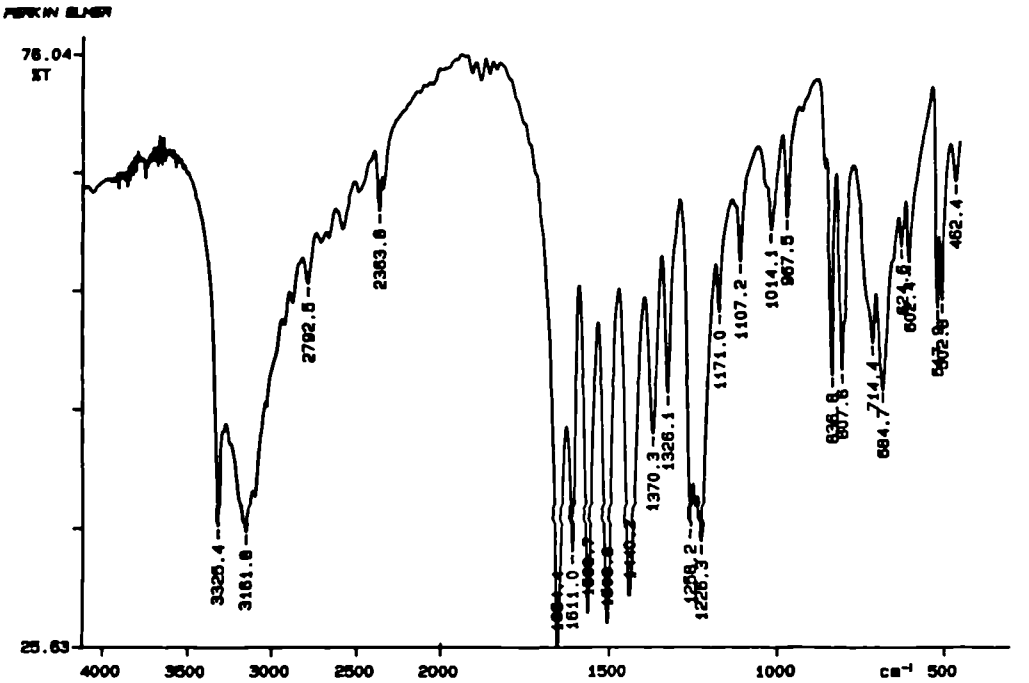


Figure 7.9 The IR spectra of a) untreated paracetamol particles, and paracetamol crystallized from medium containing 0.5% w/v of (b) PVP 2000, (c) PVP 10000 and (d) PVP 50000.

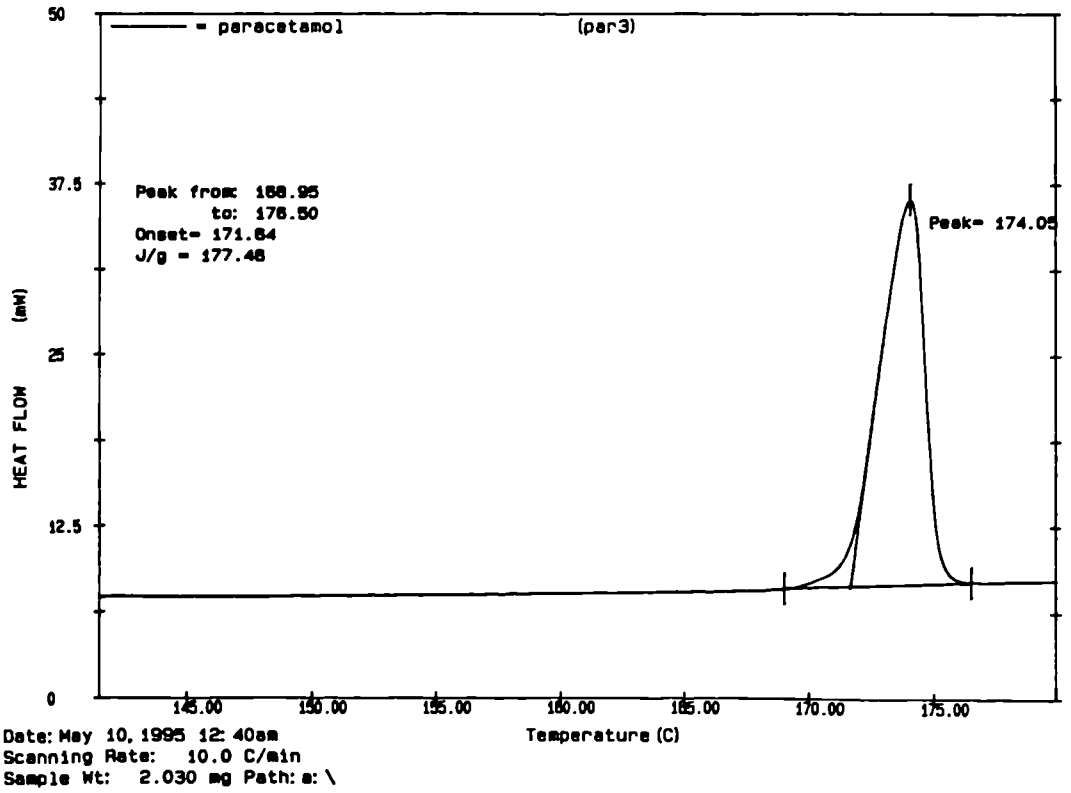
Table 7.2 The onset of melting point (T_m) and enthalpy of fusion (ΔH_f) for untreated paracetamol and particles crystallized in the presence of 0.5% w/v of different grades of PVP.

	Onset of T_m (±SD) (°C)	ΔH_f (±SD) (J/g)
Untreated crystals	171.6±0.2	176.1±2.2
Particles obtained in presence of PVP 2000	171.4±0.3	155.1±3.3
Particles obtained in presence of PVP 10000	171.2±0.3	148.5±5.7
Particles obtained in presence of PVP 50000	170.9±0.2	138.3±4.3

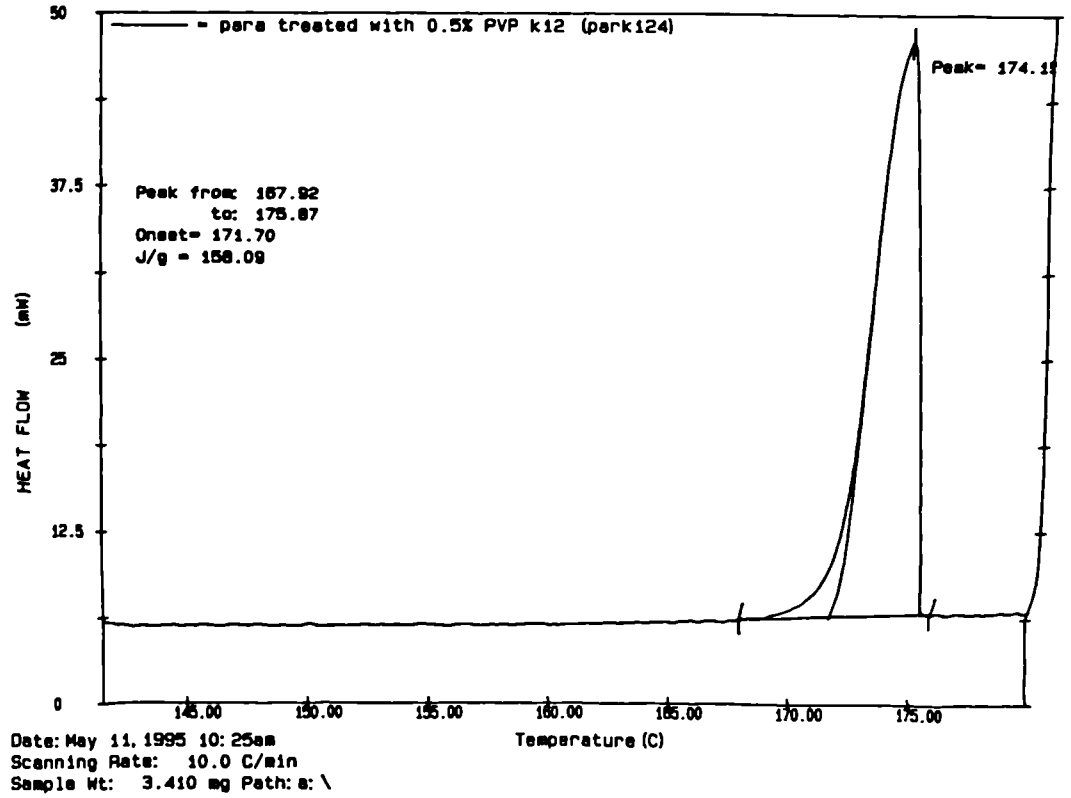
Table 7.2 indicates that the onsets of melting point and enthalpies of fusion of paracetamol crystallized in the presence of PVP decreased by 0.2-0.7°C and 21-38 J/g, as compared to the untreated samples. Decrease in enthalpy of fusion and onset of melting point may be attributed to the presence of amorphousness in the particles, or due to weakening and disruption of the crystal lattice and order, or in this case, may be attributed to an interaction between paracetamol and PVP in the particles. It was shown that particles crystallized in the presence of PVP, contained small amounts of PVP (table 7.1).

In section 6.3.5.2, the DSC was carried out for physical mixtures of paracetamol and PVP and their onsets of melting points and enthalpies of

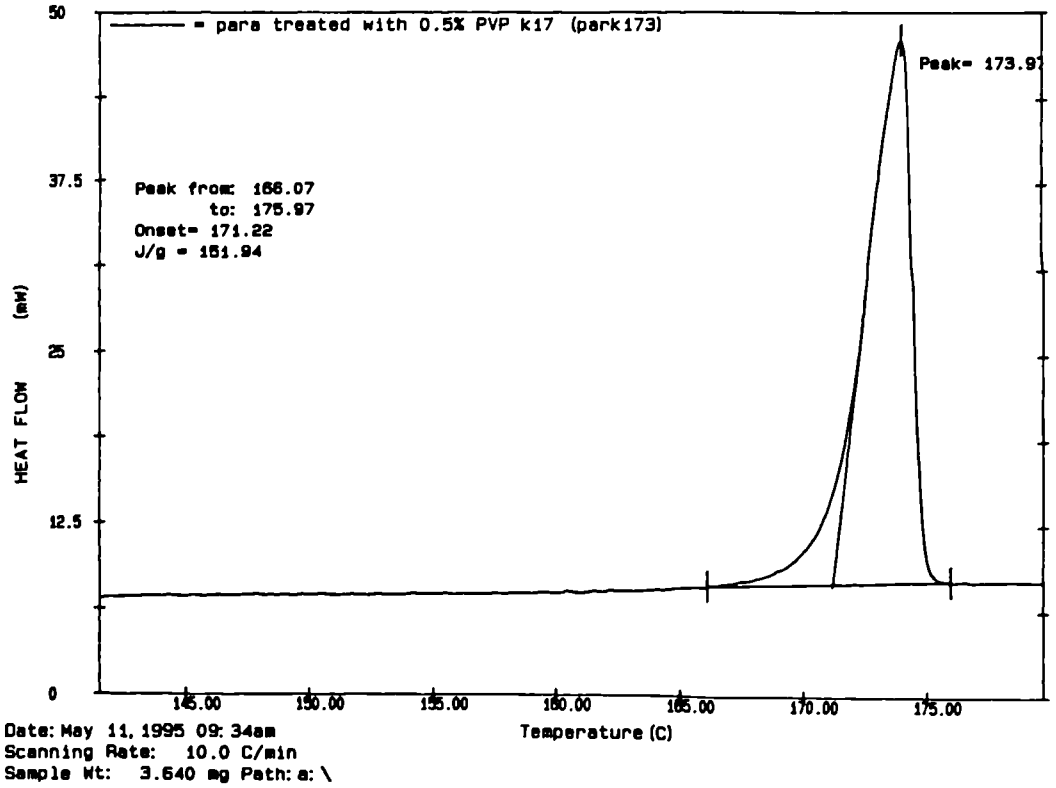
(a)


50
37.5
25
12.5
0
HEAT FLOW (mW)
= paracetamol (par3)
Peak from: 168.95
to: 176.50
Onset= 171.64
J/g = 177.48
Peak= 174.05
145.00
150.00
155.00
160.00
165.00
170.00
175.00
Temperature (C)
Date: May 10, 1995 12: 40am
Scanning Rate: 10.0 C/min
Sample Wt: 2.030 mg Path: a: \

(b)


50
37.5
25
12.5
0
HEAT FLOW (mW)
= para treated with 0.5% PVP k12 (park124)
Peak from: 167.82
to: 175.87
Onset= 171.70
J/g = 158.09
Peak= 174.1
145.00
150.00
155.00
160.00
165.00
170.00
175.00
Temperature (C)
Date: May 11, 1995 10: 25am
Scanning Rate: 10.0 C/min
Sample Wt: 3.410 mg Path: a: \

(c)



(d)

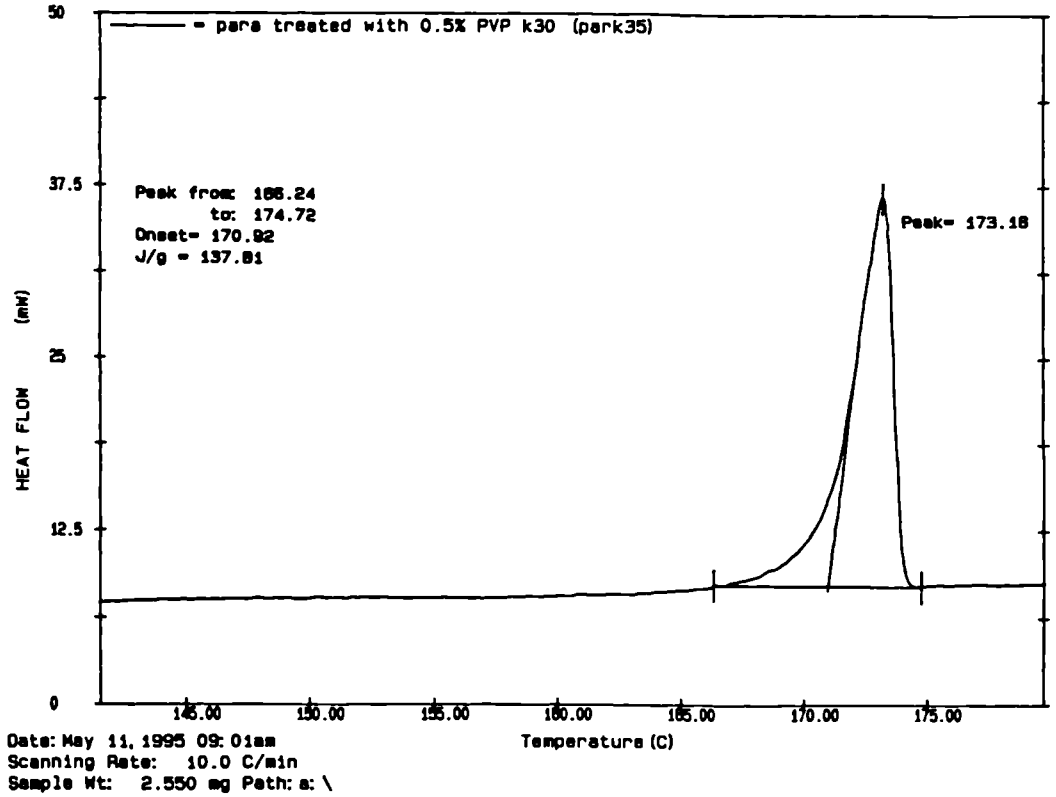


Figure 7.10 DSC scans of a) untreated paracetamol crystals and paracetamol crystallized from media containing 0.5% w/v of: (b) PVP 2000, (c) PVP 10000 or (d) PVP 50000.

fusion were given in table 6.3. These data (table 6.3) clearly indicated that the enthalpies of fusion of paracetamol decreased as the proportion of PVP in the physical mixtures increased. According to table 7.1 the crystals of paracetamol formed in the presence of PVP 50000 contained 4.3% of PVP. The values of enthalpy and onset of temperature of these particles (table 7.2) are similar to those of the physical mixture containing 5% PVP 50000 (table 6.3). It is likely therefore that the low enthalpies of fusion for paracetamol crystallized in the presence of PVP (table 7.2) are not due to amorphousness or crystal disruption. Additionally data (IR and XPD) confirmed that no structural modifications occurred in the samples crystallized in the presence of PVP.

7.4 CONCLUSIONS

It was found that PVP is an effective additive during crystallization of paracetamol and significantly influenced the crystallization process and changed the crystal habit. These effects were attributed to adsorption of PVP onto the surfaces of growing crystals. It was found that the higher molecular weights of PVP (PVP 10000 and PVP 50000) were more effective additives than lower molecular weight PVP (PVP 2000).

Paracetamol particles obtained in the presence of 0.5% w/v of PVP 10000 or PVP 50000 had near spherical agglomerated structure and consisted of numerous rod-shape microcrystals which had stuck together. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals.

DSC, XPD and IR experiments showed that paracetamol particles crystallized in the presence of PVP, did not undergo structural modifications compared to untreated paracetamol crystals.

CHAPTER 8. COMPACTION PROPERTIES OF PARACETAMOL CRYSTALLIZED IN THE PRESENCE OF POLYVINYLPYRROLIDONE

8.1 INTRODUCTION

There are several reports in the pharmaceutical literature of attempts to change the morphology of drug crystals using alternative crystallization procedures to improve their compaction properties. Examples include spherical crystallization, which transforms crystalline drugs into agglomerated forms (Morishima et al, 1994; Gordon & Chowhan 1990; Guillaume & Guyot-Herman, 1993), crystallization from different solvents to produce different crystal habit (Gordon & Amin 1984) and incorporation of additives by co-precipitation (Kaul et al 1992).

Attempts have been made to modify the paracetamol crystals using different crystallization techniques, to improve its compaction properties (Fachaux et al 1992, 1993; Di Martino et al 1994, 1995; Abdelilah et al 1995). In chapter 4 two modified forms of paracetamol crystals (thin plate-like and polyhedral crystals) were prepared. These crystals did not exhibit any improvement in their compaction properties compared to untreated paracetamol (see chapter 5). The aims of the work presented in this chapter were to investigate the compaction properties of paracetamol particles crystallized in the presence of different grades of PVP, as described in chapter 7.

8.2 MATERIALS AND METHODS

8.2.1 MATERIALS

Paracetamol particles crystallized in the presence of 0.1, 0.3 or 0.5% w/v of PVP of molecular weight 2000, 10000 or 50000, as described in chapter 7, were used. Several batches of each crystals were combined prior to study. Untreated paracetamol, PVP of molecular weight 50000 and magnesium stearate, as explained in chapter 2, were also used for this part of study.

8.2.2 METHODS

8.2.2.1 Particle size fractions

Sieved fractions of paracetamol particles crystallized in the presence of 0.5% w/v of different grades of PVP (<90 μm), untreated paracetamol crystals (<90 μm), PVP 50000 (<45 μm) and magnesium stearate (<45 μm) were obtained as detailed in section 2.2.13. Particles crystallized in the presence of 0.1 or 0.3% w/v of different grades of PVP were used unsieved as harvested from crystallization medium. These particles had different ranges of size and therefore it was impossible to obtain a specific sieved fraction for each of them.

8.2.2.2 Preparation of physical mixtures

In order to investigate the effect of addition of PVP to paracetamol, on the crushing strength of tablets, sieved fractions of paracetamol (<90 μm) with

different contents of PVP 50000 (<45 μm) were mixed using a tumbler mixer prior to compression.

A useful method to predict the mechanism of compaction of particles is to determine the crushing strength of tablets with and without magnesium stearate (Duberg & Nystrom, 1982). Sieved fractions of paracetamol (<90 μm) with 0.5% w/w of magnesium stearate (<45 μm) were mixed using a tumbler mixer for 1 h. This long mixing time was chosen to provide a layer or film of magnesium stearate upon the surfaces of paracetamol particles (Bolhuis et al, 1975).

8.2.2.3 Compression

All the samples were dried in an oven at 55°C for 24 h and then stored in tightly closed jars before compression. Compression was carried out using a compaction simulator (section 2.2.11). Four tablets, 400 mg weight each, were made at compression speeds of 10, 50, 100 or 250 mm s^{-1} up to a maximum compaction force of 30 kN.

8.2.2.4 Crushing strength and capping tendency of tablets

The crushing strength of tablets were determined 24 h after compaction, as described in section 2.2.14. Tablets were assessed visually for capping by observation of the final tablets for horizontal striations. The tablets were divided into four groups: no capping (-), low capping (+), high capping (++) and very high capping (+++).

8.2.2.5 Analyses of compaction data

Analyses of the data according to the Heckel equation were carried out as detailed in section 2.2.12.2. Mean yield pressures (MYP), the relative densities of powders at zero pressure (D_o) and before appreciable load (D_a), and the extents of particle rearrangement (D_b) were determined. The plastic and elastic energies were measured using energy analyses on the force-punch separation plots (section 2.2.12.1). The percentages of elastic recovery in the die at different compaction forces were determined, as detailed in section 2.2.12.3. The results of analysis of compaction data of untreated paracetamol particles, <90 μm (chapter 3), are included in this chapter for comparison.

8.3 RESULTS AND DISCUSSION

8.3.1 CRUSHING STRENGTHS OF PARACETAMOL TABLETS

8.3.1.1 Influence of compression force on the crushing strength of tablets

The effects of compression force on the crushing strengths of tablets made from paracetamol particles crystallized in the presence of different amounts of PVP of molecular weight 2000, 10000 or 50000 are shown in figures 8.1, 8.2 and 8.3, respectively. The tendency of tablets made from these particles to cap are presented in table 8.1. In chapter 3 it was shown that tablets made from untreated paracetamol were very weak with no measurable hardness and had a high tendency to cap. The data (figures 8.1, 8.2, 8.3 and table 8.1)

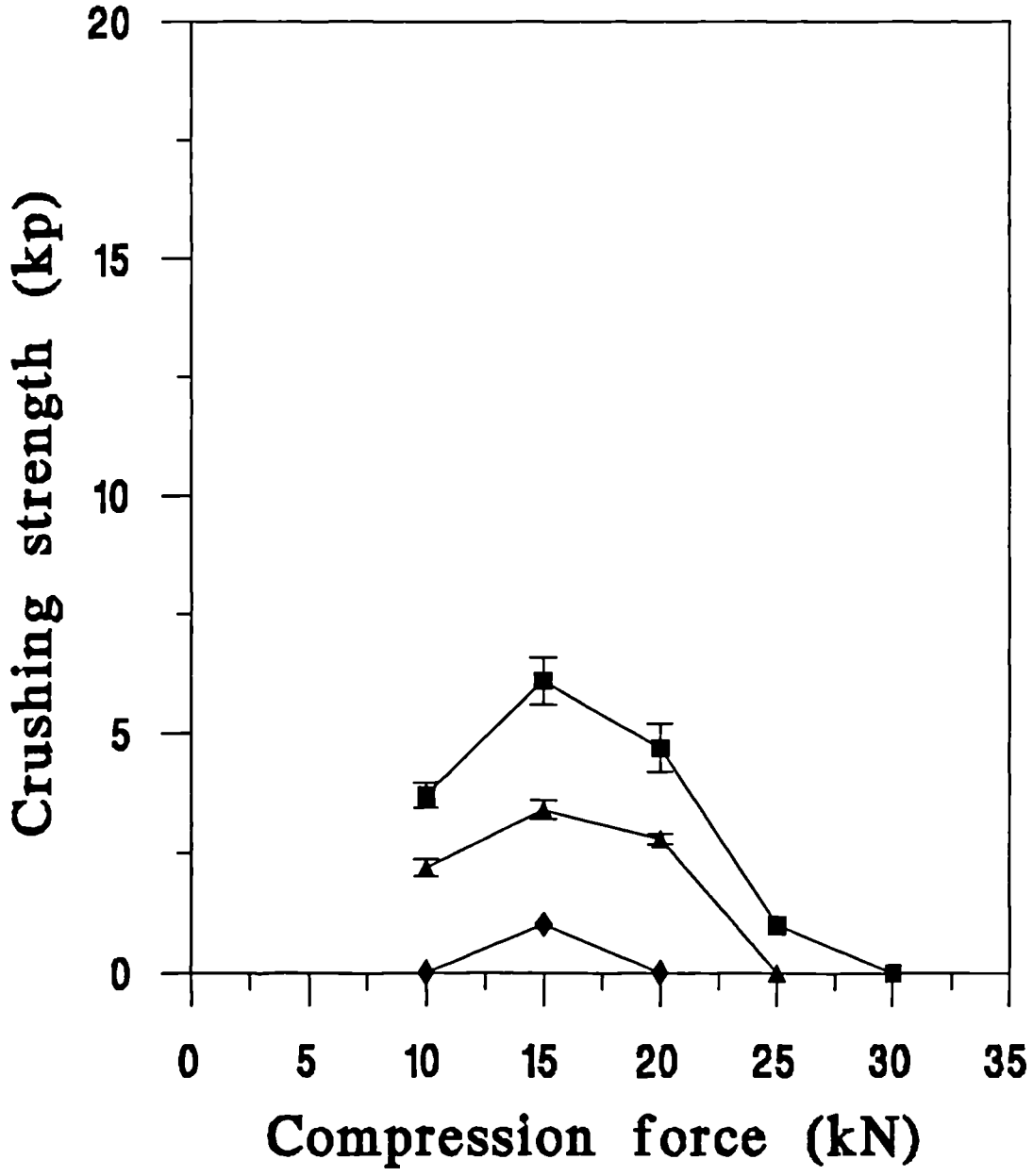


Figure 8.1 Effect of compression force on the crushing strengths of tablets prepared from paracetamol crystallized in the presence of: (♦) 0.1, (▲) 0.3 or (■) 0.5% w/v of PVP 2000, at a compression speed of 10 mm s^{-1}.

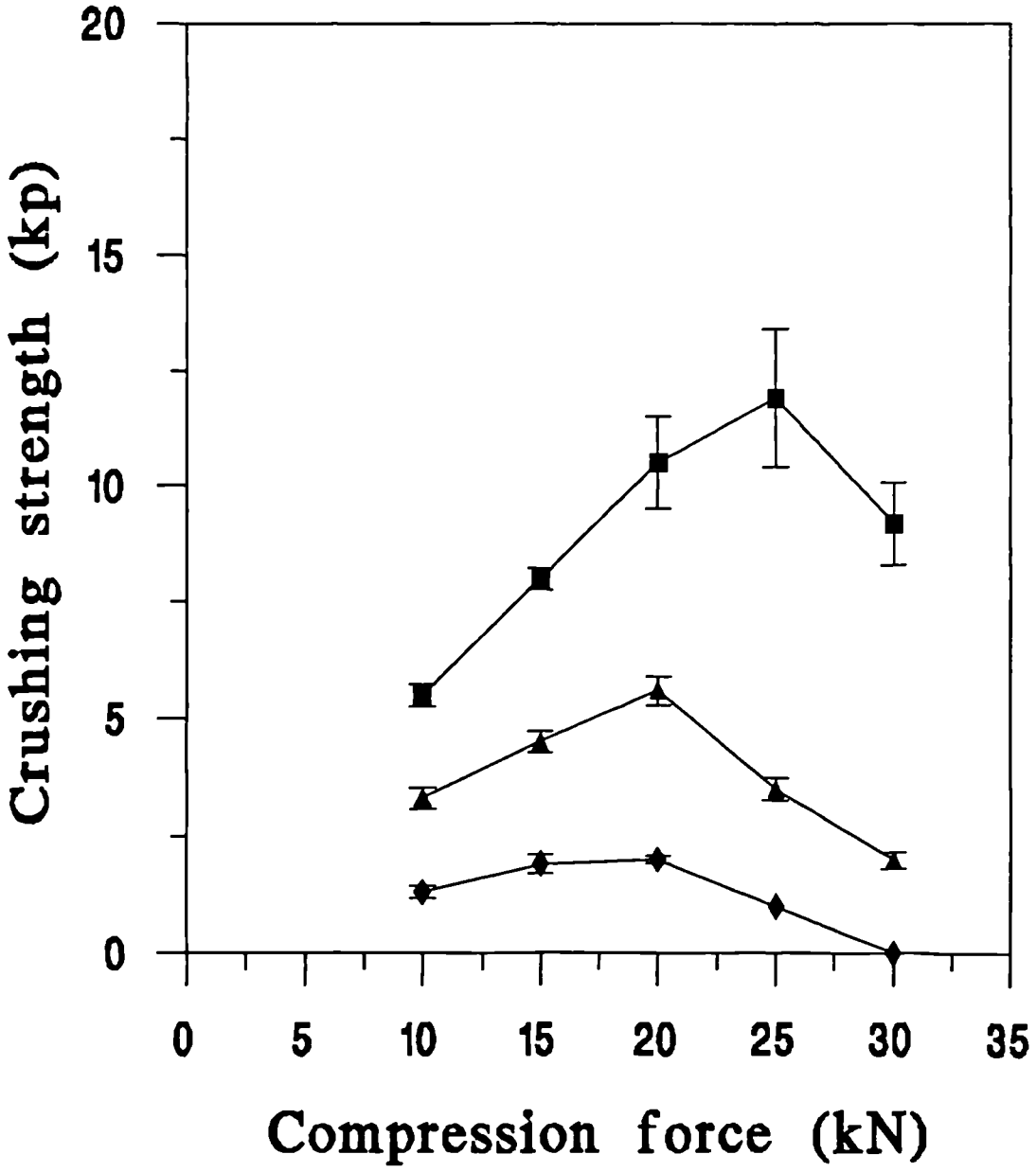


Figure 8.2 Effect of compression force on the crushing strengths of tablets prepared from paracetamol crystallized in the presence of: (♦) 0.1, (▲) 0.3 or (■) 0.5% w/v of PVP 10000, at a compression speed of 10mm s^{-1}.

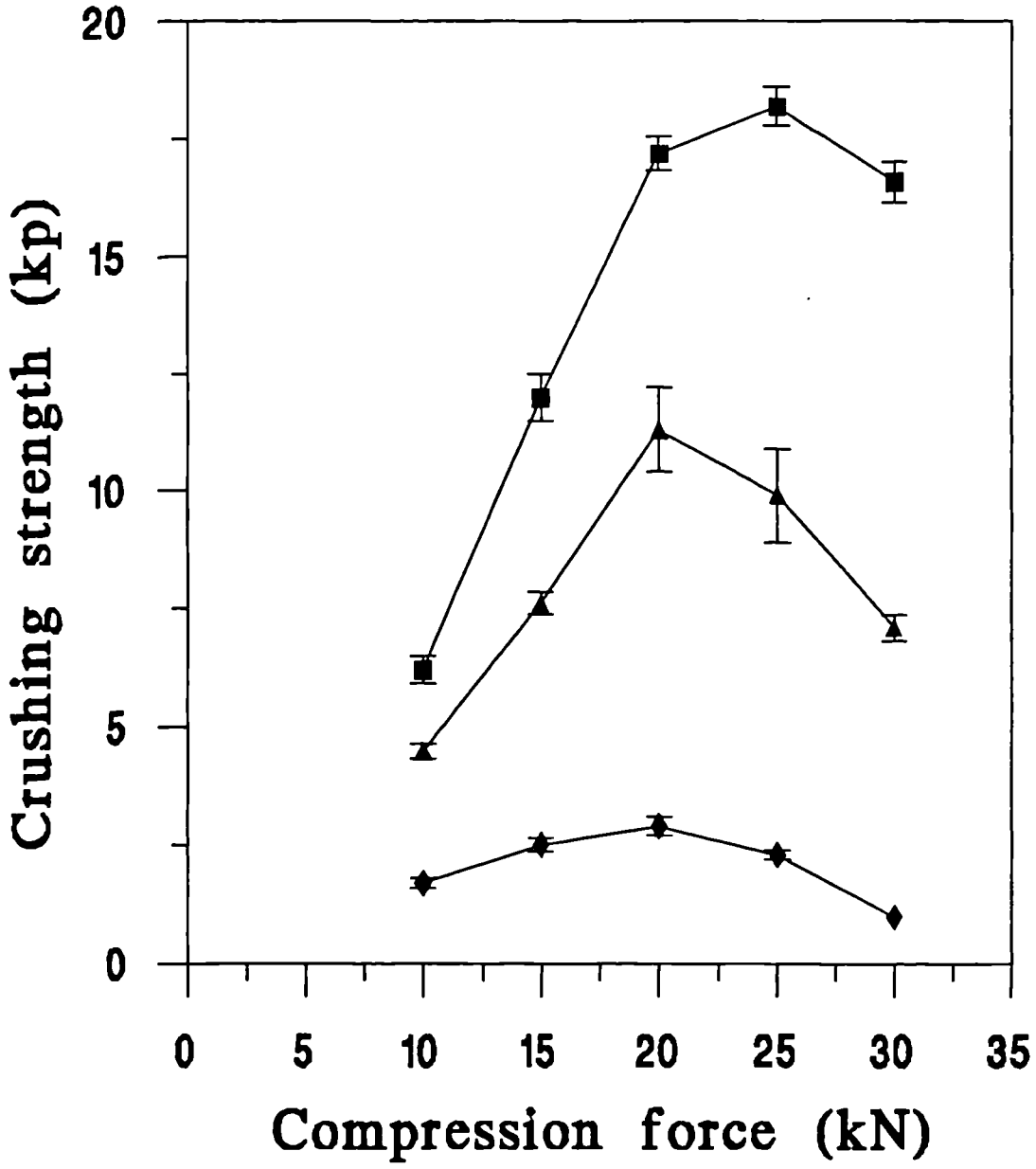


Figure 8.3 Effect of compression force on the crushing strengths of tablets prepared from paracetamol crystallized in the presence of: (♦) 0.1, (▲) 0.3 or (■) 0.5% w/v of PVP 50000, at a compression speed of 10 mm s^{-1}.

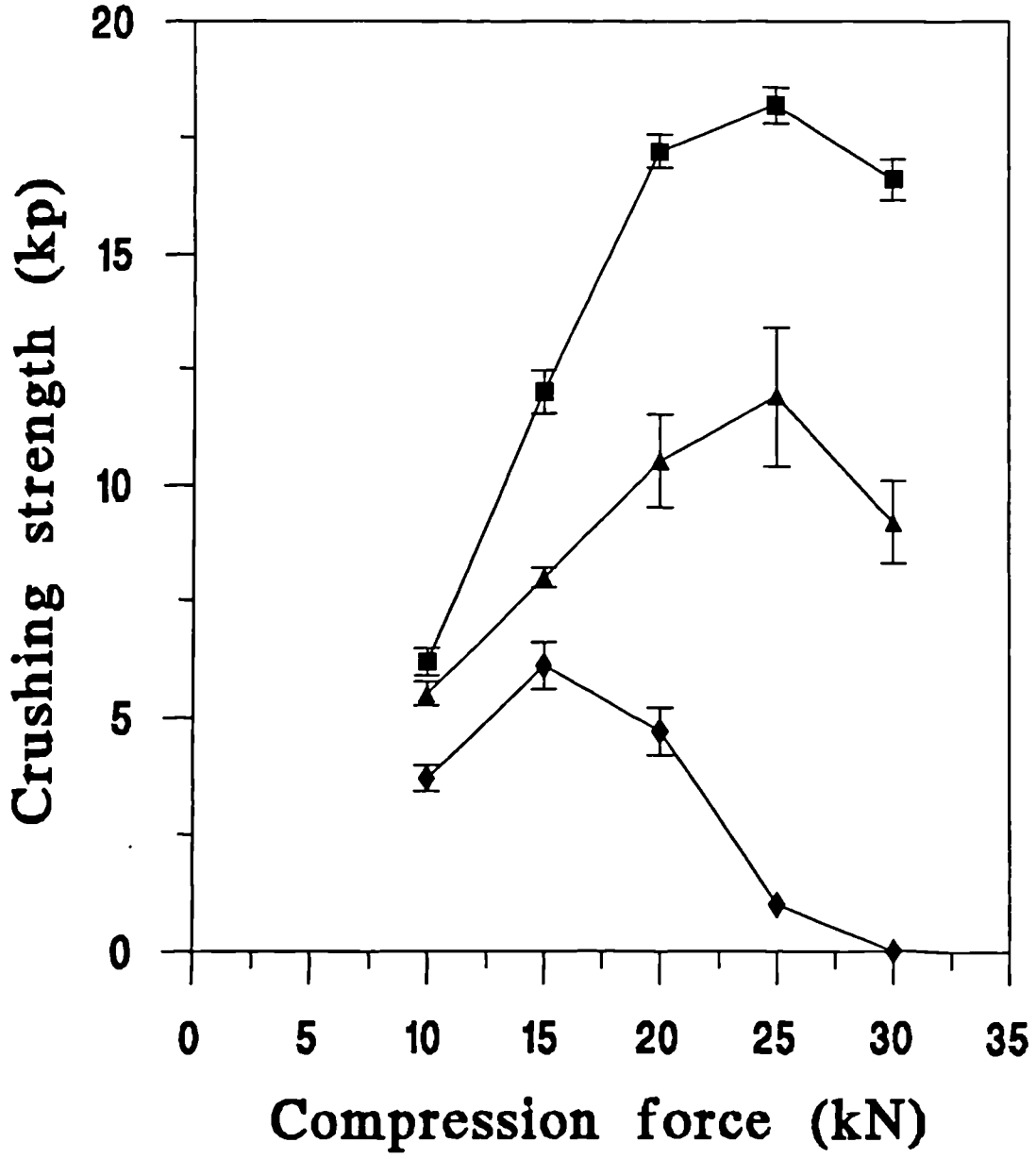


Figure 8.4 Effect of compression force on the crushing strengths of tablets made from paracetamol crystallized in the presence of 0.5% w/v of: (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at compression speed of 10 mm s^{-1}.

Table 8.1 Effect of compression force on the capping tendency of tablets made from paracetamol crystallized in the presence of 0.1, 0.3 or 0.5% w/v of different grades of PVP, at a compression speed of 10 mm s^{-1}.

Compression force (kN)	Particles crystallized in presence of:								
	PVP 2000 (%w/v)			PVP 10000 (%w/v)			PVP 50000 (%w/v)		
	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5
10	+++	++	+	++	_	_	+	_	_
15	+++	++	+	++	_	_	+	_	_
20	+++	++	++	++	+	_	+	_	_
25	+++	+++	++	+++	+	_	++	+	_
30	+++	+++	+++	+++	++	_	+++	+	_

(-, +, ++ and +++) as defined in section 8.2.2.4

indicate improvement in the compaction properties of paracetamol particles crystallized in the presence of PVP. These figures indicate that the crushing strengths increased with increasing molecular weight and/or the concentration of PVP in the crystallizing solution.

Figure 8.4 compares the crushing strengths of tablets made from particles obtained in the presence of 0.5% w/v PVP. These results demonstrate that particles crystallized in the presence of 0.5% w/v PVP 10000 or PVP 50000

produced tablets with excellent hardness and lack of tendency to cap. However, particles obtained in the presence of PVP 2000 showed little improvement in their compaction properties. The high crushing strengths of the tablets are indicative of stronger interparticulate bondings between the particles crystallized in presence of PVP compared to untreated paracetamol.

8.3.1.2 Influence of compression speed on the crushing strength of tablets

The effects of compression speed on the crushing strengths and capping tendencies of tablets made from paracetamol crystallized in the presence of 0.5% w/v PVP were investigated. The results are shown in figure 8.5 and table 8.2. Tablets made from particles obtained in the presence of PVP 10000 or PVP 50000 exhibited good hardnesses with no tendency to cap, even at the highest compaction speed (250 mm s^{-1}). However, for tablets made from particles crystallized in the presence of PVP 2000, dramatic decreases in crushing strength occurred with increasing compression speed. Tablets made from particles crystallized in the presence of PVP 10000 or PVP 50000 did not show a major reduction in their crushing strength with increase in compaction speed. Tukey's test revealed that the crushing strengths of tablets were significantly different only at 10 and 250 mm s^{-1} ($P<0.05$). The lack of reduction in crushing strength with increasing compaction speed may be attributed to fragmentation of the particles under the applied load.

The crushing strengths of tablets made from materials such as xylitol or

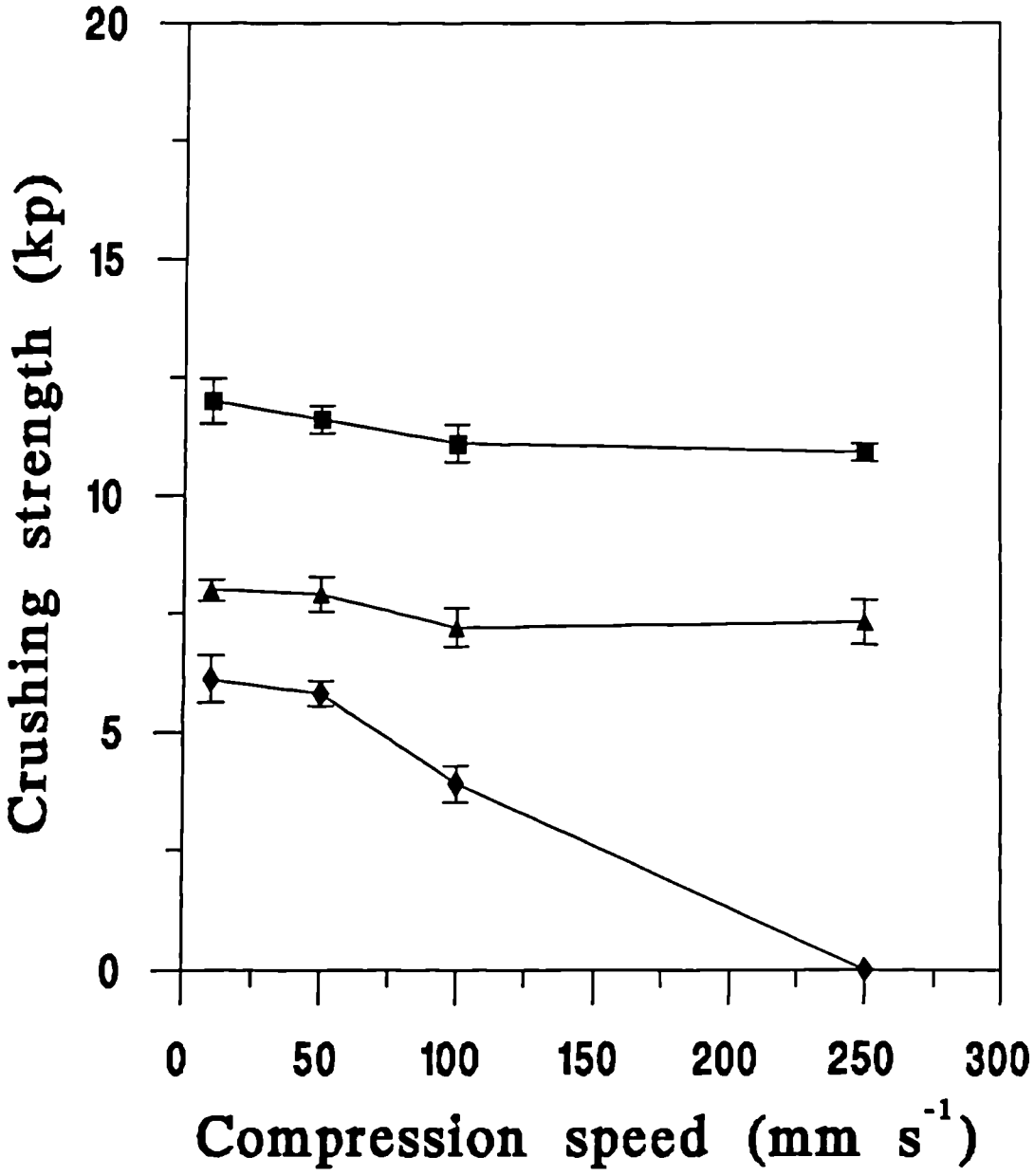


Figure 8.5 Effect of compression speed on the crushing strengths of tablets made from paracetamol crystallized in the presence of 0.5% w/v of: (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compression force of 15 kN.

Table 8.2 Effect of compaction speed on the capping tendency of tablets made from paracetamol particles crystallized in the presence of 0.5% w/v of different grades of PVP, at a compaction force of 15 kN.

Compression speed (mm s^{-1})	Particles crystallized in presence of:		
	PVP 2000	PVP 10000	PVP 50000
10	+	-	-
50	+	-	-
100	++	-	-
250	++	-	-

(-, +, ++ and +++) as defined in section 8.2.2.4

dicalcium phosphate dihydrate (Emcompress®) which consolidate by a dominant fragmentation mechanism were independent of compression speed (Garr & Rubinstein, 1990; Garr 1992). Emcompress consists of aggregates of smaller primary particles. These aggregates are extensively fragmented during compression (Duberg & Nystrom, 1982). Paracetamol crystallized in the presence of 0.5% w/v of PVP 10000 or PVP 50000 had an agglomerated structure which consisted of numerous fine microcrystals which had stuck together (figures 7.6b and c). It is reasonable to assume therefore that these agglomerates undergo fragmentation during compaction.

8.3.2 HECKEL ANALYSIS OF PARACETAMOL TABLETS

Figure 8.6 shows typical Heckel plots of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP, obtained at a compaction speed of 10 mm s^{-1}. This figure indicates that paracetamol crystallized in the presence of PVP 2000 exhibited higher relative densities (greater densification) for a given applied pressure than particles obtained in the presence of PVP 10000 or PVP 50000. This can be attributed to increased frictional and cohesive forces between the latter particles, due to their small size, and rough and dented surfaces (figure 7.6b,c) which would restrict particle sliding and thus reduce densification (McKenna & McCafferty, 1982; Roberts & Rowe, 1986).

The slope for particles crystallized in the presence of PVP 2000 was greater than that of PVP 10000 or PVP 50000 (figure 8.6). Table 8.3 indicates that the slope (K) was highest for paracetamol crystallized in the presence of PVP 2000. Therefore the mean yield pressure (1/K) was lower. Table 8.3 also indicates that the densification due to die filling (D_o) is the same for all particles, but the value of D_a (densification due to die filling and particle rearrangement) was greater for particles crystallized in the presence of PVP 2000 than those obtained in the presence of PVP 10000 or 50000. This indicates a higher degree of densification for the former particles.

Table 8.3 indicates that the correlation coefficient of the initial part of the Heckel plot (0-20 MPa) was slightly lower for particles crystallized in the

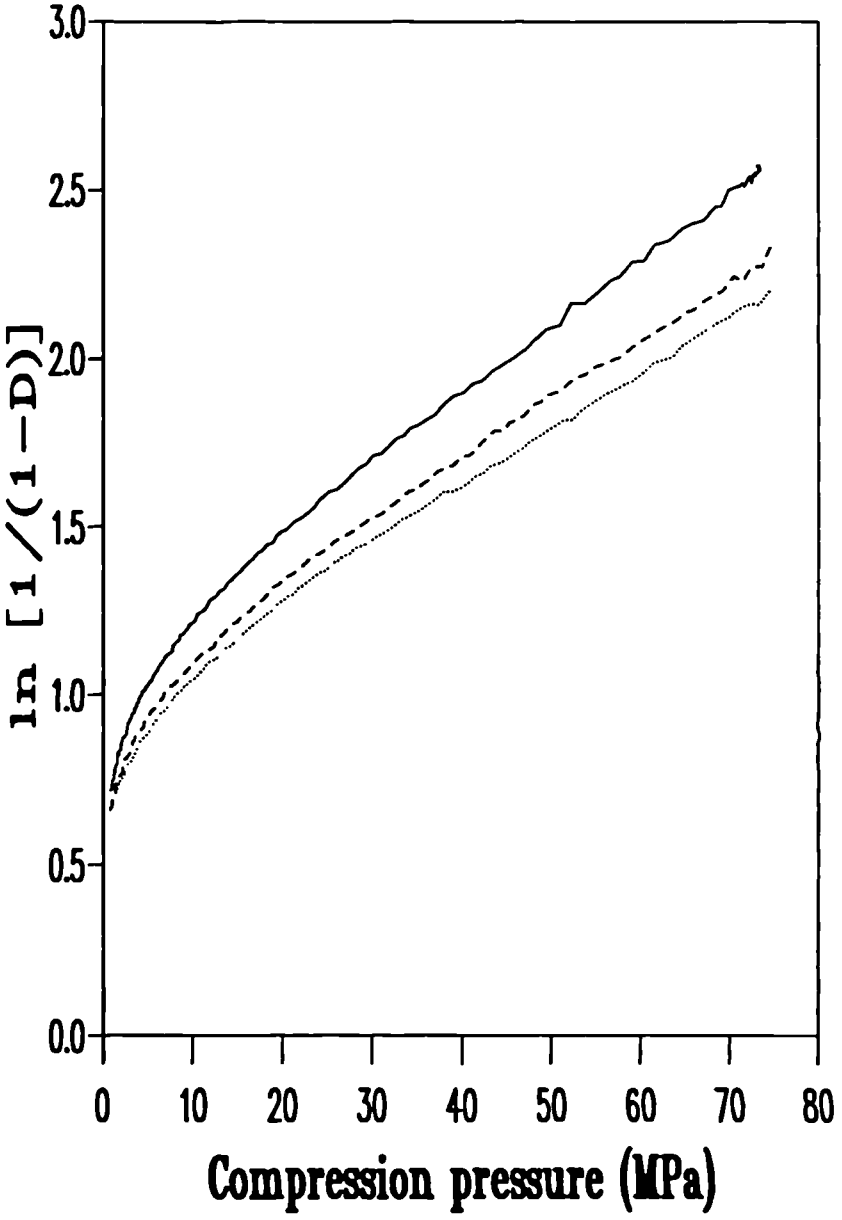


Figure 8.6 Typical Heckel plots of paracetamol particles crystallized in the presence of 0.5% w/v of: (—) PVP 2000, (---) PVP 10000 or (....) PVP 50000, at a compression speed of 10 mm s^{-1}.

presence of PVP 2000. These results indicate that these particles possibly underwent more fragmentation during the first stage of compaction (Duberg & Nystrom, 1986; Humbert-Droz et al, 1983).

Table 8.3 The values derived from the Heckel plots of figure 8.6 of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP, compressed at a compaction speed of 10 mm s^{-1}.

	Paracetamol crystallized in presence of:		
	PVP 2000	PVP 10000	PVP 50000
K	0.021	0.018	0.017
1/K=Mean yield pressure (MPa)	47.3	56.0	59.1
D_a	0.65	0.64	0.61
D_o	0.51	0.51	0.51
r*	0.958	0.967	0.975
r**	0.998	0.997	0.998

r*=Correlation coefficient of initial curve of Heckel plot (0-20 MPa)

r**=Correlation coefficient of straight line portion of Heckel plot (20-65 MPa)

Figure 8.7 shows the whole compression cycle (compression and decompression phase) for particles crystallized in the presence of 0.5% w/v PVP 10000 at a compaction speed of 10 mm s^{-1}. As mentioned in section

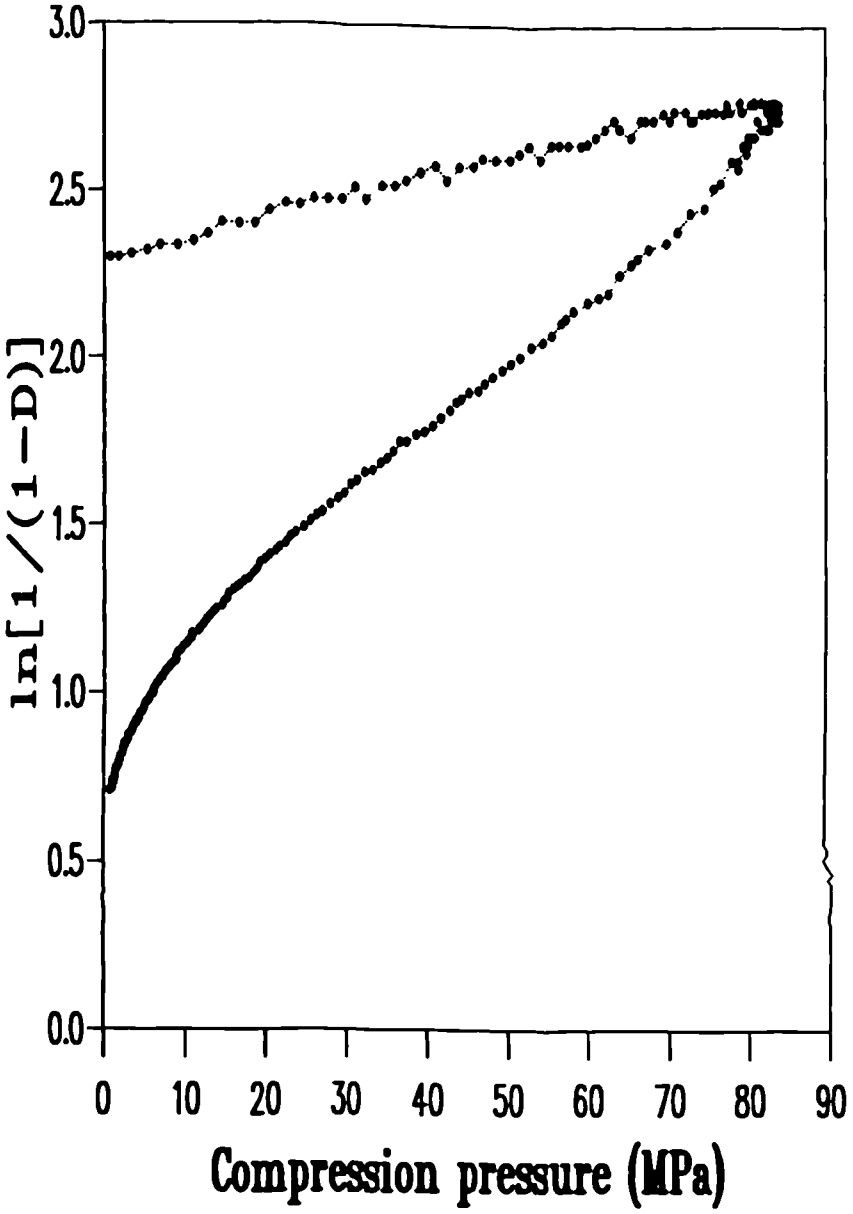


Figure 8.7 Heckel plot, including compression and decompression phase, of paracetamol crystallized in the presence of 0.5% w/v of PVP 10000, obtained at a compaction speed of 10 mm s^{-1}.

1.4.5.2, phase III of a Heckel plot can be indicative of the behaviour of a material under applied load (Duberg & Nystrom, 1986). A large deviation from the horizontal in decompression phase for untreated paracetamol (figure 3.3) was attributed to a high degree of elastic behaviour (section 3.3.2). The deviation from horizontal in phase III for particles crystallized in the presence of PVP (figure 8.7) was less than that of untreated paracetamol (figure 3.3). This indicates that the elastic behaviour of paracetamol crystallized in the presence of PVP was lower than untreated paracetamol.

8.3.3 INFLUENCE OF COMPRESSION SPEED ON HECKEL CONSTANTS

The effects of compression speed on the mean yield pressure, D_o, D_a and D_b of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP were investigated (tables 8.4, 8.5).

Two way analysis of variance showed that there were no significant differences ($P>0.05$) between the mean yield pressures of particles obtained in the presence of PVP 10000 and PVP 50000. However, differences between paracetamol obtained in the presence of PVP 2000 and those obtained in the presence of PVP 10000 or 50000 were significant (table 8.4). As the compression speed increased, the MYP for all samples generally increased. One way analysis of variance showed that there were significant differences ($P<0.05$) between the MYP with increasing compaction speed for all particles. However, particles crystallized in the presence of the higher molecular weight

Table 8.4 Effect of compression speed on the mean yield pressures (MYP) of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP.

Compression speed (mm s^{-1})	MYP±SD (MPa)		
	Particles obtained in presence of:		
	PVP 2000	PVP 10000	PVP 50000
10	48.9±1.2	56.8±1.7	59.4±2.2
50	53.7±2.7	59.5±0.6	61.5±2.3
100	55.8±1.3	61.5±1.4	64.3±1.9
250	57.5±1.1	62.0±2.0	63.1±1.3

of PVP (10000 or 50000) were less sensitive to changes in compaction speed. The changes of MYP with different compaction speeds were quantified as strain rate sensitivity (SRS), using equation 3.1 (section 3.3.2.1). The values of SRS for particles crystallized in the presence of PVP 2000, PVP 10000 or PVP 50000 were 5.9, 8.4 or 14.9%, respectively. As mentioned in section 1.4.6, due to the time dependent nature of plastic flow, the mean yield pressures increase with increasing punch velocity for plastic materials which consequently show higher values of SRS (Roberts & Rowe, 1985, 1986). The lower values of SRS for paracetamol crystallized in the presence of PVP 10000 or PVP 50000 indicate that these particles were less sensitive to

compaction speed, suggesting that a high degree of fragmentation occurred during compression. It has been reported that materials which consolidate by fragmentation show no significant change in mean yield pressure with increasing compaction speed and therefore exhibit a low SRS (Roberts & Rowe, 1985; Garr, 1992).

The correlation coefficients of the initial parts of the Heckel plots (table 8.3) indicated that during the first stage of compaction, particles obtained in the presence of PVP 2000 probably underwent more fragmentation than paracetamol obtained in the presence of PVP 10000 or 50000. This can be attributed to the ease of fracture of the former particles at lower pressures (0-20 MPa). However, at higher compaction pressures, more fragmentation occurred for particles obtained in the presence of the higher molecular weight PVP. Paracetamol crystallized in the presence of PVP 10000 or PVP 50000 consisted of numerous fine microcrystals which had stuck together (figure 7.6). Therefore, it may be expected that these particles underwent more fragmentation during compaction.

The values of D_o, D_a and D_b (table 8.5) for all paracetamol particles tended to decrease with increasing punch speeds. One way analysis of variance revealed that there were significant differences ($P<0.05$) between the values of D_o, D_a or D_b with increasing compaction speed for all samples. As mentioned in section 3.3.2.1, at higher punch speeds the frictional and adhesive forces between the particles increase (York, 1978), and the air

escape from powder bed would be lower than at slower speeds. Therefore these factors will reduce densification of powder bed at higher punch speeds (Roberts & Rowe 1985).

Table 8.5 also indicates that at each compaction speed, the value of D_o is almost the same for all particles. Tukey's test revealed that at the majority of compaction speeds the differences between the values of D_o were not significant. However, the values of D_a and D_b show a slight decrease for particles crystallized in the presence of higher molecular weight of PVP (PVP 10000 or PVP 50000) as compared to those obtained in the presence of PVP

Table 8.5 The effect of compression speed on the values of D_o, D_a and D_b ($\times 10^{-1}$) (±SD) of paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP .

Compression speed (mm s^{-1})	Particles crystallized in presence of:								
	PVP 2000			PVP 10000			PVP 50000		
	D_o	D_a	D_b	D_o	D_a	D_b	D_o	D_a	D_b
10	5.03 ±0.20	6.53 ±0.10	1.50 ±0.08	5.15 ±0.05	6.45 ±0.05	1.30 ±0.00	5.10 ±0.08	6.35 ±0.05	1.23 ±0.05
50	4.83 ±0.08	6.33 ±0.05	1.50 ±0.08	4.87 ±0.05	6.35 ±0.10	1.48 ±0.09	4.80 ±0.08	6.07 ±0.20	1.30 ±0.09
100	4.78 ±0.10	6.18 ±0.05	1.43 ±0.10	4.87 ±0.05	6.10 ±0.00	1.23 ±0.04	4.68 ±0.09	5.90 ±0.20	1.28 ±0.09
250	4.58 ±0.10	5.75 ±0.05	1.18 ±0.15	4.80 ±0.00	5.80 ±0.08	1.00 ±0.08	4.73 ±0.05	5.58 ±0.09	0.85 ±0.10

2000. Tukey's test showed that at most compaction speeds, the values of D_a or D_b were significantly different. The degree of densification that occurred during compression depends on the surface structure, size and shape of particles (Heckel 1961; York 1978; York & Pilpel 1973; McKenna & McCafferty, 1982; Roberts & Rowe, 1985, 1986). As discussed earlier (section 8.3.2), particles obtained in the presence of PVP 10000 or PVP 50000 were very fine with rough and dented surfaces. Therefore it is expected that frictional forces associated with these particles tend to restrict the particle sliding and rearrangement and thus will reduce densification.

8.3.4 INFLUENCE OF COMPRESSION FORCE ON THE ELASTIC RECOVERY OF PARACETAMOL TABLETS

The effect of compression force on the elastic recoveries in the die of tablets made from paracetamol crystallized in the presence of 0.5% w/v of PVP is shown in figure 8.8. The elastic recoveries of tablets made from untreated paracetamol <90 μm, (chapter 3) are also shown. Tablets made from particles crystallized in the presence of PVP exhibited lower elastic recoveries than untreated paracetamol. Tablets made from particles obtained in the presence of PVP 10000 or PVP 50000 exhibited lower elastic recoveries than those obtained in the presence of PVP 2000 following the removal of compression pressure.

The crushing strengths and elastic recoveries indicated that the interparticulate bondings between particles crystallized in the presence of

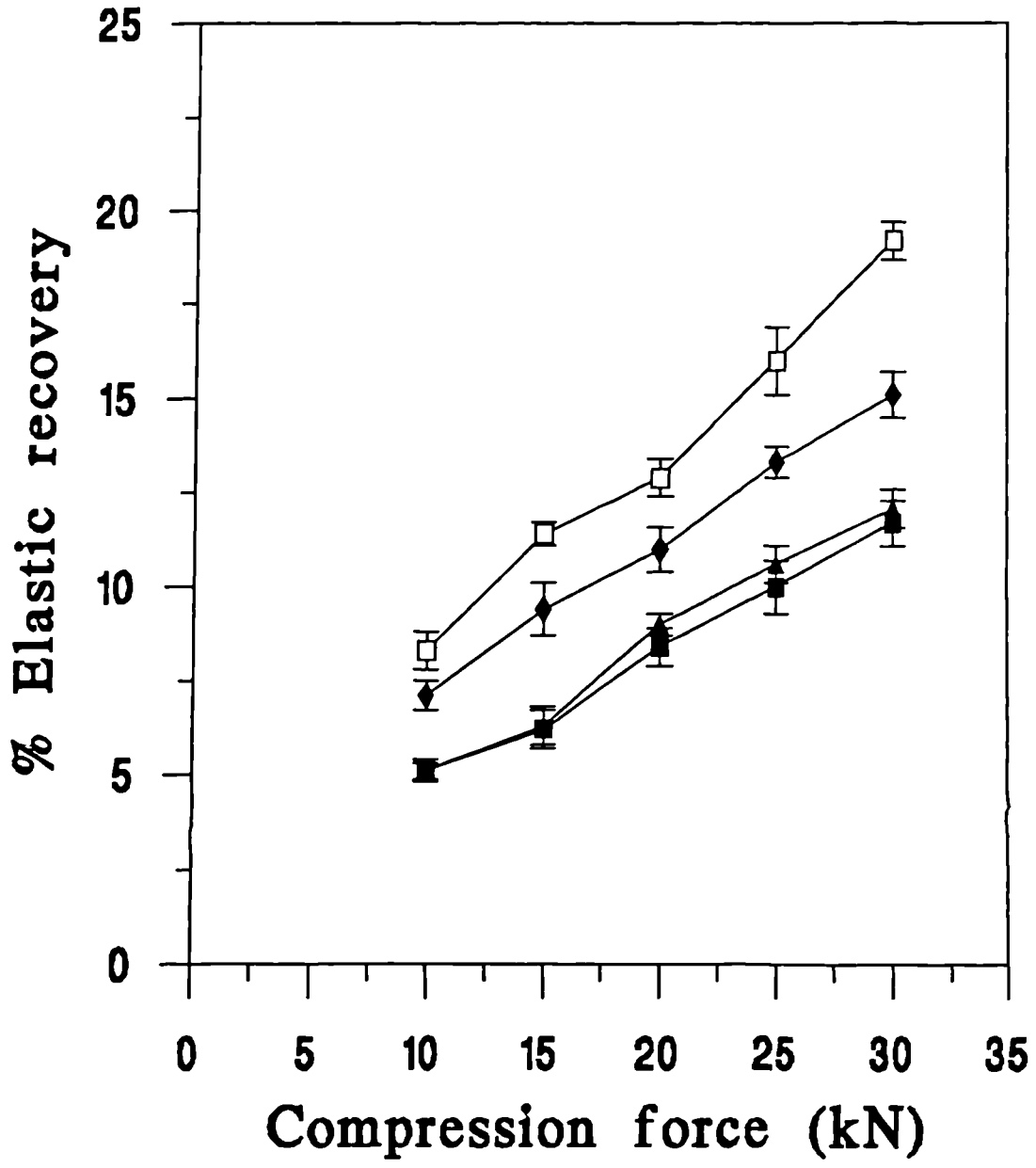


Figure 8.8 Effect of compression force on the elastic recovery in the die of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction speed of 10 mm s^{-1}.

PVP should be much stronger than untreated paracetamol. Particles crystallized in the presence of PVP were very fine (almost 20 μm) and each particle consisted of numerous microcrystals which had stuck together (figure 7.6). Fragmentation of each particle under load will produce numerous fresh and clean surfaces which can probably form bonds between each other.

8.3.5 ENERGIES INVOLVED DURING COMPACTION OF PARACETAMOL

8.3.5.1 Influence of compression force or speed on the gross energies

The effects of compaction force or compaction speed on the gross energies of tablets made from paracetamol crystallized in the presence of 0.5% w/v of different grades of PVP are illustrated in figures 8.9 and 8.10. Increasing the compaction force or speed, resulted in an increase in gross energies for all samples.

Figures 8.9 and 8.10 indicate that at all compaction forces or speeds, the gross energies of tablets made from untreated paracetamol were less than samples crystallized in the presence of PVP. These figures also indicate that the gross energies of tablets made from paracetamol crystallized in the presence of PVP followed the order PVP 50000>PVP 10000>PVP 2000. However, Tukey's test revealed that there were no significant differences ($P>0.05$) between the gross energies of samples obtained in the presence of PVP 10000 or PVP 50000 at 20 kN compaction force, and also at compaction speeds of 50, 100 and 250 mm s^{-1}. The gross energies of paracetamol

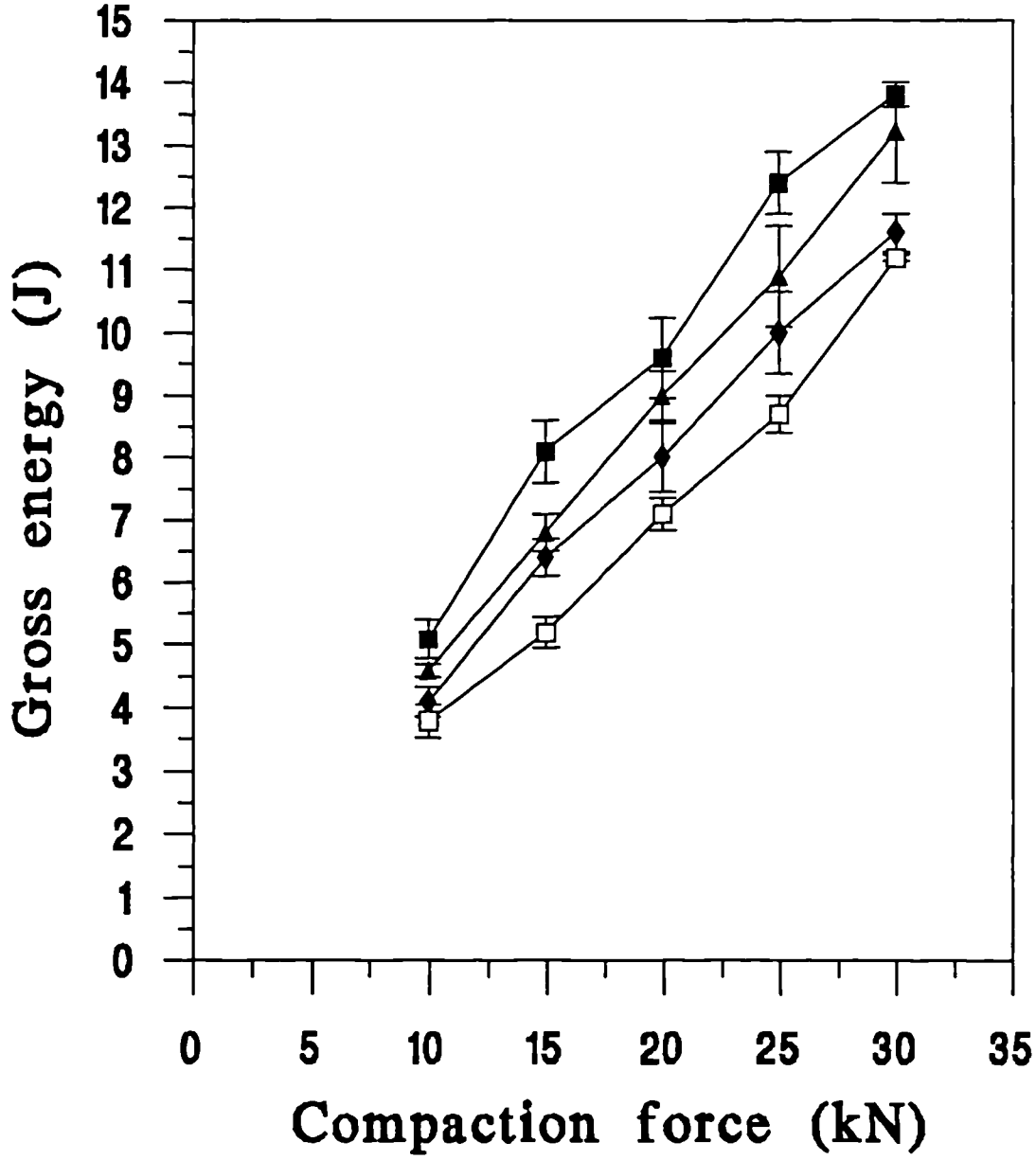


Figure 8.9 Effect of compression force on the gross energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction speed of 10 mm s^{-1}.

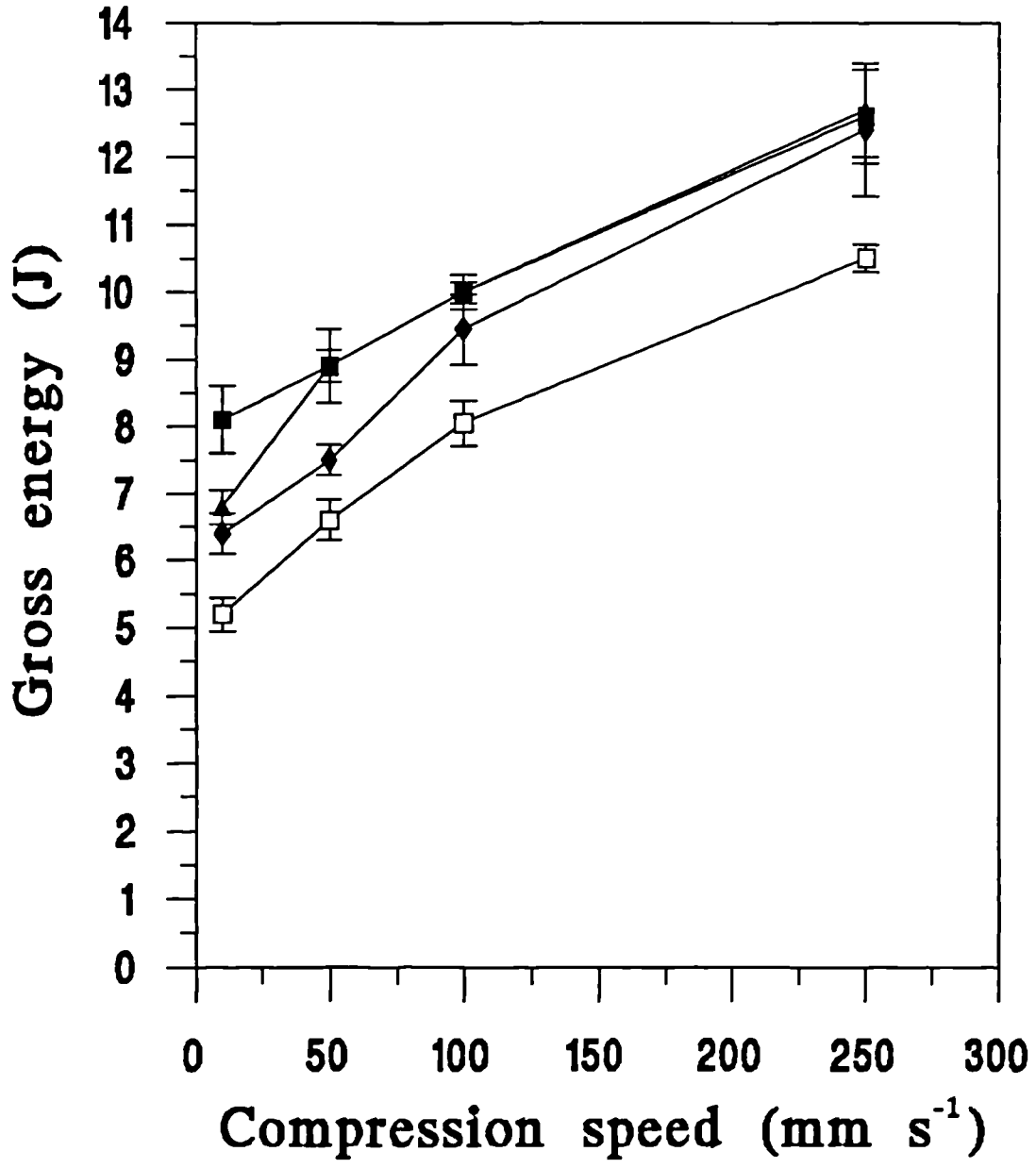


Figure 8.10 Effect of compression speed on the gross energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction force of 15 kN.

crystallized in the presence of PVP 2000 or PVP 10000 were significantly different ($P<0.05$) only at a compaction speed of 50 mm s^{-1}, and at compaction forces of 10, 20 and 30 kN. The increased gross energies for tablets made from particles obtained in the presence of PVP could be attributed to an increase in plastic (net compaction) energies and/or elastic energies of tablets. This will be further studied in the following sections.

8.3.5.2 Influence of compression force or speed on elastic energies

The effects of compression force or compression speed on the elastic energies of tablets made from paracetamol crystallized in the presence of 0.5% w/v PVP illustrated in figures 8.11 and 8.12. These figures indicate that, at different compaction forces or speeds, the elastic energies of tablets made from particles crystallized in the presence of PVP were less than that of the untreated paracetamol. These figures also reveal that the elastic energies of tablets made from particles crystallized in the presence of higher molecular weight PVP were less than for particles obtained in presence of lower molecular weight PVP. However, Tukey's test showed that there were no significant differences ($P>0.05$) between the elastic energies of samples obtained in the presence of PVP 10000 or PVP 50000 at all compaction forces, and also at 10 or 50 mm s^{-1} compaction speeds. The results of elastic recoveries and elastic energies indicated that particles crystallized in the presence of PVP showed less elastic behaviour than the untreated paracetamol.

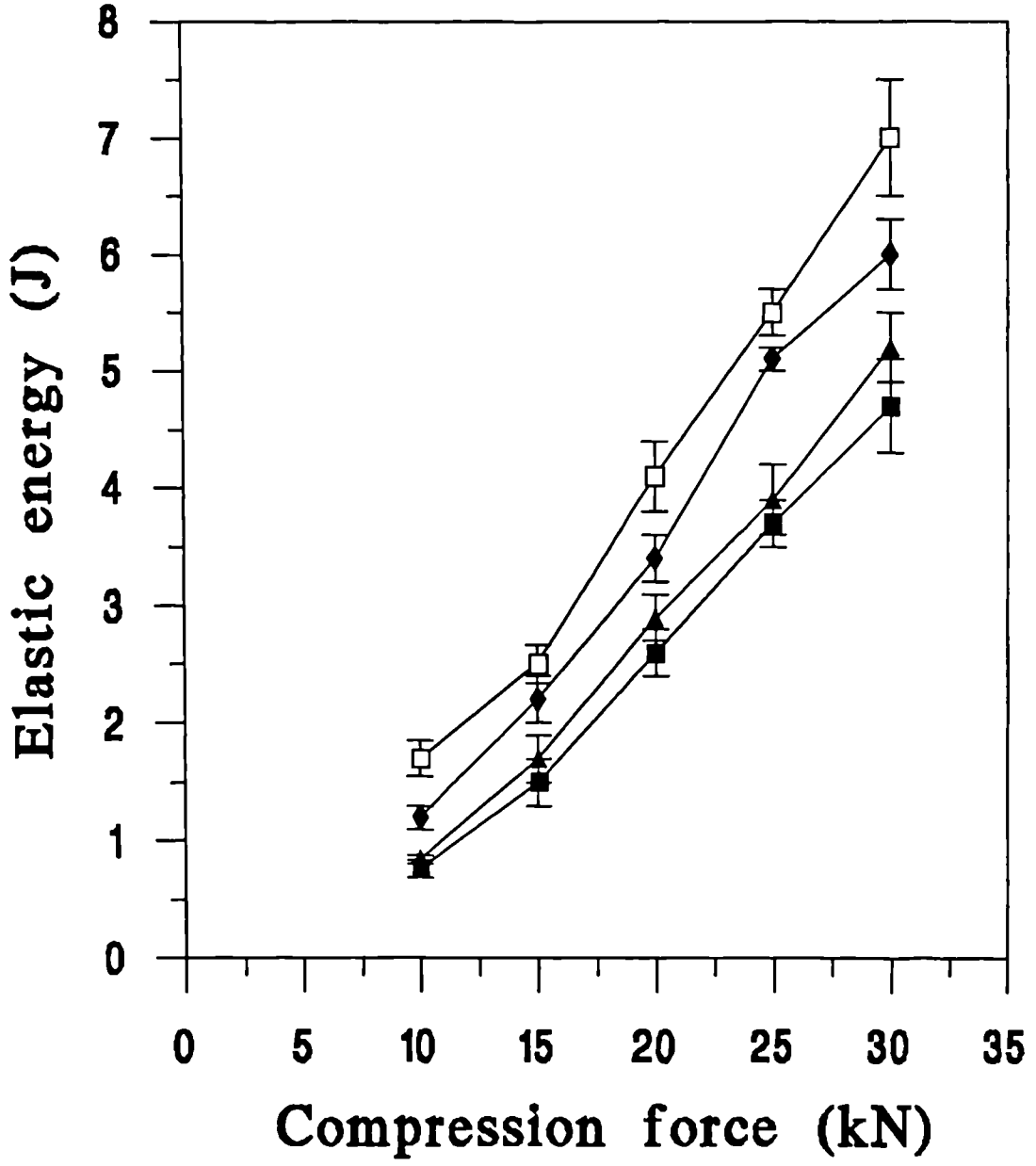


Figure 8.11 Effect of compression force on the elastic energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction speed of 10 mm s^{-1}.

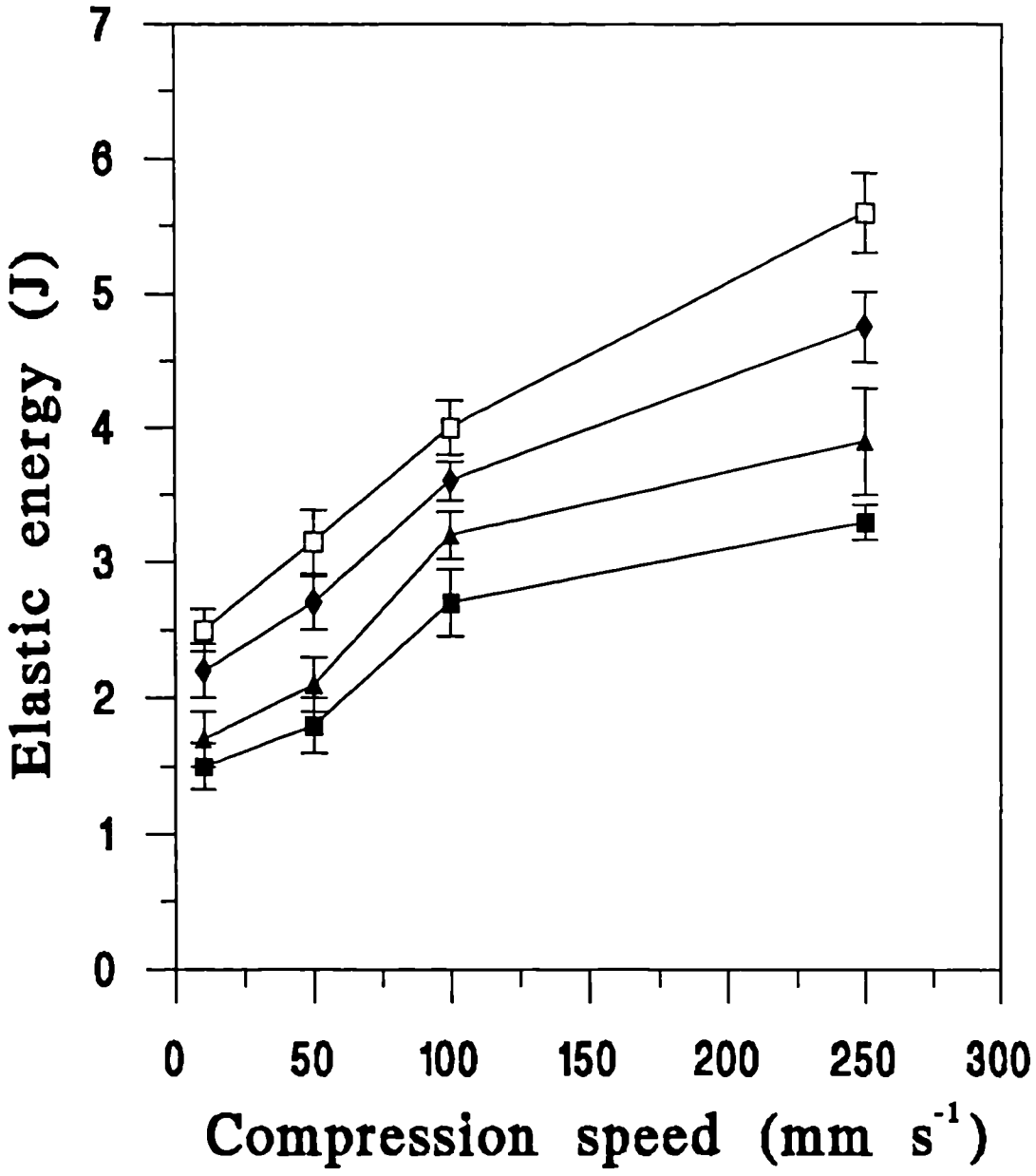


Figure 8.12 Effect of compression speed on the elastic energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction force of 15 kN.

8.3.5.3 Influence of compression force or speed on the plastic (net compaction) energies

Figures 8.13 and 8.14 show the plastic energies of tablets made from particles crystallized in the presence of PVP. These figures clearly indicate that the plastic energies of tablets made from particles crystallized in the presence of PVP were much higher than for untreated particles. This figures also indicate that the plastic energies increased as the molecular weight of PVP increased. Tukey's test revealed that the differences between the plastic energies of paracetamol crystallized in the presence of PVP 10000 or PVP 50000 were not significant at 20 kN compaction force, and also at 50, 100 and 250 mm s^{-1} compaction speeds. The increases in plastic energy of tablets made from particles crystallized in the presence of PVP may be attributed to the energy required for fragmentation of these particles and most importantly to the formation of bonds between the particles during compaction. The high crushing strengths of the tablets made from particles obtained in the presence of PVP indicated strong interparticulate bonding.

8.3.5.4 Influence of compaction force or speed on the ratio of elastic energy/plastic energy

Tables 8.6 and 8.7 show the ratio of elastic energy/plastic energy (EE/PE) of tablets made from paracetamol crystallized in the presence of PVP, at varying compaction forces or speeds, respectively. The ratios of EE/PE for particles crystallized in the presence of PVP were much lower than for untreated crystals.

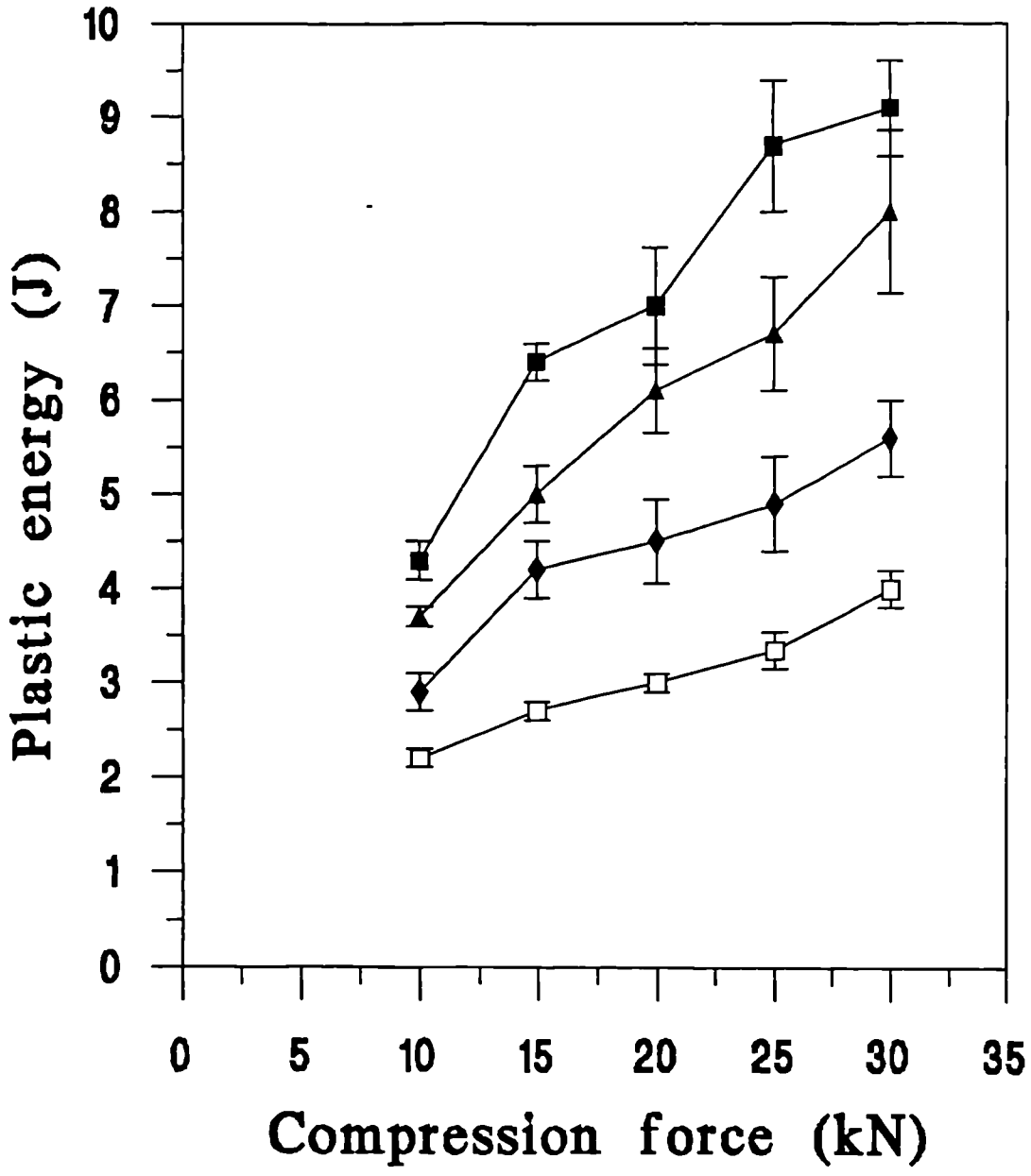


Figure 8.13 Effect of compression force on the plastic energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction speed of 10 mm s^{-1}.

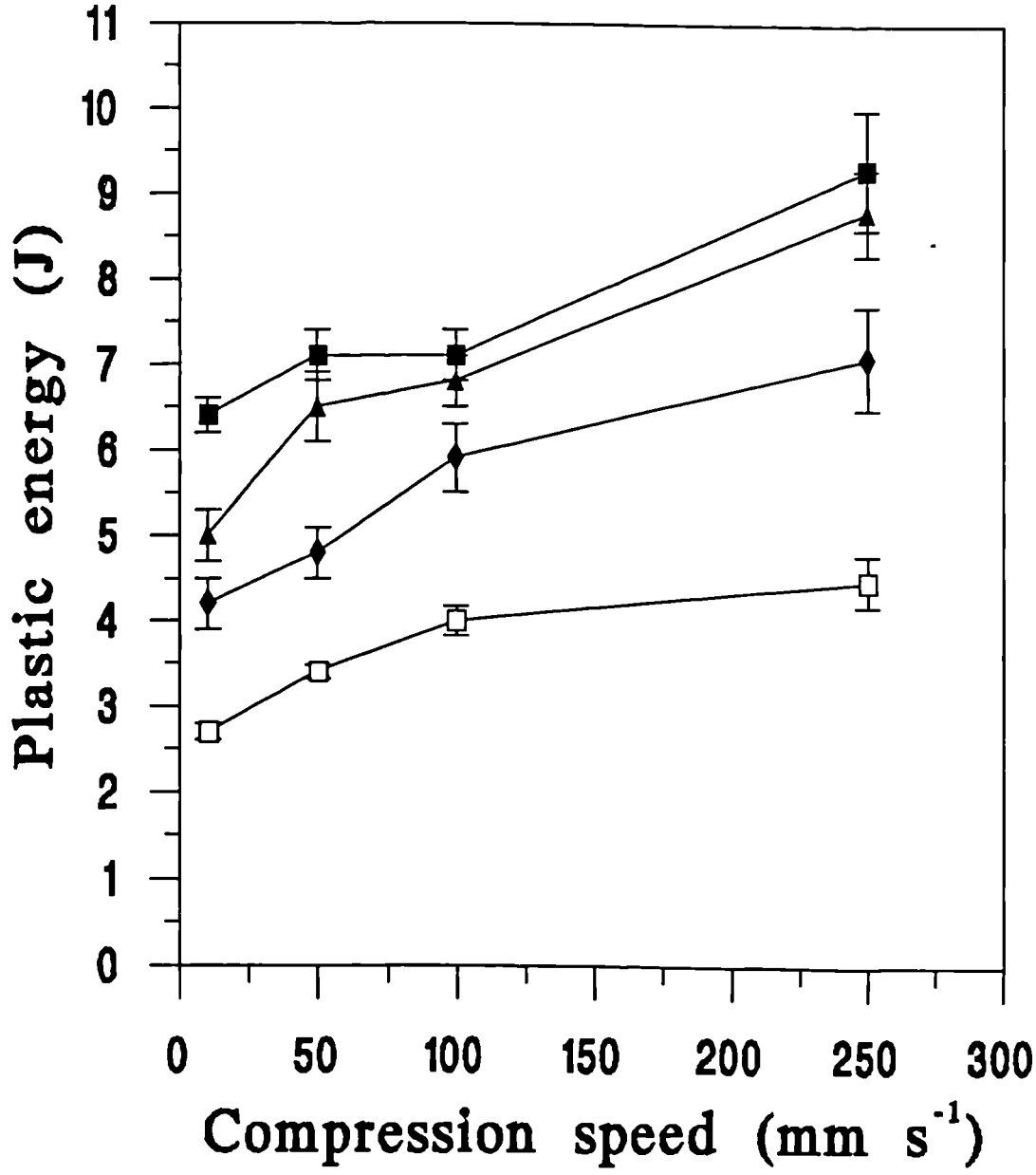


Figure 8.14 Effect of compression speed on the plastic energies of tablets made from: (□) untreated paracetamol, and paracetamol crystallized in the presence of 0.5% w/v of (♦) PVP 2000, (▲) PVP 10000 or (■) PVP 50000, at a compaction force of 15 kN.

Table 8.6 Effect of compression force on the ratio of EE/PE of tablets made from paracetamol crystallized in the presence of 0.5% w/v different grades of PVP, at a compaction speed of 10 mm s^{-1}.

Compression force (kN)	EE/PE ratio±SD			
	Particles crystallized in the presence of:			Untreated paracetamol*
	PVP 2000	PVP 10000	PVP 50000	
10	0.41±0.04	0.23±0.02	0.18±0.01	0.74±0.06
15	0.52±0.05	0.34±0.05	0.23±0.03	0.91±0.04
20	0.75±0.07	0.47±0.05	0.38±0.03	1.36±0.14
25	1.00±0.07	0.59±0.09	0.44±0.06	1.73±0.11
30	1.10±0.15	0.66±0.09	0.52±0.07	1.78±0.17

* Taken from table 3.4

These results indicate that for untreated particles the major portion of compaction energy is utilised as elastic energy, while for particles obtained in the presence of PVP a minor portion is used as elastic energy. These results again confirmed that tablets made from particles crystallized in the presence of PVP exhibited lower elastic behaviour than untreated paracetamol. Tables 8.6 and 8.7 also indicate that paracetamol crystallized in the presence of higher molecular weight of PVP (10000 or 50000) exhibited lower EE/PE ratios than those obtained in the presence of PVP 2000. However, Tukey's test revealed that there were no significant differences ($P>0.05$) between the EE/PE ratios for particles crystallized in the presence

of PVP 10000 or PVP 50000 at compaction speeds of 50 and 250 mm s^{-1}, and also at a compaction force of 30 kN.

Table 8.7 Effect of compression speed on the ratio of EE/PE of tablets made from paracetamol crystallized in the presence of 0.5% w/v different grades of PVP, at a compaction force of 15 kN.

Compression speed (mm s^{-1})	EE/PE ratio±SD			
	Particles crystallized in presence of:			Untreated paracetamol*
	PVP 2000	PVP 10000	PVP 50000	
10	0.52±0.05	0.34±0.05	0.23±0.03	0.91±0.04
50	0.56±0.09	0.32±0.05	0.26±0.03	0.92±0.08
100	0.62±0.04	0.47±0.05	0.38±0.03	1.00±0.06
250	0.67±0.04	0.44±0.06	0.36±0.03	1.24±0.10

* Taken from table 3.5

8.3.6 INFLUENCE OF ADDITION OF MAGNESIUM STEARATE ON THE CRUSHING STRENGTH OF TABLETS

The crushing strengths and Heckel analyses at different compaction speeds revealed that particles crystallized in the presence of PVP 10000 or PVP 50000 underwent fragmentation during compression. Another useful method for estimating the degree of fragmentation of particles under load is to determine the crushing strength of tablets with and without magnesium stearate (Duberg & Nystrom, 1982).

Materials which mainly deform by plastic deformation such as amylose V or sodium chloride are sensitive to even small additions of lubricant and exhibit a dramatic decrease in their crushing strength, but materials such as Emcompress® which undergo complete fragmentation under pressure are practically uninfluenced by mixing with magnesium stearate (Duberg & Nystrom, 1982). These phenomena have been attributed to the formation of a film by magnesium stearate over the surfaces of particles (Bolhuis et al, 1975).

In the case of a plastic material which undergoes plastic deformation without any fragmentation, addition of lubricant decreases the adhesion and bonding properties between particles and therefore the crushing strength will be dramatically decreased. The crushing strength of tablets made from amylose V decreased from 19.5 kg to zero, and for sodium chloride from 7.5 to 0.5 kg, without and with 0.5% magnesium stearate, respectively (De Boer, et al 1978). On the other hand, materials that fragment during compaction such as Emcompress® show little or no reduction in tablet strength, when lubricant is added. This is due to the creation of new, fresh, clean and unlubricated surfaces which are able to form bonds between particles (Deboer et al, 1978).

Paracetamol particles crystallized in the presence of PVP 10000 or PVP 50000 were mixed with 0.5% w/w of sieved fraction of magnesium stearate (<45 μm) and were compressed at different compaction forces and the percentage of reduction in crushing strength of tablets (compared to tablets

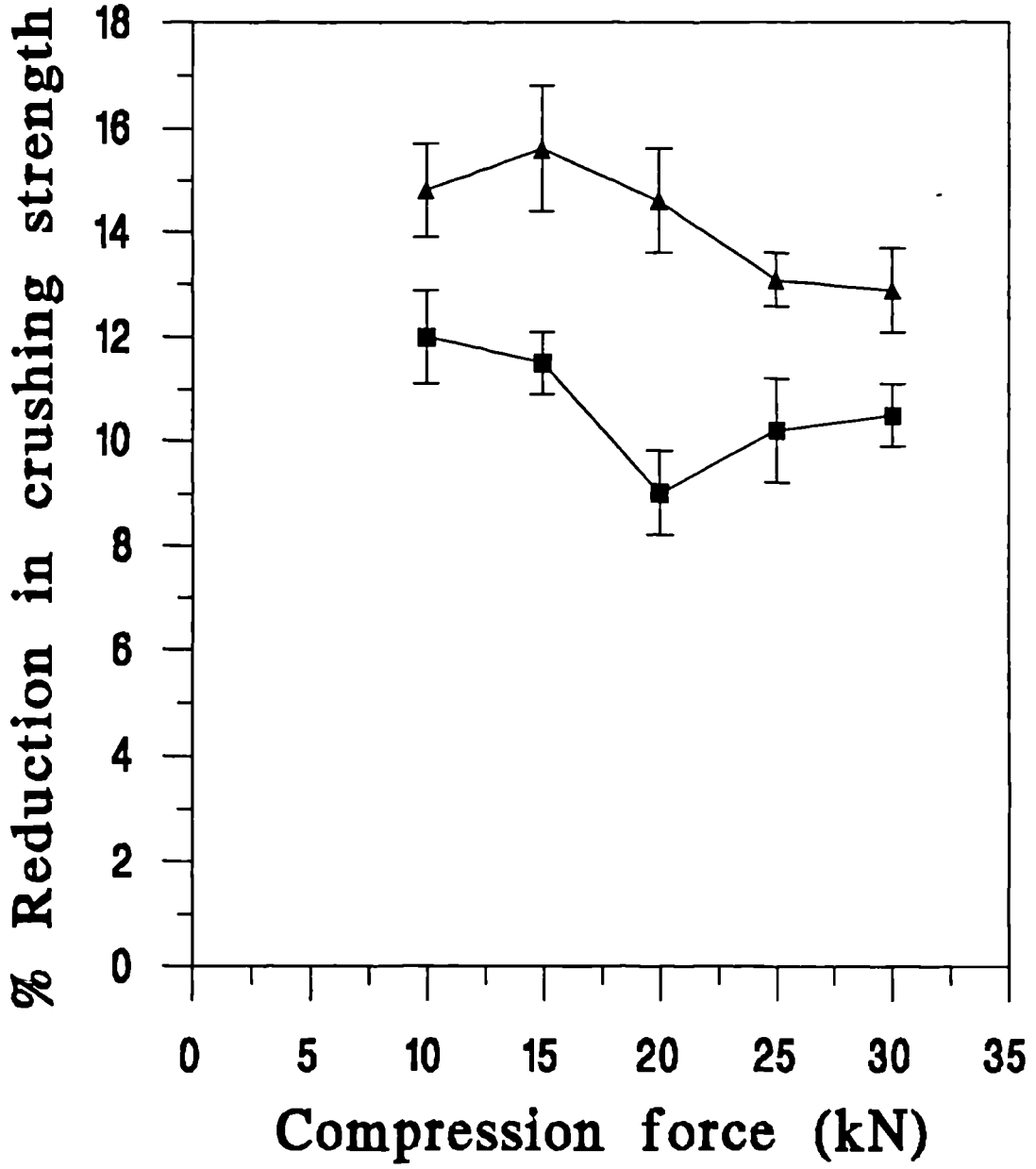


Figure 8.15 Effect of compaction force on the reduction in crushing strengths of tablets made from particles crystallized in presence of 0.5% w/v of (▲) PVP 10000 or (■) PVP 50000, mixed with 0.5% w/w magnesium stearate.

made from particles without magnesium stearate) were determined (figure 8.15). Particles crystallized in the presence of PVP 10000 or PVP 50000 did not show a major reduction in their crushing strengths following the addition of magnesium stearate. The maximal percentage reduction in their crushing strength was less than 15%. This can be attributed to the fragmentation of these particles under pressure, producing fresh and unlubricated surfaces for particle bondings. The reduction in crushing strengths was lower for particles crystallized in the presence of PVP 50000 than for particles obtained in the presence of PVP 10000, indicating the greater tendency to fragment for the former particles.

8.3.7 CRUSHING STRENGTHS OF TABLETS MADE FROM PHYSICAL MIXTURES OF PARACETAMOL AND PVP 50000

In section 8.3.1, it was demonstrated that particles crystallized in the presence of 0.5% w/v of PVP 50000 produced tablets with high crushing strengths and no tendency to cap. In section 7.3.3 it was shown that these particles contained 4.3% w/w of PVP. The question now is whether the improved compaction properties of these particles was due to the presence of PVP in the particles or is due to the morphology (i.e. agglomerated structure) of these particles. There are some reports that the addition of some binders such as Avicel, HPMC or PVP to paracetamol increased the crushing strength of its tablets. However, among these binders, PVP was the least effective (Krycer & Pope, 1983). Nystrom and Glazer (1985) and Nystrom et al (1982) found that the tablet strength of physical mixtures of a poorly compressible

Table 8.8 Effect of compression force on the crushing strength (kp) and capping tendency of tablets made from physical mixtures of paracetamol with different contents of PVP 50000 (5, 10, 20, 30 or 50% w/w).

Compression force (kN)	5%		10%		20%		30%		50%	
	CS	CT	CS	CT	CS	CT	CS	CT	CS	CT
10	*	+++	0.0±0.0	+++	0.4±0.0	++	1.0±0.1	+	1.2±0.1	+
15	*	+++	0.3±0.0	+++	0.7±0.1	++	2.2±0.1	+	3.0±0.0	+
20	*	+++	*	+++	1.0±0.0	++	3.0±0.1	+	4.5±0.1	_
25	*	+++	*	+++	0.0±0.0	+++	2.6±0.1	++	5.0±0.1	+

KEY:

CS=Crushing strength, CT=Capping tendency

(*) very weak tablets with no measurable hardness, (-, +, ++ and +++) as defined in section 8.2.2.4

substance such as paracetamol with binders such as PVP, increased with an increase in the concentration of binder and also with a decrease in the particle size of binder.

The physical mixtures of sieved fractions of PVP 50000 (<45 μm) and paracetamol were compressed at different compression forces and the crushing strength of tablets are presented in table 8.8. These data clearly indicate that the crushing strengths of tablets, even at the highest ratio of PVP (50% w/w), were less than 5 kp, whereas, particles crystallized in the presence of 0.5% w/v of PVP 50000, which contained about 4% w/w PVP (table 7.1), produced tablets with crushing strengths of more than 15 kp (figure 8.3). Although PVP is in intimate contact with particles crystallized in the presence of PVP, i.e PVP has adsorbed onto the paracetamol particles which is in different manner with physical mixture. The compaction properties of particles crystallized in the presence of 0.5% w/v of different grades of PVP followed the order: PVP 50000>PVP 10000>PVP 2000. However, there were no major differences between the amount of PVP in these particles (table 7.1). Figure 7.6 indicated that particles obtained in the presence of PVP 10000 or PVP 50000 consisted of more microcrystals as compared to those obtained in the presence of PVP 2000. Therefore, these results indicate that an improvement in compaction properties of paracetamol crystallized in the presence of PVP was due to the morphology of particles i.e agglomerated structure, not due to the presence of small amounts of PVP in the particles.

8.4 CONCLUSIONS

Particles crystallized in the presence of 0.5% w/v PVP 10000 or PVP 50000 produced tablets with excellent hardness with no tendency to cap even at high compaction speeds. However, particles crystallized in the presence of PVP 2000 exhibited little improvement in their compaction properties.

It was found that particles crystallized in the presence of PVP 10000 or PVP 50000 underwent a high degree of fragmentation during compaction resulting in the formation of numerous fresh and clean surfaces for particle bondings. The results of elastic recovery, elastic energy and elastic energy/plastic energy ratio revealed that particles crystallized in the presence of PVP exhibited much less elastic behaviour under pressure, as compared to untreated paracetamol particles.

CHAPTER 9. DISSOLUTION STUDY OF PARACETAMOL CRYSTALLIZED IN THE PRESENCE OF POLYVINYLPYRROLIDONE

9.1 INTRODUCTION

Many methods have been used to enhance dissolution rates of poorly water-soluble drugs. The methods include, for example, micronization, formation of water soluble salts of compounds and solid dispersions (Chiou & Riegelman, 1971).

Chiou et al (1976) introduced a unique method to enhance the dissolution rate of poorly water-soluble drugs. The basic method simply involved the crystallization of the drug in an aqueous surfactant solution (polysorbate 80), which caused a marked enhancement in the dissolution rates of obtained drugs. There are several other reports of attempts to enhance the dissolution rate of poorly water-soluble drugs based on crystallization in the presence of surfactants or hydrophilic polymers *such as polyvinylpyrrolidone*, polyethylene glycol or hydroxypropylmethylcellulose (Naggar et al, 1980; El-Gindy & Shalaby 1982; Al-Meshal & York, 1984; El-Barry et al, 1990; Shawky & Mesiha, 1988).

In chapter 8, it was shown that the crystallization of paracetamol in the presence of PVP improved its compaction properties. Since paracetamol is a sparingly water-soluble drug, the aim of the work presented in this chapter

was to investigate the dissolution properties of paracetamol crystallized in the presence of different grades of PVP to evaluate if its dissolution properties were modified.

9.2 MATERIALS AND METHODS

9.2.1 MATERIALS

Untreated paracetamol as described in sections 2.1.1; paracetamol particles crystallized in the absence of PVP (thin plate-like crystals) or in the presence of 0.1, 0.3 or 0.5% w/v of PVP 2000, 10000 or 50000, as described in section 7.2.2.1, were used.

9.2.2 METHODS

9.2.2.1 Particle size fractions

Sieved fractions of untreated paracetamol (<90 μm) and samples crystallized in the absence of PVP or in the presence of 0.5% w/v of different grades of PVP (<90 μm), were obtained, as detailed in section 2.2.13. In the case of particles crystallized in presence of 0.1 or 0.3% w/v of different grades of PVP, they were used unsieved, as harvested from crystallization medium. These particles had different ranges of size and therefore it was impossible to obtain a specific seived fraction for each of them.

9.2.2.2 Determination of solubility of paracetamol

In order to determine the aqueous solubility of modified paracetamol particles crystallized in the presence of PVP, the following was carried out: Samples (2.5 g) of paracetamol obtained in the presence of 0.5% w/v of PVP 10000 (as a representative of a grade of PVP) were dispersed in 100 ml water in stoppred conical flasks. The paracetamol concentration was determined in the filtered solutions after 24 h, as described in section 2.2.7.1.

9.2.2.3 Determination of dissolution of paracetamol powders

The dissolution profiles of untreated paracetamol, and paracetamol particles crystallized in the absence or presence of 0.1, 0.3 or 0.5% w/v of PVP 2000, PVP 10000 or PVP 50000 were obtained as described in section 2.2.8. In all tests, an appropriate amount of powder was taken which was equivalent to 35 mg of paracetamol.

When untreated paracetamol was directly added to the dissolution medium by dusting onto the surface of water, the particles floated on the surface of dissolution medium (water) and were not dispersed uniformly. Under these conditions the dissolution results were not reproducible. To overcome this problem and to give a uniform wetting of the drug powder, some workers transferred the drug crystals into an empty tea bag which was then suspended in the dissolution medium (El-Bary et al, 1990). In the present study, as described in section 2.2.8, the paracetamol powders were placed into small bags made from metal gauze with 25 μm mesh size. Then the bags

were sunk into the water.

9.3 RESULTS AND DISCUSSION

9.3.1 AQUEOUS SOLUBILITY OF PARACETAMOL CRYSTALLIZED IN THE PRESENCE OF PVP

The aqueous solubility of paracetamol crystallized in the presence of 0.5% w/v of PVP 10000 is listed in table 9.1. There was no significant difference between the solubility of untreated particles and samples crystallized in the presence of PVP. According to table 7.1, the paracetamol particles crystallized in the presence of 0.5% w/v PVP 10000 consisted of 3.96% w/w of PVP. Therefore, the concentration of PVP in the medium was 0.12% w/v. As described in section 6.3.1, this concentration is far below that which affected the solubility of paracetamol.

Table 9.1 Aqueous solubility of untreated paracetamol and paracetamol crystallized in the presence of 0.5% w/v PVP 10000.

Sample	Solubility (g/100 ml)±SD
Untreated paracetamol	2.02±0.04*
Paracetamol crystallized in the presence of 0.5% w/v of PVP 10000	2.11±0.09

* Taken from table 6.1

9.3.2 DISSOLUTION STUDIES OF PARACETAMOL CRYSTALLIZED IN THE PRESENCE OF PVP

Figures 9.1, 9.2 and 9.3 show the dissolution profiles of paracetamol crystallized in the presence of 0.1, 0.3 or 0.5% w/v of different grades of PVP, respectively. The dissolution profiles of untreated paracetamol and samples crystallized in the absence of PVP are also included in these figures. The percentages of paracetamol dissolved within the first two minutes of study are presented in figure 9.4. These figures indicate that there was a marked enhancement in the dissolution characteristics of paracetamol crystallized in the presence of PVP. This can be attributed to the followings.

1- Adsorption of PVP to paracetamol particles crystallized in the presence of PVP (table 7.1) would undoubtly increase the wettability of these particles and thereby increase the dissolution rate. The wetting of a powder is the first step in the dissolution process. It is frequently difficult to disperse a poorly water-soluble powder in a fluid owing to an adsorbed layer of air. Wetting is the displacement of air from the surfaces of particles by a liquid (Hem et al, 1982). When the drug particles are encircled by the water-soluble polymers or surfactant, the polymer can readily dissolve and cause the water to contact and wet the particles (Chiou & Riegelman, 1971).

Chiou et al, (1976) reported that the crystallization of chloramphenicol, sulphathiazole and prednisolone in the presence of polysorbate 80 significantly increased the dissolution rates of these drugs. This was

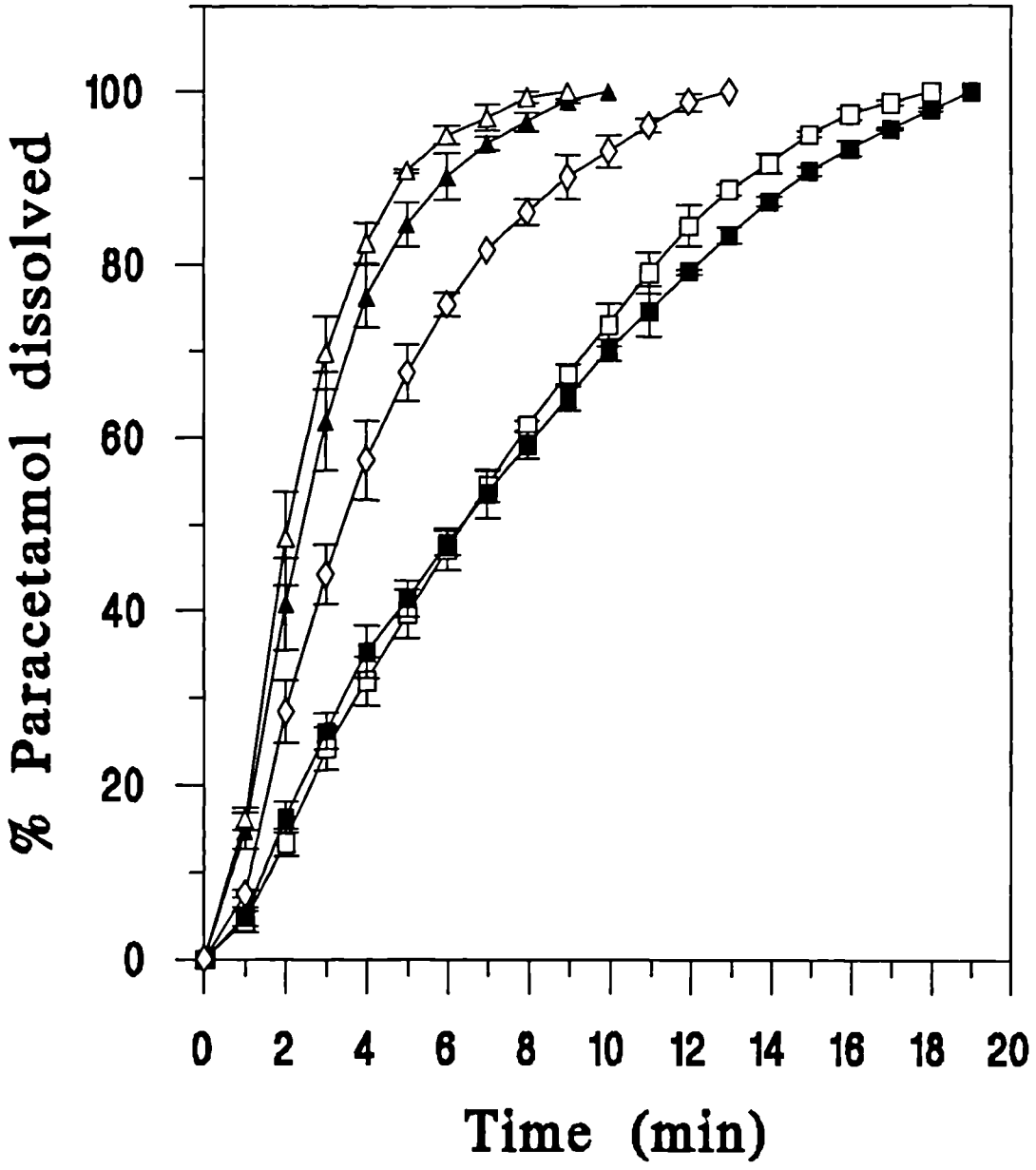


Figure 9.1 Percentage of paracetamol disolved against time (min) for: (□) untreated paracetamol, and paracetamol crystallized in (■) absence of PVP, or in the presence of 0.1% w/v of (◊) PVP 2000, (▲) PVP 10000 or (△) PVP 50000.

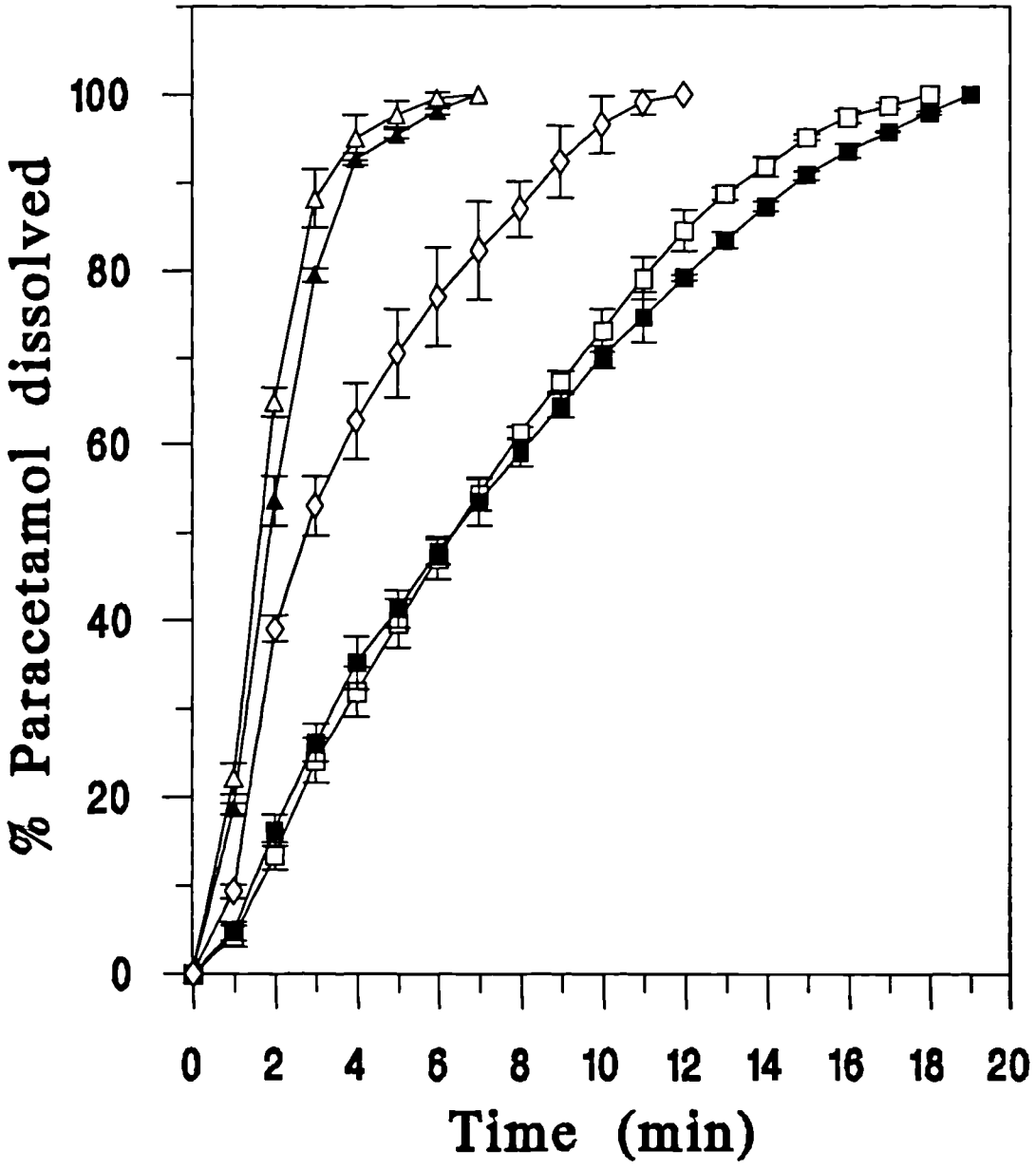


Figure 9.2 Percentage of paracetamol dissolved against time (min) for: (□) untreated paracetamol, and paracetamol crystallized in (■) absence of PVP, or in the presence of 0.3% w/v of (◊) PVP 2000, (▲) PVP 10000 or (△) PVP 50000.

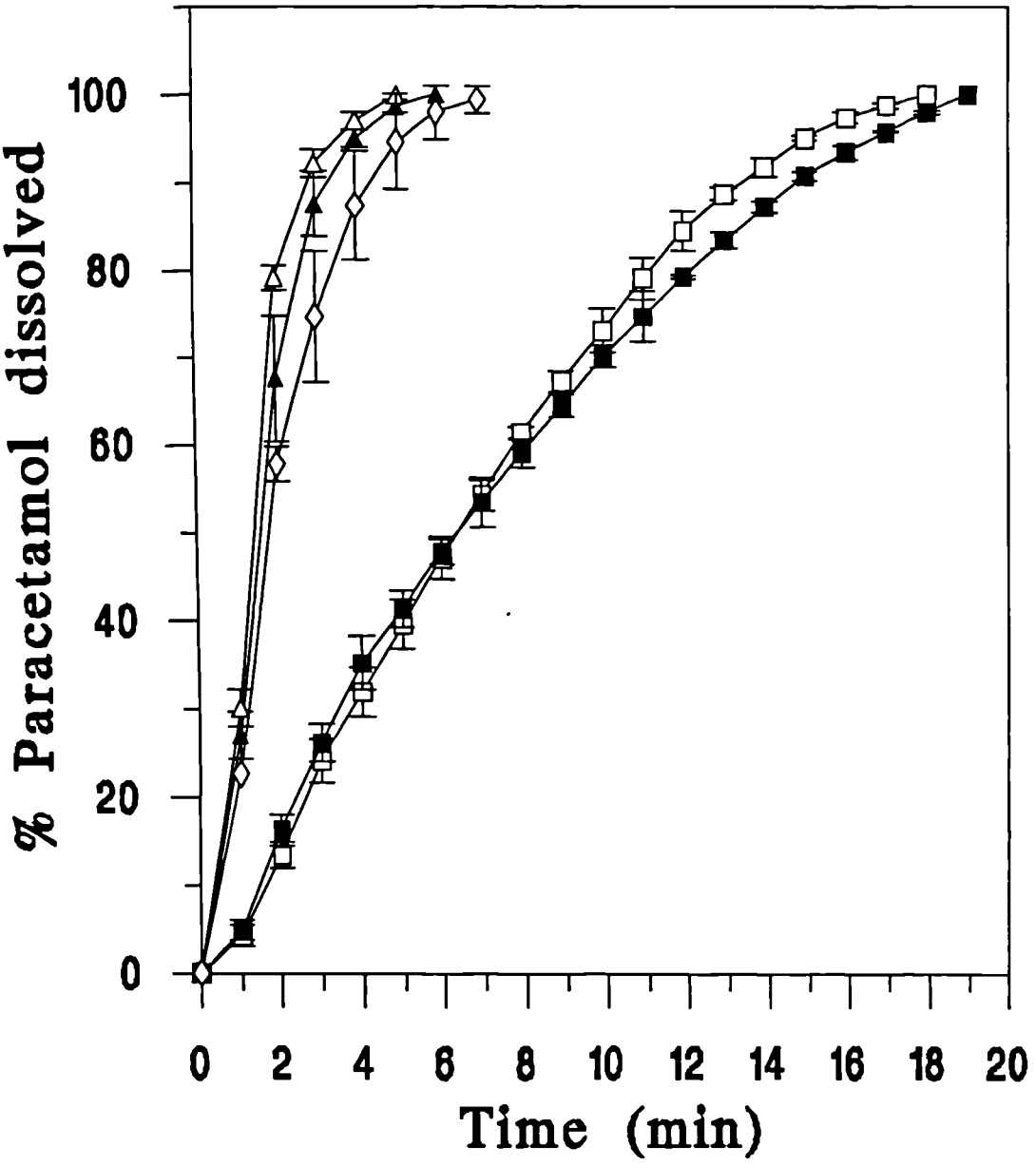


Figure 9.3 Percentage of paracetamol dissolved against time (min) for: (□) untreated paracetamol, and paracetamol crystallized in (■) absence of PVP, or in the presence of 0.5% w/v of (◊) PVP 2000, (▲) PVP 10000 or (△) PVP 50000.

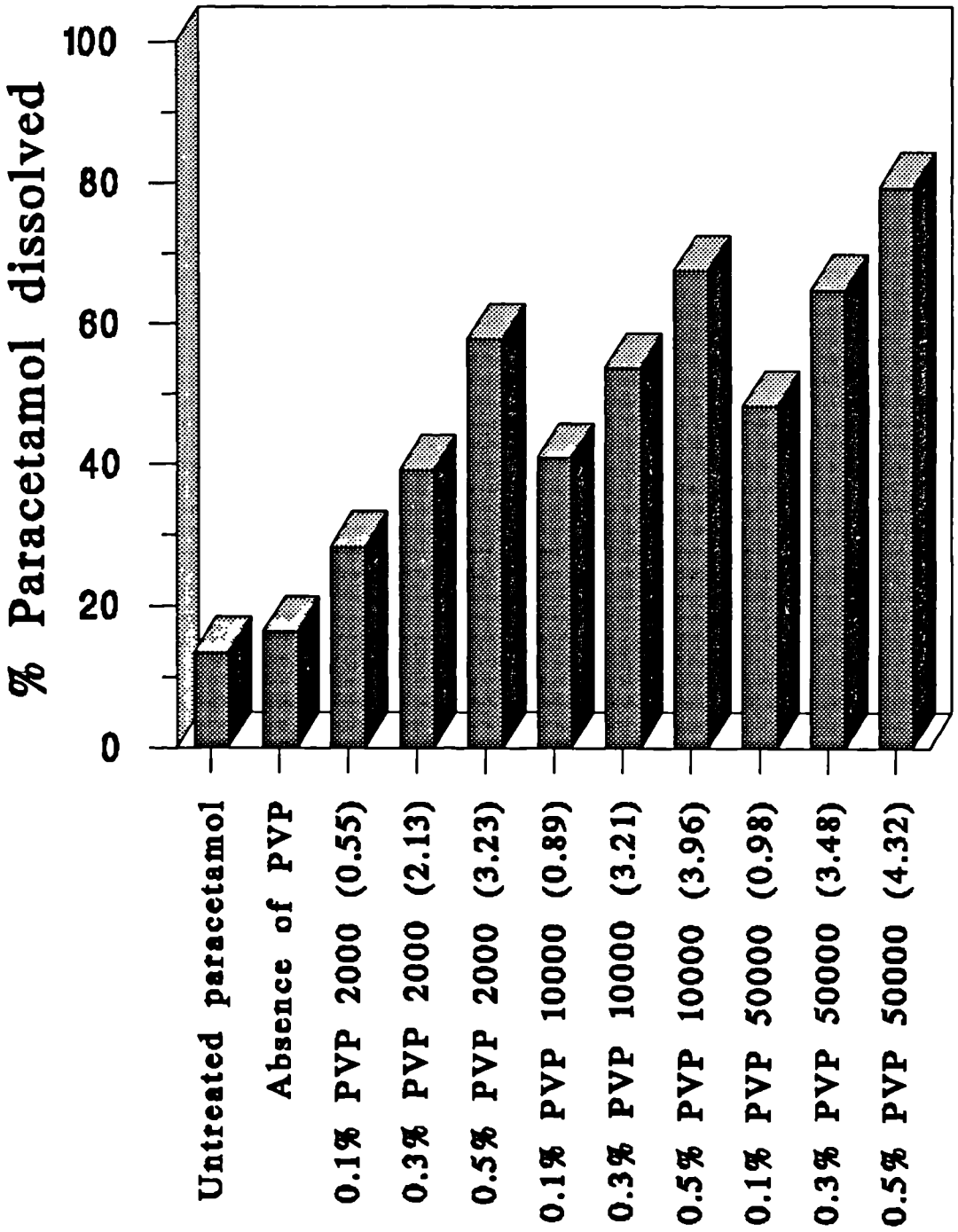


Figure 9.4 Percentage of paracetamol dissolved within the first two minutes during dissolution studies of untreated paracetamol and samples crystallized in the absence or presence of different amounts of various grades of PVP (numbers in brackets are the percentage, %w/w, of PVP in the particles which were taken from table 7.1).

attributed to adsorption of small amounts of surfactant onto the drug particles, which increased their wettability and therefore dissolution rate. El-Bary et al, (1990) demonstrated that crystallization of chlorpropamide in the presence of polysorbate 80, polyethylene glycol or PVP caused marked enhancement in its dissolution rates. The authors claimed that washing the crystals caused a marked decrease in the dissolution rate of chlorpropamide. This was attributed to removing some of the adsorbed surfactant or polymer during washing.

2- The faster dissolution rate of paracetamol crystals obtained in the presence of PVP can be also attributed to reduction in the size of paracetamol crystals following crystallization from PVP solutions. In section 7.3.4, it was shown that paracetamol particles obtained in the presence of <0.3% w/v of PVP had agglomerated structures which consisted of numerous fine microcrystals (figures 7.3-7.6). Decrease in particle size would increase the surface area of paracetamol exposed to the dissolution media and subsequently increases the dissolution rate. El-Bary et al (1990) and El-Samaligy et al (1994) similarly reported that increase in dissolution rate of some drugs crystallized in the presence of surfactants or soluble polymers was due to reduction in their particle size.

Naggar et al (1980) reported that increase in dissolution rate of phenylbutazone following crystallization in presence of polysorbate 80 may be attributed to a slight increase in its solubility. However, Chiou et al (1976)

suggested that although the surfactants can increase the solubility of poorly soluble compounds, the amounts of surfactant adsorbed onto the drug particles crystallized in the presence of surfactants are probably too negligible to affect the solubility of the drug in bulk solution. In the present study, the results of solubility studies (section 9.3, table 9.1) indicated that the aqueous solubility of paracetamol crystallized in presence of PVP was not significantly different to untreated paracetamol.

Figures 9.1-9.4 indicate that with increasing the concentration and/or molecular weight of PVP in the crystallization medium, the obtained paracetamol exhibited faster dissolution rates. This may be attributed to firstly, an increase in the amount of adsorbed PVP onto the particles (table 7.1) or secondly, with increasing the molecular weight and/or the concentration of PVP in crystallization medium, the size of particles decreased (figures 7.3-7.6). These factors lead to an increase in dissolution rate of paracetamol. El-Barry et al (1990) & El-Samaligy et al (1994) similarly demonstrated that by increasing the concentration and/or the molecular weight of hydrophilic polymers such as PVP or polyethylene glycol during the crystallization of salicylhydroxamic acid or chlorpropamide, the dissolution rates of obtained crystals increased.

El-Gindy et al (1982) and Shawky and Mesiha (1988) reported that crystallization of lorazepam or nalidixic acid in the presence of PVP caused a faster dissolution rate than other polymers or surfactants (polysorbate 80

or polyethylene glycol). The authors suggested that PVP is probably able to form a water-soluble complex with these drugs on the surface of their crystals. This may cause a faster dissolution rate. It was also shown that when lorazepam crystallized in the presence of PVP produced crystals with the smallest size and highest specific surface area than other polymers. This may also increase the dissolution rate.

Chiou et al (1976) also suggested that presence of the surfactant during crystallization process might also cause a defect in the crystal structure and crystal would become thermodynamically unstable and, hence, dissolves faster. The results of differential scanning calorimetry (table 7.2, section 7.3.7.4) exhibited that the paracetamol crystallized in the presence of PVP had a lower enthalpy of fusion than untreated paracetamol, which was attributed to the presence of PVP in the particles. This may make the particles less stable, therefore they dissolve faster.

9.4 CONCLUSION

Crystallization of paracetamol in the presence of PVP caused a marked enhancement in its dissolution rate. This enhancement was attributed to adsorption of PVP onto the surfaces of paracetamol crystals which increased their wettability. Decrease in crystal size of paracetamol obtained in presence of PVP was another reason for the higher dissolution rate.

CHAPTER 10. GENERAL DISCUSSION

10.1 INTRODUCTION

Paracetamol is a widely used analgesic which exhibits poor compressibility during compaction, often resulting in weak and unacceptable tablets with a high tendency to cap (Krycer et al, 1982). Some attempts have been made to modify the properties of paracetamol crystals using different crystallization techniques, in order to improve its compaction properties (Fachaux et al, 1992, 1993; Di Martino et al, 1994, 1996; Abdelillah et al, 1995). However, one of the disadvantages of the methods of these co-workers was the use of toxic solvents, such as dioxane or tetrahydrofuran. The main aim of this project was to study the consequences of altering the crystal properties of paracetamol, using different crystallization procedures and toxicologically safe solvents, on their compaction behaviour.

10.2 COMPACTION PROPERTIES OF PARACETAMOL

In general, the strength of a compact depends on the inherent ability of the powder to reduce in volume during compression and the amount of interparticulate attraction in the final compact (Milosovitch, 1963). The poor compaction properties of paracetamol have been attributed to a low degree of plastic flow and high elasticity (Duberg & Nystrom, 1986) and weak bonding between particles (Obiorah & Shotton, 1976). In order to study the fundamental compression characteristics of paracetamol, two different particle size fractions (<90 μm and 105-210 μm), were compressed at different

compression forces and speeds.

Compression of two particle sizes of paracetamol, at all compression forces (10-30 kN), even at the lowest compression speed (10 mm s^{-1}), produced extremely weak tablets which had no measurable strength and a high tendency to cap. Heckel analysis indicated that the larger particles (105-210 μm) underwent more densification than smaller particles (<90 μm), during compaction. This was attributed to increased frictional and cohesive forces associated with the smaller particles which tended to restrict particle sliding and thus reduced densification (York, 1978; Roberts & Rowe, 1986). Furthermore, during compaction, the smaller particles yielded from fragmentation of the larger angular shaped particles, probably tended to fill the remaining interparticulate voids between the particles. This would lead to a further increase in the relative density of the compacts made from larger particles. In contrast, it would be expected that only a relatively small amount of fragmentation would occur in the smaller particle size fractions due to their spherical shape, as reported by McKenna and McCafferty (1982) and Roberts and Rowe (1986).

The values of mean yield pressures (MYP) obtained for the <90 μm and 105-210 μm particle sizes of paracetamol were 44.5 and 34.4 MPa, respectively. A low MYP (less than 50 MPa), obtained for materials such as Avicel®, indicates a high degree of plastic deformation under pressure (Roberts & Rowe, 1987b; Garr & Rubinstein, 1991b). However, York (1978) and Duberg

and Nystrom (1986) reported that the value of MYP derived from the slope of the linear portion of a Heckel plot depends on the elastic and plastic deformation of the material under an applied load. Thus, for elastic materials a false, low MYP is obtained (Fell & Newton, 1971). Therefore, it is difficult to distinguish between plastic and elastic deformation evaluated from the slope of the linear portion of Heckel plot. In an attempt to distinguish between plastic and elastic deformation of materials, Duberg and Nystrom (1986) divided the Heckel plot into three phases and showed that a considerable deviation from the horizontal in phase III (decompression phase) indicated elastic behaviour of material under pressure. A large deviation from horizontal observed in the phase III of Heckel plot for paracetamol was therefore indicative of a high degree of elastic propensity of these particles under pressure. Therefore the low MYP found for paracetamol is attributed to its elastic behaviour and not to plastic deformation.

The correlation coefficient of the initial part of Heckel plot (0-20 MPa) was lower for larger particles, indicating a higher degree of fragmentation for the larger particles than smaller fractions. It has been reported that a linear segment (high value of correlation coefficient) for the initial part (phase I) of a Heckel plot is obtained for non-fragmenting materials such as sodium chloride. A non linear curve with a low value for the correlation coefficient, corresponds to materials, such as Emcompress®, which consolidate by a fragmentation mechanism (Duberg & Nystrom, 1982).

The change of MYP with compaction speeds was calculated as strain rate sensitivity (SRS). The calculated values of SRS for the <90 μm and 105-210 μm fractions of paracetamol were 13.6 and 18.7%, respectively. SRS is a useful index which can show the plastic or brittle nature of a material. Due to the time dependent nature of plastic deformation, the MYP increases with increasing punch velocity for plastic materials such as Avicel® and sodium chloride, which consequently show high values of SRS (>40%) (Roberts & Rowe, 1985; 1987a). However, for lactose, which deforms by a combination of particle fracture and plastic deformation, the SRS was about 16% (Roberts & Rowe, 1985). Therefore the rather low degree of SRS found for paracetamol, is indicative that fragmentation is the dominant mechanism during compaction. Similar results were obtained during the compaction of paracetamol by Roberts and Rowe (1985).

At each compaction speed, as the particle size of paracetamol decreased, the MYP increased. It has been reported that for plastically deforming materials such as sodium chloride (Hersey et al, 1973; Humbert-Droz et al, 1983) and microcrystalline cellulose (Roberts & Rowe, 1986) and starch (McKenna & McCafferty, 1982), the measured MYPs were independent of particle size. However, for materials that deform by particle fragmentation such as lactose and calcium carbonate, the MYP increased with reduction in particle size (Hersey et al, 1973; York, 1978; Roberts & Rowe, 1986). Therefore, the findings in this study again indicated that paracetamol belongs to the group of materials that deform by fragmentation.

Tablets made from the larger particles of paracetamol (105-210 μm) exhibited lower elastic recovery and elastic energy than smaller fractions (<90 μm). This may be attributed to higher interparticulate bondings for the larger fraction. Increased fragmentation of the larger size fractions of paracetamol during compaction, probably caused an increase in interparticulate bonding due to the formation of fresh and clean surfaces, as reported by McKenna and MaCafferty (1982). The high values of the ratio of elastic energy/plastic energy (EE/PE), indicated that the majority of the energy involved during compaction was utilized as elastic energy. The ratio of EE/PE generally increased with increasing compression force or speed. This indicated that at higher compaction forces or speeds the tablets became more elastic. Similar results were reported by Garr and Rubinstein (1991a). They observed that the EE/PE ratio increased with compression speed and suggested that the increases in capping tendencies with compression speed were related to an increase in the EE/PE ratio.

The results of this study demonstrated that paracetamol is a poorly compressible substance. The main mechanism of compression of paracetamol was fragmentation. Paracetamol particles underwent a high elastic deformation during compaction, resulting in weak and capped tablets.

10.3 HABIT MODIFICATION OF PARACETAMOL CRYSTALS AND THEIR TABLETING CHARACTERISTICS

Crystallization of paracetamol from a wide range of solvents such as water,

ethanol or dioxane (Fachaux et al, 1992), isopropanol, dioxane or acetone and their mixtures with water (El-Said, 1995) or alcohols, esters, ketones and acetonitrile (Fairbrother, 1974) produced essentially prismatic polyhedral crystals. The polyhedral habit is the predominant form in paracetamol crystals.

In an attempt to modify the crystal habit of paracetamol, concentrated solutions of paracetamol in hot ethanol (5g/12ml) were rapidly added to 50 ml of cold water at 3°C. After 15 min, with no agitation, the precipitated crystals were collected. This crystallization process, termed the "watering-out" method, caused marked modification to the crystal habit of paracetamol and produced thin plate-like crystals. However, the crystallization of paracetamol using the same method but at 25°C, produced prismatic polyhedral crystals. Alternative crystallization procedures (from water, ethanol or water/ethanol at 3°C or 25 °C) revealed that crystallization solvent (ethanol/water) and crystallization temperature (3°C), i.e. rapid cooling, were both critical in the production of thin plate-like crystals. Elimination of either of these factors inhibited the production of thin plate-like crystals. Crystallization at 3°C produced a high degree of supersaturation for the water/ethanol system. It has been reported that a high degree of supersaturation may cause preferential growth of crystals in one particular direction, leading to the formation of different crystal habits (Mullin, 1993). Some workers have shown that cooling rate has a major influence on the crystal habit. For instance, naphthalene crystallized as thin plates from methanol by rapid

cooling but when it was slowly crystallized, compact (grain-like) crystals were formed (Wells, 1946). Garti and Tibika (1980) demonstrated that by increasing the cooling rate during crystallization of nitrofurantoin from a formic acid/ethanol mixture, more elongated crystals were collected.

DSC, IR and XPD studies revealed that the thin plate-like paracetamol crystals obtained by the watering-out method at 3°C and the prismatic polyhedral crystals obtained from water at 25°C, were habit modifications and not polymorphic modifications.

Prismatic polyhedral crystals of paracetamol obtained from water at 25°C and thin plate-like crystals obtained by the watering-out method at 3°C, were compressed at different compaction forces or speeds to investigate whether crystal habit had any significant effect on the compaction behaviour of paracetamol and whether the modified crystals showed improved compaction properties.

Compression of the thin plate-like and polyhedral crystals at all compression forces (10-30 kN), even at the lowest compression speed (10 mm s^{-1}), produced very weak tablets with no measurable strength and a high capping tendency. The Heckel plots and their associated constants were dependent on the crystal habit. The degree of densification that occured during compression was greater for the polyhedral crystals than for thin plate-like crystals. This was attributed to increased frictional and cohesive forces between the plate-

like crystals, due to their large and flat surfaces which would increase the contact points between them, restrict particle sliding and thus reduce densification.

The correlation coefficients of the initial part of Heckel plots (0-20 MPa) were considerably lower for the plate-like crystals. This was indicative of greater fragmentation of the plate-like crystals as compared to the polyhedral crystals. Marshall and York (1991) reported that different crystal habits of nitrofurantoin (needle and plate-like), crystallized from different solvents, similarly exhibited different Heckel plots. They reported that the degree of densification that occured during compression was greater for plate-like crystals as compared to needle-like crystals. Needle-like crystals showed higher mean yield pressure than plate-like crystals.

The values of SRS for polyhedral and thin plate-like crystals of paracetamol were 27 and 14% respectively, which clearly indicate that plate-like crystals were more brittle during compaction than polyhedral crystals.

The tablets made from plate-like crystals exhibited higher elastic recoveries than those made from the polyhedral crystals. This may be attributed to the interparticulate bondings between the former particles being weaker than between the latter particles. Milosovich (1963) reported that the poor compaction properties of a specific habit of a drug can be attributed to the presence of crystal faces that give poor adhesion to each other and the

absence of faces that are required for optimal adhesion. It is obvious that for plate-like and polyhedral crystals the relative abundance of the different faces within the crystals were modified. This can affect the interparticulate bonding between these crystals resulting in different elastic recoveries for these two habits of paracetamol.

The results of elastic energies supported the elastic recoveries. The plate-like crystals underwent more elastic deformation during compaction than the polyhedral crystals. Hong-Guang and Ru-Hue (1995) investigated the compaction properties of paracetamol of different crystalline shapes. They reported that needle-like crystals of paracetamol exhibited poorer compressibility with a greater extent of capping and lamination compared to tablets made from polyhedral crystals. This was attributed to greater elastic deformation of the needle-like crystals.

The results of this study indicated that the crystal habit had a great influence on the compaction behaviour of paracetamol. However, neither polyhedral nor thin plate-like crystals exhibited any major improvement in the compaction properties as compared to untreated paracetamol.

10.4 TABLETING CHARACTERISTICS OF PARACETAMOL CRYSTALLIZED IN THE PRESENCE OF PVP

There are several reports on attempts to change the crystal habit of a particular substance using additives during the crystallization process

(Michael & Colville, 1960; Fairbrother & Grant, 1978, 1979; Chow et al, 1985; Femi-Oyew & Spring, 1994; Kaul et al, 1992). One group of additives used during the crystallization processes is long chain polymeric materials (Mullin, 1993). There are several examples in the literature where PVP has been demonstrated to be a strong crystal growth inhibitor for drugs such as sulphathiazole, salicylic acid and paracetamol by adsorption on to their crystal surfaces (Simmonelli, 1970; Ziller & Rupprecht, 1988 & 1990).

Paracetamol was crystallized in the presence of PVP using a watering-out method, similar to that described in the previous section. Hot ethanolic solutions of paracetamol (5g/12ml) were rapidly added to 50 ml quantities of cold water at 3°C containing 0, 0.1, 0.3 or 0.5% w/v PVP of molecular weight 2000, 10000 or 50000. The resultant solutions were maintained at about 3±1°C without agitation. After 15 min the precipitated particles were collected. The presence of PVP in the crystallization medium increased the induction time required for appearance of crystals and decreased the crystal recovery. The obtained paracetamol particles contained small amounts of PVP. The use of PVP in the crystallization media had a major effect on the morphology of the crystals. Paracetamol crystals obtained in the absence of PVP were very thin and flaky, whereas those obtained in the presence of ≥0.3% w/v of PVP 10000 or PVP 50000 were near spherical in shape. The particles were agglomerates (clusters) of numerous fine rod-shape microcrystals which had stuck together. The particles obtained in the presence of PVP 2000, even at its highest concentration (0.5% w/v), consisted

of a few microcrystals which had stuck together. Davey (1982) reported that active additives influence the crystallization process and produce crystals of different shape to those formed from a pure solution. Furthermore, the active additives increase the induction time and also reduced the crystal growth and yield. The observed changes in crystal habit of paracetamol, the delay in the appearance of crystals, reduction in crystal yield and sorption of PVP by paracetamol particles, were indicative that PVP is an effective additive during the crystallization of paracetamol. It appeared that the highest molecular weight of PVP was the most effective additive. The relative effectiveness of the three grades of PVP, as considered by the parameters mentioned above, followed the order PVP 50000>PVP 10000>PVP 2000. All these observed effects of PVP during crystallization of paracetamol were attributed to the adsorption of PVP onto the paracetamol particles during crystal growth.

Particles crystallized in the presence of 0.5% w/v of PVP 2000, PVP 10000 or PVP 50000 contained 3.23, 3.96 or 4.32% w/w of PVP, respectively. DSC, XPD and IR experiments showed that paracetamol particles crystallized in the presence of PVP, did not undergo internal structural modifications compared to untreated paracetamol. However, DSC studies showed that the enthalpy of fusion of paracetamol crystallized in the presence of PVP decreased. This was attributed to the presence of PVP in the particles, and not crystal disruption.

The paracetamol particles crystallized in the presence of PVP were compressed at different compaction forces and speeds. The tablets made from these particles showed crushing strengths which increased with increasing molecular weight and/or the concentration of PVP in the crystallizing solution. The results of crushing strength demonstrated that particles crystallized in the presence of 0.5% w/v PVP 10000 or PVP 50000 produced tablets with excellent hardness and a lack of tendency to cap. These particles did not show a major reduction in their crushing strength with increase in compaction speed. This may be attributed to fragmentation of the particles under applied load. It has been reported that the crushing strength of tablets made from materials such as xylitol or Emcompress®, which consolidate by fragmentation, were independent of compression speed (Garr & Rubinstein, 1990; Garr, 1992). Particles obtained in the presence of PVP 2000 showed little improvement in their compaction properties.

The SRS values of particles crystallized in the presence of 0.5% w/v of PVP 2000, PVP 10000 or PVP 50000 were 5.9, 8.4 or 14.9%, respectively. The lower values of SRS for paracetamol crystallized in the presence of PVP 10000 or PVP 50000 indicate that these particles were less sensitive to compaction speed, suggesting that a high degree of fragmentation occurred during compression. Materials which consolidate by fragmentation show no significant change in mean yield pressure with increasing compaction speed and therefore exhibit a low SRS (Roberts & Rowe, 1985; Garr, 1992). Another reason which indicates that particles crystallized in the presence of PVP

underwent extensive fragmentation during compaction was the lack of major reduction in the crushing strengths of the tablets following the addition of magnesium stearate to the particles. It has been reported that materials which mainly deform by plastic deformation such as sodium chloride are sensitive to even small additions of lubricant and exhibit a dramatic decrease in their crushing strength but materials, such as Emcompress®, which undergo fragmentation, are practically uninfluenced by mixing with magnesium stearate (Duberg & Nystrom, 1982).

A low deviation from the horizontal of the decompression phase (phase III) of the Heckel plots of particles crystallized in the presence of PVP and the elastic recoveries indicated that tablets made from particles crystallized in the presence of PVP exhibited lower elastic behaviour than untreated paracetamol. Tablets made from particles obtained in the presence of PVP 10000 or PVP 50000 exhibited lower elastic recoveries than those obtained in the presence of PVP 2000 following the removal of compression pressure. Similarly, the elastic energies indicated that tablets made from particles crystallized in the presence of PVP underwent less elastic deformation than those composed of the untreated paracetamol. The tablets made from particles crystallized in the presence of higher molecular weight PVP were less elastic than for particles obtained in presence of lower molecular weight PVP.

The energy analysis also revealed that plastic energies of tablets made from

particles crystallized in the presence of PVP were higher than for the untreated particles. The increases in plastic energy of tablets made from particles crystallized in the presence of PVP may be attributed to the energy required for fragmentation of these particles and most importantly to the formation of bonds between the particles during compaction. The high crushing strengths of the tablets made from particles obtained in the presence of PVP indicated strong interparticulate bonding.

The ratios of EE/PE for particles crystallized in the presence of PVP were much lower than for untreated crystals. These results indicate that for untreated particles the major portion of compaction energy was utilised as elastic energy, while for particles obtained in presence of PVP a minor portion was used as elastic energy. These results again confirm that tablets made from particles crystallized in the presence of PVP exhibited lower elastic behaviour than untreated paracetamol. It was also shown that paracetamol crystallized in the presence of higher molecular weights of PVP (PVP 10000 or PVP 50000) exhibited lower EE/PE ratios than those obtained in the presence of PVP 2000.

The results of this study showed that particles crystallized in the presence of 0.5% w/v of PVP 10000 or PVP 50000 produced tablets with excellent hardness with no tendency to cap, even at highest compaction speed (250 mm s^{-1}). These particles exhibited considerably less elastic behaviour during compaction, as compared to untreated paracetamol.

CHAPTER 11. CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE WORK

11.1 CONCLUSIONS

Paracetamol as a model of a poorly compressible drug was subjected to different crystallization procedures to produce different crystal morphologies. The obtained particles were compressed at different compaction forces or speeds to investigate whether crystal morphology had any significant effect on the compaction behaviour of paracetamol and whether the modified crystals showed any improvement in their compaction properties, as compared to untreated paracetamol.

Untreated paracetamol exhibited poor compaction properties and produced very weak tablets with a high tendency to cap. The results of Heckel analysis indicated that the main mechanism of compaction of paracetamol was fragmentation. The phase III of Heckel plot, elastic recovery, elastic energy and elastic energy/plastic energy ratio indicated that paracetamol particles underwent high elastic deformation during compaction, resulting in weak and capped tablets.

Crystallization of paracetamol by a combination of "watering-out" from an ethanolic solution and rapid cooling produced thin plate-like crystals. These findings indicated a marked modification in the crystal habit compared to the prismatic polyhedral crystals obtained from water. Compression of polyhedral

and thin plate-like crystals revealed that crystal habit influenced the compaction behaviour of paracetamol. Polyhedral crystals exhibited a greater plasticity during compaction compared to the thin plate-like crystals, which were more brittle. Thin plate-like crystals underwent more elastic deformation during compaction than polyhedral crystals. These two crystal habits of paracetamol did not exhibit major improvement in their compaction properties compared to untreated particles.

Crystallization of paracetamol by a combination of "watering-out" from ethanolic solutions at low temperature and in the presence of 0.5% w/v of PVP molecular weight of 10000 or 50000 produced near spherical, agglomerated particles of paracetamol. These agglomerates consisted of numerous rod-shaped microcrystals which had stuck together. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals. The most important advantages of this crystallization method were using water as the major portion of solvent and ethanol as the minor portion of solvent (water and ethanol are the cheapest and safest solvents), and using a safe and widely used excipient, PVP, as additive. Particles obtained in the presence of PVP 10000 or PVP 50000 produced tablets with excellent hardness and with no tendency to cap even at high compaction speed. Particles obtained in the presence of PVP 2000 exhibited little improvement in their compaction properties. The results of elastic recovery, elastic energy and elastic energy/plastic energy ratio revealed that particles crystallized in the presence of PVP exhibited much less elastic behaviour under pressure, as

compared to untreated paracetamol. Paracetamol crystallized in the presence of PVP also exhibited a marked enhancement in dissolution rate. This was attributed to adsorption of PVP onto the surfaces of paracetamol crystals which increased their wettability and therefore dissolution rate.

11.2 RECOMMENDATIONS FOR FUTURE WORK

1- After crystallization of paracetamol in the presence of PVP, the residual solvent contained PVP and paracetamol. Therefore, it is necessary to find an appropriate method to separate and recover the PVP and paracetamol from the residual solvent.

2- In this study, the paracetamol crystallized in the presence of PVP was compressed without any excipients or adjuvants. Therefore, it would be useful to find a suitable formulation in order to optimize the hardness, and disintegration and therefore dissolution time of tablets made from paracetamol crystallized in the presence of PVP.

3- In this study, the crystallization of paracetamol in the presence of PVP was carried out using watering-out method. It would be interesting to see if crystallization of paracetamol in the presence of PVP using the same solvents (water/ethanol), but by evaporation of solvent in vacuum which will be a rapid crystallization, can produce such compressible particles as obtained by the watering-out methods.

4- Crystallization of paracetamol by watering-out technique from its ethanolic solution in the presence of PVP improved its compressibility. It would be interesting to see if this technique would also prove useful in improving the compression properties of other poorly compressible drugs.

5- Crystallization of paracetamol was carried out in presence of only PVP. However, there are some reports that other polymers such as HPMC which can inhibit the crystallization of drugs. Therefore, the potential of using other polymers during the crystallization of paracetamol should be investigated.

APPENDIX 1

1- Composition of 0.006 N iodine solution for photometric measurement of PVP in aqueous solution:

0.81 g of sublimed iodine and 1.44 g of potassium iodide dissolved in 1000 ml of water.

2- Composition of blank solution for photometric measurement of PVP in aqueous solution:

50 ml of water + 25 ml of 0.2 M citric acid solution + 10 ml 0.006 N iodine solution.

ABBREVIATIONS

ΔH_f	Enthalpy of Fusion
µm	Micrometer
BDH	British Drug Houses
BP	British Pharmacopoeia
C	Concentration
CS	Crushing Strength
CT	Capping Tendency
D	Relative Density
DSC	Differential Scanning Calorimetry
EDTA	Ethylendiamine Tetra-Acetic Acid
EE	Elastic Energy
ER	Elastic Recovery
g	Gram
h	Hour
IR	Infrared
J	Joule
kg	Kilo gram
kN	Kilo Newton
kp	Kilo Pound
kV	Kilo Volt
Ln	Natural Logarithm
LVDT	Linear Variable Differential Transformer
mPa s	Milli Pascal Seconds
M	Molar
mg	Milligram
min	Minute
ml	Millilitre
mm	Millimetre
Mol. Wt.	Molecular Weight
MPa	Mega Pascal
MYP	Mean Yield Pressure
N	Normal

nm	Nanometre
PE	Plastic Energy
PF	Pyrogen Free
PH	Polyhedral
psi	Pounds per square inch
PVP	Polyvinylpyrrolidone
r	Correlation Coefficient
s	Second
SD	Standard Deviation
SEM	Scanning Electron Microscopy
SRS	Strain Rate Sensitivity
TA	Thermal Analysis
T_m	Melting point
TPL	Thin Plate-like
USP	United State Pharmacopoeia
UV	Ultraviolet
v/v	Volume in Volume
w/v	Weight in Volume
w/w	Weight in Weight
XPD	X-ray Powder Diffraction

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ATTENDANCE AT CONFERENCES

1- British Pharmaceutical Conference, Warwick, UK, September, 1995.

2- 15th Pharmaceutical Technology Conference, Oxford, UK, March, 1996.

3- The 1st and 2nd Seminars of Iranian Pharmacy Postgraduate Students, Manchester, UK, June and December, 1994.

4- Attending Postgraduate Research Seminars at the School of Pharmacy and Chemistry, Liverpool John Moores University.

PUBLISHED COMMUNICATIONS AND PRESENTATIONS

The following have been published or presented in advance of this thesis. Copies may be found in the pocket at the end of this thesis:

1- The role of crystalline modifications on the compaction properties of paracetamol.

Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.

Presented to the Postgraduate Research Seminar, School of Pharmacy and Chemistry, Liverpool John Moores University (January, 1995).

2- Effect of crystal habit on the compaction properties of paracetamol.

Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.

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3- Highly compressible paracetamol: Crystallization and characterization.

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4- Habit modification of paracetamol crystals and their tableting characteristics.

Garekani, H.A., Ford, J.L., Rubinstein, M.H., Rajabi-Siahboomi, A.R.

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5- Manipulation of acetaminophen crystals for direct compression.

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