THE FORMULATION AND EVALUATION OF INDOMETHACIN TABLETS

BY

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CONTENTS

CHAPTER II: METHODS AND PREFORMULATION STUDIES

PAGE NO

CHAPTER III: TABLETTING

LIST OF TABLES

PAGE NO

LIST OF FIGURES

INTRODUCTION AND OBJECTIVES

Indomethacin is an anti-inflammatory analgesic with antipyretic properties. It is used to relieve the painful symptoms of ankylosing spondylitis and osteoarthritis, and to relieve the pain and swelling in gout, rheumatoid arthritis, and acute musculoskeletal disorders.

Indomethacin is currently only available as a capsule dosage form in South Africa. The drug is poorly soluble, its absorption is erratic and it can cause gastro-intestinal irritation. In addition, capsules are generally more expensive to produce than tablets. It is postulated that the formulation of indomethacin tablets, in which the drug is present in an apparently more soluble form, could provide an alternative (and, possibly, cheaper) dosage form having an improved bioavailabililty, a more rapid onset of action and less potential for gastro-intestinal disturbances caused by the accumulation of undissolved drug.[1]

The overall objective of this research is to attempt to produce, by direct compression, indomethacin tablets which have good dissolution characteristics and an improved bioavailability profile, when compared to the capsule formulations currently available. In order to use the direct compression method, the solubilized form of indomethacin should have good flow properties, as well as a small bulk volume for incorporation into reasonably sized tablets.

With the above in mind, the specific purpose of this project was:

(a) to improve the solubility of indomethacin by changing its solid state properties, using cheap and simple methods of solubilization;

(b) to select the most promising solubilized form of indomethacin (using preformulation tests), for incorporation into directly compressed tablets; and

(c) to evaluate these tablets with respect to their bioavailability.

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[1] A recent study has shown that a prodrug of indomethacin (having a minimum of a 2000-fold increase in solubility) was at least 30% more bioavailable than the parent drug, following a single oral equimolar solution dose in rats. In addition, it was significantly less irritating to gastric mucosa than the parent drug, following single-dose and chronic oral administration in rats (Tammara, V.K., Narurkar, M.M., Crider, A.M. and Khan, M.A. Synthesis and Evaluation of Morpholinoalkyl Ester Prodrugs of Indomethacin and Naproxen. Pharm. Research., 10 (1993) 1191).

CHAPTER I

LITERATURE SURVEY

1.1 SOLID SOLUBILIZATION

1.1.1 INTRODUCTION

Aqueous solubility has long been recognized as a key factor in controlling drug efficacy. Before an orally administered drug becomes available to its receptor, it first has to dissolve in the gastro-intestinal fluid. Both the dissolution rate and the maximum amount of drug that can be dissolved are governed by the solubility of the drug in the medium (Yalkowsky and Morozowich, 1980).

Various techniques exist to improve the aqueous solubility of chemical substances. One such technique is the formation of prodrugs. However, for the purpose of this study, this method has been excluded. Another approach is to increase the solubility of the drug by changing the solid state properties of the drug. When the drug is to be formulated as a directly compressed tablet dosage form, the method of solubilization used is limited by the necessity of producing a more soluble form of the drug which, in the solid state, will have good flow properties to ensure good tabletting properties. Furthermore, a high drug to solubilizing excipient ratio is necessary to ensure reasonably sized tablets.

1.1.2 THEORETICAL CONCEPTS

1.1.2.1 **Factors causing insolubility**

To decide whether a drug can be solubilized to a specific extent and, if so, which solubilization technique will be most effective, requires an understanding of why the drug is insoluble.

According to Yalkowsky (1981) the aqueous solubility of a drug is governed by three major factors:

1. The entropy of mixing which favours complete miscibility of all components.

2. The difference between the sum of the drug-drug (DD) and water-water (WW) interactions, on the one hand, and the drug-water (DW) interactions on the other. This difference is related to the activity coefficient (γ_w) of the drug in water, as expressed by the equation:

   $$RT \ln \gamma_w = DD + WW - 2DW \qquad (1)$$

   where R = gas constant

   T = temperature in degrees Kelvin

   If $DD + WW - 2DW > 0$, then there is less than complete mixing of the drug with water. This is usually the case for nonelectrolytes, giving the drug a finite solubility in water. The greater the difference between the adhesive and cohesive interactions of the drug and water molecules, the lower the solubility.

3. The additional drug-drug interactions (DD) which are associated with the lattice energy between individual molecules of crystalline drugs. This effect is measured as the ideal solubility of a crystalline solute (X_i). The ideal solubility is dependent on the melting point and other thermodynamic properties of fusion. The ideal solubility represents the solubility of a solute in a perfect solvent (i.e. when the activity coefficient of the solvent is equal to unity).

Mathematically, the observed solubility (X_w) is related to the ideal solubility and the activity coefficient (γ_w) by the following equation :

$$\log X_w = \log X_i - \log \gamma_w \qquad (2)$$

Molecular interactions in crystalline structures as reflected by X_i, as well as solution interactions as reflected by γ_w, can contribute to the insolubility of the compound. These factors can both be modified as a means of solubilizing the drug.

1.1.2.2 The influence of melting point on solubility

Using equations 1 and 2 , Yalkowsky and Valvani (1980) obtained, on the basis of a semi-empirical analysis, equation (3) which enables the estimation of the aqueous solubility of either liquid or crystalline organic nonelectrolytes:

$$\log S_w \approx -1.00 \log PC - 1.11 \frac{\Delta S_f (MP - 25)}{1364} + 0.54 \qquad (3)$$

where log PC and ΔS_f are estimated from the chemical structure and MP (melting point) is either known or experimentally determined. Analysis of this equation provides a means of assessing the role of crystal structure [as reflected by the melting point (m.p.) and the entropy of fusion (ΔS_f)] and of the activity coefficient [as reflected by the octanol-water partition coefficient (PC)] in controlling the aqueous solubility of a drug.

It can clearly be seen from equation (3) that the melting point of a drug is an important factor in determining the observed aqueous solubility. When attempting to solubilize a drug, the choice of a method depends on a variety of factors, including the nature of the solute and the degree of solubilization required. However, the first step in selecting a method of solubilization is to determine why the drug is insoluble, i.e. whether the difference between the sum of the drug-drug interactions and the water-water interactions, on the one hand, and the drug-water interactions on the other (DD + WW - 2DW), or only the drug-drug interactions (DD), or a combination of these parameters is responsible for the insolubility of the drug.

The easiest way to determine whether DD is a determinant of the drug's insolubility is to look at its melting point. If m.p. > 200°C, DD is probably a significant factor in reducing solubility. If m.p. > 300°C, DD is definitely a major factor. In fact, each 100 degree increase in melting point above 25°C corresponds to at least a 10-fold decrease in in solubility. If the drug is a liquid or it melts below 100°C, it is not likely that crystal interactions have any significant effect on solubility.

For liquids and low-melting drugs the most fruitful techniques of solubilization are those that alter the solvent in such a way as to decrease DD + W'W' - 2DW', where W' represents the aqueous phase. Surfactants, cosolvents, and soluble complexing agents can be used to decrease W'W' or to increase DW'. In other words, they make the aqueous phase a more favourable environment for the drug. These techniques will usually not be very efficient for solubilizing highly crystalline solutes. Such solutes, which tend to be insoluble in nearly all solvents, require an alternate mechanism for a significant increase in solubility. Their crystal interaction energy must be overcome so that the ideal solubility can be increased. This can be accomplished by altering the nature of the crystal. Since microcrystalline indomethacin has a melting point of 160°C and is poorly soluble in water, i.e less than 1 in 10 000 (Reynolds, 1982), modifying the crystal structure is the line of approach chosen to solubilize indomethacin in this study. The crystal structure can be modified in a solid dispersion system.

When it is not possible nor practical to alter solubility by these conventional techniques, it becomes necessary to chemically alter the drug. The prodrug approach offers the advantage of retaining the drug's activity while increasing its solubility. As stated previously, the prodrug approach is beyond the scope of this study.

1.1.3 SOLID DISPERSION SYSTEMS

1.1.3.1 Introduction

Various names for solid dispersions have been used and the term needs to be defined to prevent confusion. Chiou and Riegelman (1971) define a solid dispersion as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state. This dispersion may be achieved by melting, the use of solvents or a combination of both methods. The terms solid state dispersion or coprecipitate may also be used.

In 1961, a unique method was proposed by Sekiguchi and Obi. They proposed the formation of a eutectic mixture of a poorly soluble drug, sulphathiazole, with a physiologically inert, easily soluble carrier such as urea. The eutectic mixture of the drug and carrier (prepared by physical mixing, followed by melting and then rapid solidification), when exposed to aqueous fluids released the active drug as fine, dispersed particles due to the fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix. This development led the way to the use of glass solutions and solid solutions to improve the bioavailability of various drugs. Techniques used in the fields of chemistry, geology and metallurgy were applied to pharmaceuticals. These developments have been extensively reviewed by Chiou and Riegelman (1971).

Since the dissolution rate of a drug from a surface is affected by the second component in a multicomponent mixture, the selection of a carrier has an ultimate influence on the dissolution characteristics of the dispersed drug. Therefore, a water-soluble carrier results in the faster release of the drug from the matrix. The opposite effect could also be achieved where a water- insoluble carrier results in a slower release of the drug from the matrix. Since the overall objective of this project is to enhance the dissolution rate of the drug, the latter approach has been ignored. The dispersion of a drug in a carrier by mechanical mixing is not regarded by Chiou and Riegelman (1971) as a solid dispersion.

The methods of production of the various disperse systems and the physical appearance of the products obtained are similar. Therefore, an overview of the various dispersion systems (solid solutions, glass solutions and simple eutectic mixtures) is essential to differentiate between the methods. For the purpose of this discussion, some of the relevant information given in Chiou and Riegelman's review article on the pharmaceutical applications of solid dispersions (1971) will be presented.

1.1.3.2 **Classification of dispersion systems**

Solid dispersion systems may include more than two components. However, Chiou and Riegelman (1971) limited their review article to binary systems, i.e. those in which a poorly soluble drug is dispersed in a rapidly soluble matrix. Although there are various criteria for classifying disperse systems, these authors classified solid dispersions on the basis of their major fast- release mechanisms:

1. simple eutectic mixtures
2. solid solutions
3. glass solutions and suspensions

4. amorphous precipitations of a drug in a crystalline carrier
5. compound or complex formations between the drug and the carrier
6. any combinations of the above.

1.1.3.2.1 **Simple eutectic mixtures**

Chiou and Riegelman (1971) describe a simple eutectic mixture as one that is usually prepared from the rapid solidification of the fused liquid of two components which show complete liquid miscibility and negligible solid-solid solubility. Thermodynamically, Goldberg et al.(1966a), regard such a system as an intimately blended physical mixture of its crystalline components.

The eutectic properties can be illustrated using a phase diagram (figure 1). When a eutectic of a poorly soluble drug (composition E in figure 1) is exposed to water or gastro-intestinal fluids, the carrier may be released into the aqueous medium in fine crystalline form. Presumably both components may simultaneously crystallize out as very small particles. When a poorly soluble drug and a water-soluble carrier form part of the system, then the rate of dissolution and absorption of the drug is increased. The increase in specific area due to the reduction of particle size generally increases the rates of dissolution and oral absorption of poorly soluble drugs. In addition, various other factors may contribute to the faster dissolution rate of the drug in a matrix. These factors are discussed in section 1.1.3.4.

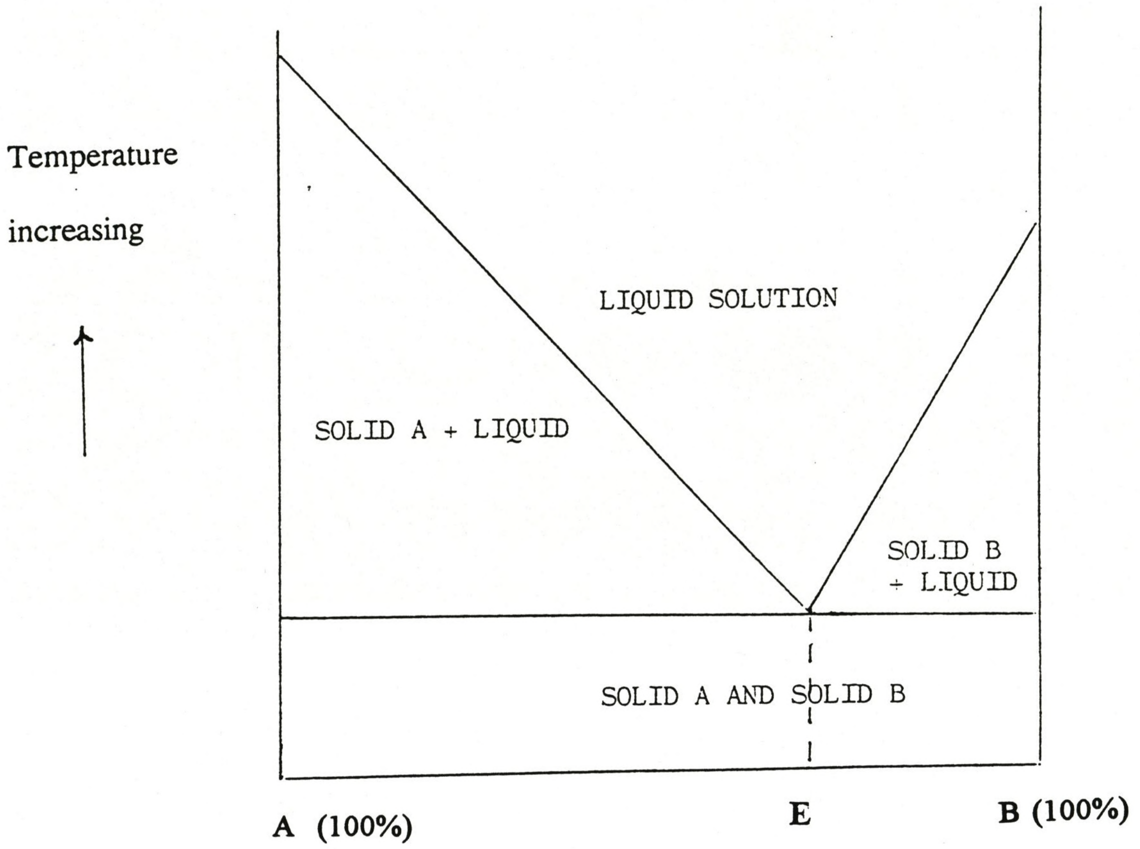


FIGURE 1: THE PHASE DIAGRAM OF A SIMPLE EUTECTIC MIXTURE WITH NEGLIGIBLE SOLID SOLUBILITY

Eutectics differ from physical or mechanical mixtures in that they are extremely hard. Savchenko (as reported by Chiou and Riegelman, 1971) studied the increased hardness of eutectics. The increased hardness was explained on the basis of a high degree of strain resulting from the action of mechanical forces. A eutectic is formed by a loose molecular or atomic interaction, which does not involve the formation of a chemical bond. The influence of hardness on dissolution has, however, not been investigated.

Referring to work done by Goldberg et al. (1966b), Chiou and Riegelman conclude that the composition of a eutectic may have a significant effect on the particle size of the crystallites of the dispersed drug. If it is made up of a high weight fraction of drug, an ultrafine crystallization of the drug may not be obtained -especially since one expects that the higher the dilution, the finer the crystalline size of its precipitate. This probably accounts for the failure to find an increased dissolution rate of acetaminophen from the eutectic with urea, containing 52% of acetaminophen (Goldberg et al., 1966a). The hardening effect of the eutectic may also play a role in retarding its dissolution.

The confusion that exists in the literature when defining solid solutions and eutectic mixtures can be avoided by using X-ray diffraction and differential thermal analysis (DTA) studies. Sekiguchi et al. (1964) have demonstrated that a 10% chloramphenicol-90% urea system gives clear diffraction peaks similar to those of pure chloramphenicol.

The similarity of the diffraction peaks of the eutectic mixture compared to those of the pure drug indicate the absence of solid solution formation. This observation is identical for DTA thermograms. Solid solution formation is characterized by the absence of diffraction peaks and endothermic DTA thermograms. Simple eutectic mixtures melt at their eutectic temperatures, while physical mixtures of the pure drug and urea melt at higher temperatures.

1.1.3.2.2 **Solid solutions**

A solid solution comprises a solid solute dissolved in a solid solvent. The two components crystallize together into a homogenous one-phase system. This definition excludes a drug dispersed onto the solid surface of an insoluble carrier, i.e. a solid surface dispersion.

Goldberg et al. (1966b) have suggested that a solid solution of a poorly soluble drug in a rapidly soluble carrier has a greater solubility than a eutectic mixture primarily because the particle size of the drug is reduced to a minimum state, i.e. to its molecular size. In addition, factors 1-4 (as discussed in section 1.1.3.4) may contribute to increased rates of dissolution and absorption of drugs dispersed in solid solutions.

The advantages of a solid solution can only be used to the fullest extent if there is enough solvent to dissolve all the drug. If not , the drug may precipitate. However, due to the maximum particle-size reduction of the drug in the solid solution and to the possible solubilization effect of the carrier in the microenvironment diffusion layer of the bulk fluids, there may be a high supersaturation of the bulk fluid. The supersaturation of the drug in the diffusion layer is temporary and would lead to the precipitation of the drug, if it is not absorbed or removed by other processes.

Solid solutions are generally classified according to the extent of miscibility between the two components, or according to the crystalline structure of the solid solution. Chiou and Riegelman (1971) divide solid solutions, based on the former criterion, into two groups: continuous (isomorphous, unlimited or complete) solid solutions and discontinuous (limited, restricted, partial or incomplete) solid solutions. Using the crystalline structure as a criterion, solid solutions are classified into substitutional and interstitial solid solutions.

Chiou and Riegelman (1971) have summarized the differences between the various solid solutions. The difference in miscibility of the two components is shown using phase diagrams (figure 2). Figure 2(a) illustrates a continuous solid solution of a binary system. In this system, the two components are miscible or soluble at solid state in all proportions. It is theoretically possible for such a solid solution to have fast-release dissolution properties, although this has not yet been shown. When the poorly soluble drug is present as the minor component, a faster dissolution rate would be obtained. When the composition is reversed and the rapidly soluble carrier is the minor component in the crystalline lattice of the poorly soluble drug, the dissolution rate may also be faster for the solubilized drug than for the pure drug with comparable particle size. This may be due to the smaller number of neighbouring drug molecules holding the dissolving drug molecule after the rapid dissolution of the neighbouring water-soluble carrier.

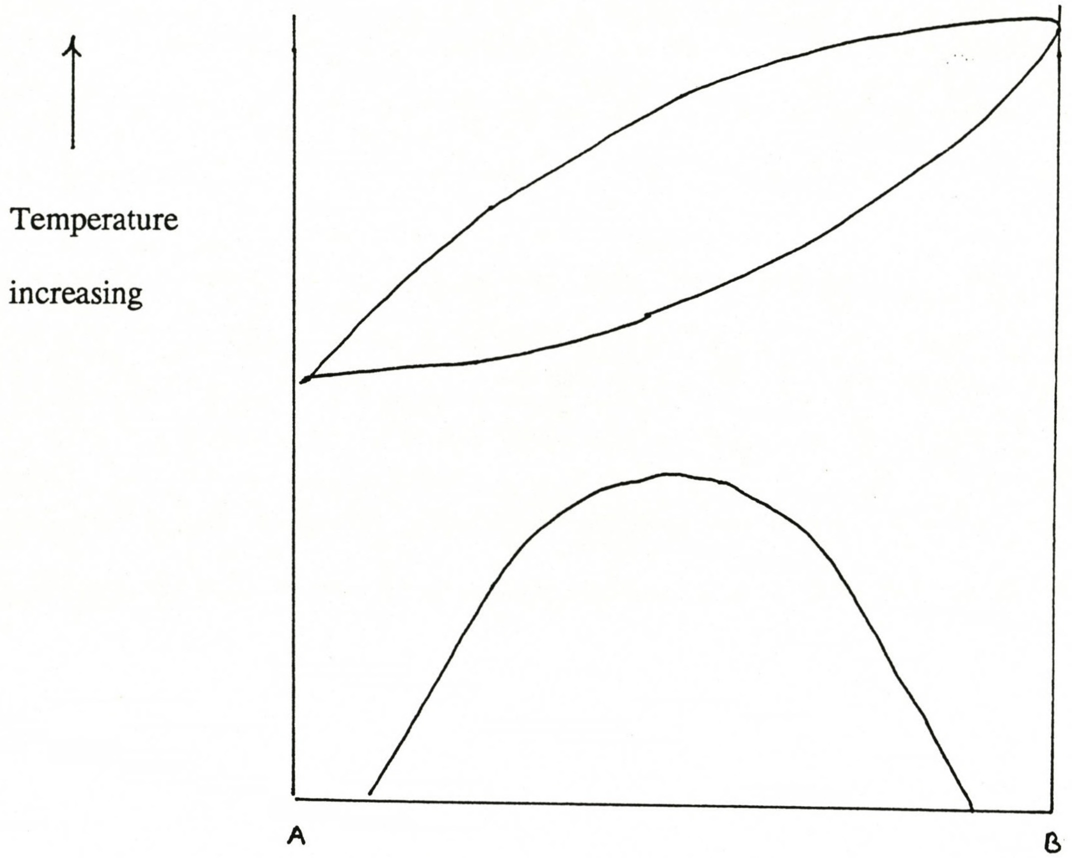


FIGURE 2: (a) CONTINUOUS SOLID SOLUTION: A typical phase diagram of a continuous solid solution of a binary system, A and B. The lowest curve indicates a solubility gap at lower temperatures.

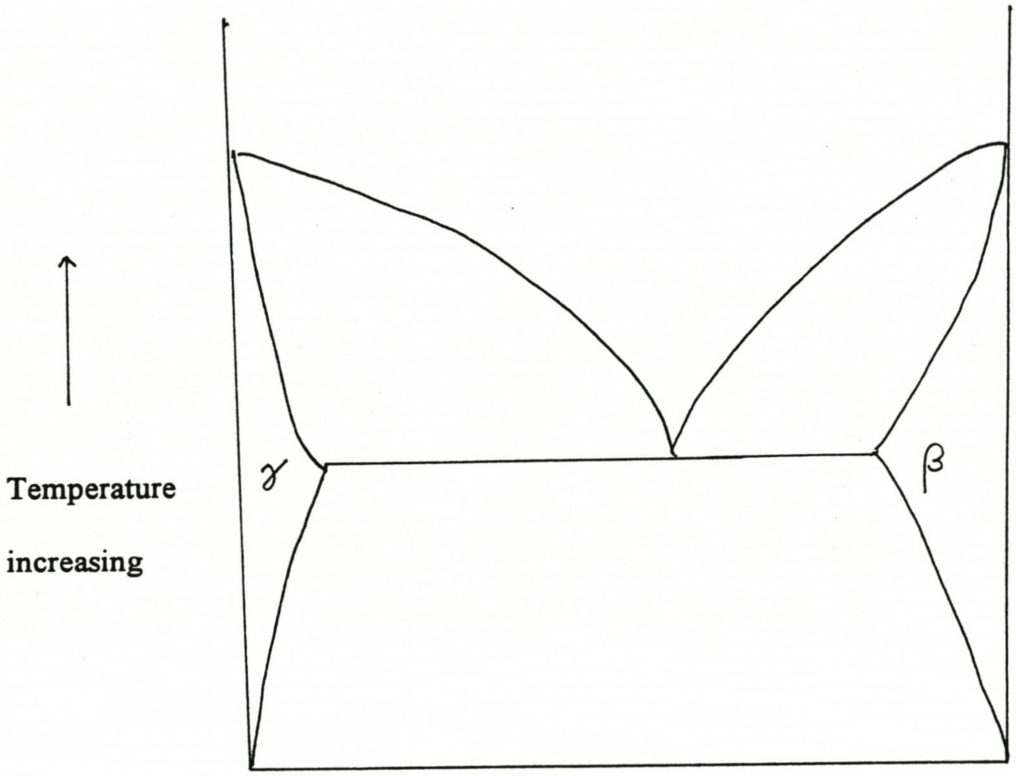


FIGURE 2: (b) DISCONTINUOUS SOLID SOLUTION: A typical phase diagram of a discontinuous solid solution of a binary system, A and B. γ and β are regions of solid solution formation.

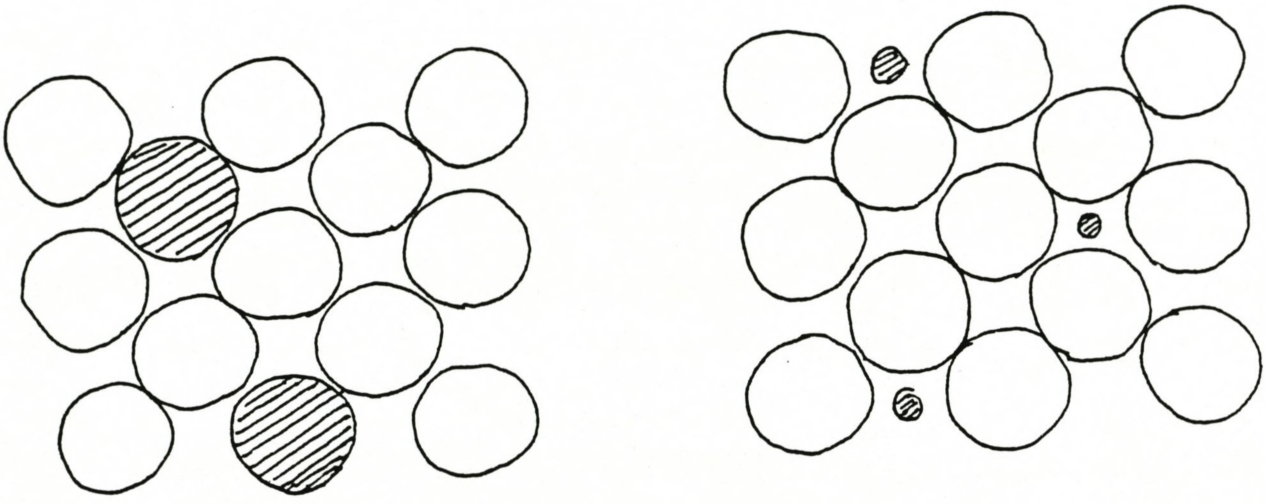
The lattice energy of the solid solution also differs from that of the pure drug. The total lattice energy between the components of a continuous solid solution, at various compositions, should be greater than the lattice energy between the individual pure components in the solid state. The area below the lower curve in figure 2(a) represents a miscibility gap that may result from a limited solid-state solubility at lower temperatures. The solid solution above the temperature of the miscibility gap in figure 2(a) is thermodynamically stable with a free energy lower than that anticipated from the mixture law.

Figure 2(b) illustrates a discontinuous solid solution. This type of solid solution is characterized by a limited solubility of the solid solute in a solid solvent and indicates the region in the phase diagram where solid solutions are formed. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature. When the temperature is lowered, the solid solution regions become narrower. Some degree of solid-state solubility can be expected for all two-component systems. However, the extent of solubility is usually small enough to be considered negligible. Originally Goldberg et al. (1965) considered a solubility of more than 5% of the one component in the other to be a solid solution. Newer, more sensitive instruments, however, allow the detection of less than 5% solute in solid solutions, making this criterion inadequate. Furthermore, many drugs with low therapeutic dosages (e.g. below 25mg) can be practically incorporated into solid solutions at concentrations of less than 5%.

Substitutional and interstitial solid solutions are schematically represented in figure 3

(Shefter, 1981). A substitutional solid solution (figure 3a) is formed when the solute molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. The size and stearic factors of the solute molecule play a decisive role in the formation of the solid solution. The size of the solute and solvent molecule should be as close as possible. According to the Hume-Ruthery rule, an extensive solid solution can only be formed when the solute differs by less than 15% in effective diameter from that of the solvent molecule (Reed-Hill, 1964). Timmermans (as reported by Chiou and Riegelman, 1971) developed a quantitative method to express the degree of similarity of the shape of the two components. He called this the degree of molecular isomorphism and this factor gives an indication of whether substances are capable of dissolving in each other.

An interstitial solid solution (figure 3b) is formed when the solute (guest) molecules occupy the interstitial space between the solvent (host) molecules. In this case, only a discontinuous solid solution is usually formed. The size of the solute is critical for it to fit into the interstices. In the case of an extensive interstitial solid solution of metals, the apparent diameter of the solute atom should be less than 0.59 that of the solvent. From this, it may be calculated that the molecular volume of the solute should be less than 20% of the solvent. This principle may also be applied to organic molecules such as water-soluble crystalline polymers of high molecular mass (acting as solvent) for the formation of interstitial solid solutions of poorly soluble drugs.



A

B

FIGURE 3: (a) A SUBSTITUTIONAL SOLID SOLUTION,

(b) AN INTERSTITIAL SOLID SOLUTION.

Dark circles indicate solute atoms or molecules, while open circles indicate solvent atoms or molecules.

Dark circles indicate solute atoms or molecules, while open circles indicate solvent atoms or molecules.

Water-soluble polymers of high molecular mass consist of two parallel helices in a unit cell and significant amounts of drug should be able to be trapped in the helical interstitial spaces when polymer-drug melts are solidified. Shefter (1981) refers to interstitial solid solutions formed by high molecular mass polymers as polymeric carriers. Drug molecules with a molecular mass of less than 1000 can be incorporated into these polymers. Polyvinylpyrrolidone (PVP) and various grades of polyethylene glycol (PEG) have been used successfully to increase the dissolution rates of poorly soluble drugs such as indomethacin and griseofulvin (Bogdanova et al., 1981 and Chiou and Riegelman, 1969).

Other factors such as high viscosity, supercooling and physical- chemical interaction between the drugs and the polymers may contribute to the formation of metastable solid solutions, if the drug-PEG melt is solidified rapidly. Even at high temperatures, the melt of PEG polymers may be highly viscous with further rapid increase in viscosity upon cooling of the melt. There is, therefore, reduced solute migration of the drug and difficulty in nucleation in the viscous medium. This principle is used to retard the crystallization of drugs in PEG. Although the melting points of some PEG polymers are higher than 50°C, the melts can often be supercooled to below 40°C. It has been found feasible to supercool various melts of griseofulvin in PEG 4000 or 6000 to about 40°C before solidification started, although their upper melting points (when mixtures completely melt) ranged from 150- 200°C.

There is also the possibility that physical or chemical interaction between the polymer and the drug may retard the crystallization of the pure drug. When the drug is in a much higher concentration than its solubility in the solid (polymer), the drug is present as ultrafine or colloidal crystals in the melt when the melt is solidified rapidly. These crystallites have been detected using X-ray diffraction studies (Allen and Kwan, 1969) and their presence is mainly due to the difficulty of growth of the crystallite in a highly viscous medium, as well as to the short time interval for the completion of solidification. Furthermore , as in the case of PEG polymers, the polymer may also act as a protective colloid in retarding the coagulation, aggregation or coarsening of the fine crystallites before solidification. These fine crystallites result in a faster dissolution of the poorly soluble drug (Chiou and Riegelman, 1969).

1.1.3.2.3 **Glass dispersions**

The familiar term "glass" may be used to describe a pure chemical in a glassy or vitreous state. However, when a dispersion of a drug in a glass is formed there is always more than one chemical present. Glassy solids of compounds should not be considered as glass dispersions, since these terms refer to the molecular state of single compounds. A glass dispersion is the dispersion of poorly soluble drug molecules in the molecular framework of a glass. When the glass is water soluble, such dispersions would be expected to rapidly dissolve in aqueous media.

Sparingly soluble drugs fused with, for example, citric acid, sugars (dextrose, galactose and sucrose) or other water-soluble compounds form glass dispersions when their melts are rapidly solidified (Summers and Enever, 1976 and Allen et al. 1977). These glasses give rapid dissolution of the drugs contained in them, in aqueous media, while absorption is also improved.

The glass is obtained when the melt of chemicals is cooled abruptly. This state is characterized by transparency and brittleness below the glass-transformation temperature (T_g). When reheating the glass, it softens without a sharp melting point. This is due to the chemical bonds differing in length and, therefore, in strength and to the fact that there is no specific temperature at which all the bonds become loosened simultaneously. Upon reheating, the glassy state can often be transformed to the crystalline state. Figure 4 shows the relation in volume between the glassy, liquid and solid states. When a liquid is cooled through its freezing point (T_f), it may either freeze into a crystalline solid, with a discontinuous change in volume, or it may continue as a supercooled liquid. Many substances may behave in either way, depending on circumstances. Supercooling is likely to occur if any crystal nuclei can be avoided. The viscosity of the supercooled liquid may be so great that the material may appear to be a solid. The temperature at which the curve in figure 4 changes slope is called the glass-transforming temperature, T_g. Below T_g, the curve is no longer an equilibrium curve and the glass is metastable. At T_g, the thermodynamic properties of a glass, such as specific volume, specific heat, viscosity, refractive index, compressibility and thermal conductivity all show a critical change.

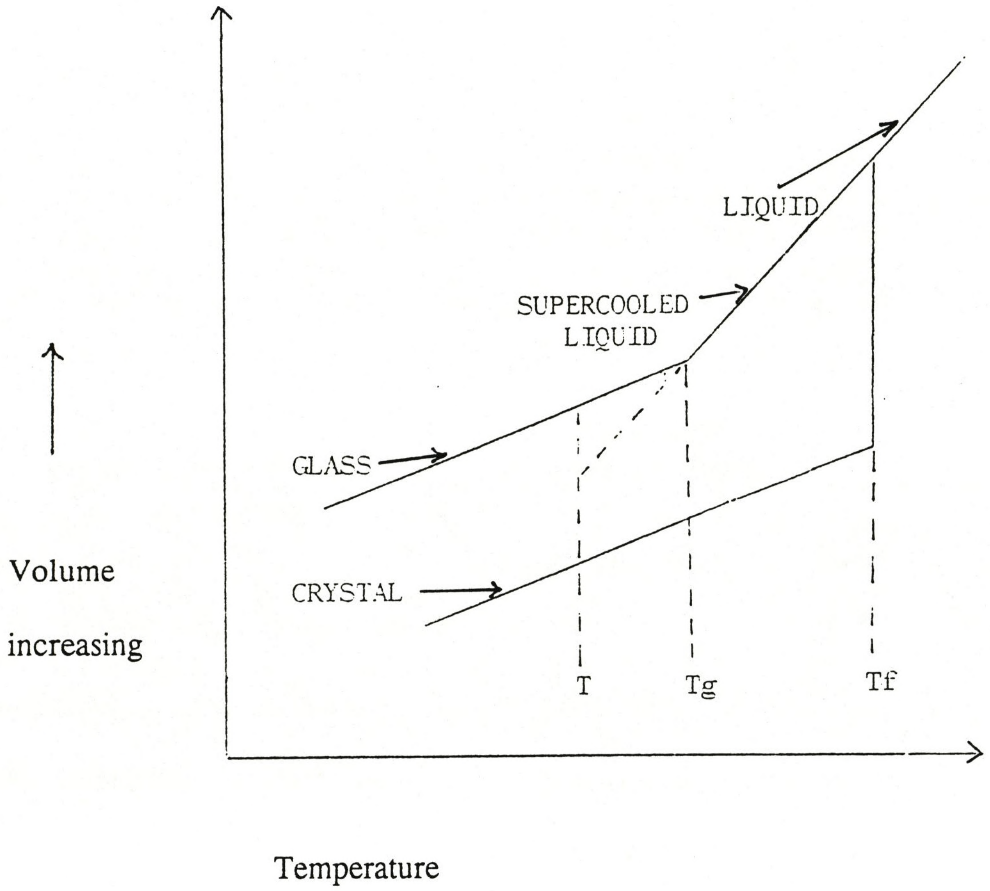


FIGURE 4: THE RELATIONSHIP BETWEEN THE GLASSY, LIQUID AND SOLID STATES

Summers and Enever (1976) used citric acid to enhance the solubility of primidone. The glasses containing primidone were unstable and devitrified after storage at 60°C for up to 3 days. It was found that the time for devitrification was inversely proportional to the amount of primidone present in the glass. X- ray diffraction studies indicated that the resulting devitrified state was a eutectic mixture showing good dissolution properties. In spite of devitrification, the dispersion contained the drug in a very fine state of subdivision. The increased dissolution of primidone in the devitrified state was attributed to a number of factors. These include the small particle size of the drug, the larger effective surface area, the improved wetting characteristics of the drug in the matrix and the solubilizing effect of citric acid which influences the solubility of the drug in the diffusion layer created by the dissolving glass.

Similar results were obtained by Kanig (1964), for the fusion of manitol with phenobarbitone, and Allen et al.(1977), who prepared glass dispersions to increase the dissolution rates of some corticosteroids using dextrose, galactose and sucrose as carriers.

Bauer et al. (1962) have described the advantages of glass dispersions over solid solutions. According to them, there is usually a relatively strong chemical binding between the solute and the solvent in the solid solution, while the lattice energy in the glass solution is expected to be much less because of its similarity to the liquid solution. Similarly, the dissolution rate from a crystal is usually slower than from an amorphous or glassy solid of the same chemical entity. Therefore, if everything is equal, the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution. Another important advantage of glass solutions over solid solutions is that when the content of solute exceeds the solubility in both solutions at ambient temperatures, the particle size of crystallization of the solute is much smaller in the glass solution due to the difficult growth of the crystal in its viscous medium. A higher supersaturation of the drug in the glass solution is also more likely to take place if the extremely viscous melt is cooled rapidly.

Of particular interest, is the use of PVP as a glass to inhibit the precipitation of drugs dispersed in it. PVP is an organic polymer that may become glassy after the evaporation of an organic solvent in which it has been dissolved. The remaining glass is extremely viscous and inhibits crystal growth of the drug. There is also the possibility of complexation between the drug and polymer. A transparent, brittle glassy solution is formed. When the drug concentration exceeds its solubility in the polymer, crystallization occurs but the crystallite size of the drug is very fine. This observation is similar to that found for PEG solid solutions. Mayersohn and Gibaldi (1966), as well as Simonelli et al. (1970) have used PVP polymers to enhance drug dissolution.

1.1.3.3 **Methods of preparation of solid dispersions**

Chiou and Riegelman (1971) differentiate between two methods of preparing solid dispersions, i.e. the solvent method and the melting method. The solvent method for preparing dispersions is used widely. A physical mixture of two solid components (drug and matrix) is dissolved in a common solvent. The solvent is evaporated leaving a disperse system. Takayama et al. (1980), for example, used this method to prepare a coprecipitate of indomethacin and PVP.

The main advantage of this method is that thermal decomposition of drugs and carriers can be prevented because low temperatures are required to evaporate organic solvents. The disadvantages of this method include the fact that it is difficult to remove the solvent completely. A negligible amount of solvent can have an effect on the chemical stability of the drug. It is often not easy to select a common solvent for drug and carrier, while it is difficult to reproduce crystal forms. Supersaturation of the solute in the solid system cannot be attained using the solvent method, except in a system having highly viscous properties.

The melting or fusion method involves the direct melting of a physical mixture of a drug and a water-soluble carrier. The melted mixture is then cooled and rapidly solidified under rigorous stirring. The dried mass is crushed, pulverized and sieved. Allen and Kwan (1969) used this method to prepare a solid solution of indomethacin in PEG.

This method is very simple and economical. Furthermore, a supersaturation of the drug in the carrier can often be obtained using rapid cooling of the melt from a high temperature. Under such conditions, the solute molecules are arrested in the solvent matrix by the instantaneous solidification process. The disadvantage of this method is the possibility of decomposition and evaporation of either drugs or carriers at elevated temperatures.

The above methods may be combined. Using the melting-solvent method, the solid dispersion is prepared by first dissolving the drug in a suitable liquid solvent. The solution is incorporated into the melt of the carrier using heat, without removing the solvent. This method has the advantages of both the melting and solvent methods. There is no significant loss of the solid properties of the carrier. Chiou and Smith (1971) used this method to prepare griseofulvin dispersed in PEG 6000. From a practical standpoint, this method is limited to drugs with a low therapeutic dose, e.g. below 50 mg.

NB.

1.1.3.4 Factors contributing to the faster dissolution rate of a drug dispersed in a matrix

An increase in surface area due to the reduction of particle size generally increases the rates of dissolution and oral absorption of poorly soluble drugs. In addition to the reduction of crystalline size, Chiou and Riegelman (1971) have singled out five factors which may contribute to the faster dissolution rate of solid dispersions. These factors are applicable to simple eutectic mixtures, while factors 1-4 may apply to solid solutions. Although not stated in the literature, these factors may also play a significant role in the dissolution of glass dispersions.

1. An increase in drug solubility may occur due to the fact that the majority of solid crystallites are extremely small.

2. A possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particle

in the early stages of dissolution , because the water-soluble carrier completely dissolves in a short time. This was clearly demonstrated by the faster dissolution rate of acetaminophen from its physical mixture with urea when compared to that of the pure compound with comparable particle size (Goldberg et al. 1966a).

3. The absence of agglomeration and aggregation between the fine particles of the pure hydrophobic drug may play an important role in increasing the dissolution and absorption rates. In a solid dispersion, the drug particles are surrounded by carrier particles and aggregation, agglomeration and lumping in the dissolution medium are rarely present. Using dissolution tests , Chiou and Riegelman (1969) demonstrated that griseofulvin dispersed in various grades of PEG (4000, 6000 and 20 000) and other matrices , gave a better dissolution rate when compared to micronized griseofulvin powder due to the absence of agglomeration and aggregation.

4. Excellent dispersibility and wettability of a drug, from a fast-release system prepared with a water-soluble matrix, result in an increased dissolution rate of the drug in aqueous media. This is due to the fact that each single crystallite of the drug is very intimately encircled by the soluble carrier. The carrier readily dissolves and causes the water to contact and wet the drug particle. Therefore, a fine homogenous suspension of the drug can be obtained with minimum stirring. In contrast, the aggregates and agglomerates, of those poorly soluble pure powders that are also poorly wettable, are surrounded by the nonpolar air, which is hard to penetrate or displace by water.

5. An increased rate of dissolution and absorption may also occur if the drug crystallizes in a metastable form after solidification of the fused solution. Takayama et al. (1980) prepared a coprecipitate of amorphous indomethacin in PVP. The amorphous coprecipitate gave an enhanced dissolution rate when compared to microcrystalline indomethacin.

1.1.4 A BRIEF OVERVIEW OF OTHER TECHNIQUES USED TO IMPROVE SOLUBILIZATION

1.1.4.1 Particle size reduction

It is a well known fact that the particle size reduction of drugs, where gastro-intestinal absorption is rate limited by dissolution, increases the rate of absorption and bioavailability. Drugs with poor water solubility benefit from particle size reduction. The role that particle size plays in the solubility of a solid in a liquid is illustrated by the following equation (Richards, 1988):

$$\log \frac{S}{S_o} = \frac{2\gamma M}{2{,}303RT\rho r} \qquad (4)$$

where: S = solubility of a small particle with radius r

S_o = normal solubility (fairly large particles)

γ = interfacial energy

M = molecular mass of solid

ρ = density of bulk solid

R = gas constant

T = absolute temperature

There is a change in the intermolecular attractive forces between molecules of a crystalline solid when they are separated during dissolution. The change in interfacial energy, that accompanies the dissolution of particles of varying sizes, causes the solubility of a substance to increase with decreasing particle size.

The relationship between particle size and rate of solution is similarly illustrated by the Noyes-Whitney equation for the dissolution of a solid in a liquid:

$$\frac{dm}{dt} = kA\,(C_s - C) \qquad (5)$$

where: m = mass

t = time for m to pass into solution

$\frac{dm}{dt}$ = rate of dissolution

A = surface area of undissolved solid in contact with the solvent

C_s = concentration of solute to saturate the solvent at experimental temperature

C = solute concentration at time t

k = intrinsic dissolution rate constant

A is affected by the size of solid particles. Therefore, smaller particles increase the dissolution rate of the solid.

Methods other than the conventional ones, such as trituration and grinding, ball milling and fluid energy micronization, which may be used to achieve particle size reduction, have also been used. Chambers et al. (1942) have reported the preparation of microcrystals of sulphathiazole, using ultrasound, thereby increasing the dissolution rate of sulphathiazole.

The main disadvantage of particle size reduction methods is that once particles are reduced, fine particles tend to agglomerate and aggregate. This is due to the increase in surface free energy and the subsequent stronger Van der Waals attraction between nonpolar molecules. Furthermore, poorly soluble drugs often show poor wettability in water. A requirement for dispersion and dissolution of a powder is good wettability. In addition, powders having plastic properties are difficult to subdivide when using conventional size reduction methods.

1.1.4.2 **Depositioning methods**

A solvent deposition system is a solid preparation in which a drug, usually hydrophobic, is deposited on the surface of a matrix. Depositioning of drugs on solid supports can be done by using solvents (Johansen and Moller, 1978) or by grinding drugs with certain materials (Ishizaku at al., 1988). Yamamoto et al. (1974) observed that the dissolution rate and bioavailability of griseofulvin was increased after mixing with microcrystalline cellulose.

Lerk et al. (1978) improved the solubility of hexobarbital by mixing it in a high speed mixer, with solutions of various concentrations of either methylcellulose or hydroxyethylcellulose. After drying, the dissolution rate of the hydrophobic hexobarbital was increased in all cases by the creation of a hydrophilic surface due to the excipients. In a similar way, Ishizaku et al. (1988) improved the dissolution rate of aspirin after mixing it with potato starch in a centrifugal rotating mixer. Friction and collision occurred in the dry mixing process. The micronized drug was spread over the potato starch surface. What was noteworthy in this case, and not mentioned by previous researchers, is that the aspirin showed a reduction in crystallinity. This was observed by doing X-ray diffraction studies.

Similar results have been achieved by depositioning drugs onto excipients using solvents. Monkhouse and Lach (1972a) used water- insoluble fumed silicon dioxide and silicic acid (precipitated) as a support for the solvent depositioning of a number of drugs, including indomethacin. The support material was suspended in a solution of the drug. After evaporation of the solvent (acetone, in the case of indomethacin), the drug was deposited onto the excipients. The dissolution rate of the drug was dependent on the weight ratio of the drug to excipient. Using this method , indomethacin showed an increase in dissolution rate when compared to dissolution tests done on the microcrystalline powder in distilled water. Dissolution tests were done at various speeds and various ratios of indomethacin to excipients were tested.

Johansen and Moller (1978) used a similar method to deposit phenylbutazone onto starch, lactose and silicon dioxide, separately. Neither reporters gave any indication of whether or not the products obtained were stable after storage.

1.1.4.3 **Solvates**

When a compound is recrystallized from solution, the resulting solid may still contain some of the solvent. The vast majority of these crystalline materials, referred to as solvates or pseudopolymorphs, contain a stoichiometric amount of solvent molecules as part of their crystalline structure and may be regarded as molecular complexes (Shefter, 1981).

Pfeiffer et al. (1970) used a variety of solvents to recrystallize cephalosporins. They observed different solubilities after recrystallization and isolated a series of complex solvates.

When solids form solvates containing water, they are called hydrates. Hydrates usually have the lowest thermodynamic activity (i.e. they are the most stable forms) and consequently are less soluble than their anhydrous forms (Shefter, 1981). When solvents other than water (e.g. pentanol) are used to produce solvates, these show an increase in solubility when compared to the stable hydrate (an eightfold increase in the case of the pentanol solvate of succinyl sulphathiazole). It is important to note that an increase in solubility of the solvate is dependent on the nature of the bound solvent and the ability of the dissolution media to dissociate the solvate.

1.1.4.4 **Racemates and enantiomers**

Racemate and enantiomeric forms of a compound do not differ only in their ability to rotate plane-polarized light, but also in their solubilities. Repta et al. (1976) used an enantiomer, rather than the racemic mixture, of a complex organic compound to improve its solubility.

1.1.4.5 **Retardation of phase transformation**

The success of solubilization by the use of the metastable crystalline form depends on the rate of change of the metastable solid to the more stable form. The high activity metastable form may transform rapidly when in contact with the dissolution medium and dissolution may be reduced. However, this transformation can be reduced by the use of additives, thus ensuring a higher degree of solubilization.

A wide variety of materials has been tested for their ability to inhibit the transformation of a drug to a less soluble form. Simonelli et al. (1970) used PVP to retard phase transformation of sulphathiazole. Miyazaki et al. (1976) studied the use of methylcellulose, acacia, gelatin, pectin and sodium alginate to achieve similar results with chlortetracycline hydrochloride.

The transformation of a metastable solid to a stable solid phase involves the formation of nuclei of the stable solid phase in the metastable solid. The exact mechanism of phase transformation retardation is unknown. However, it has been speculated that an increase in the viscosity of the crystal growth medium retards phase transformation. Crystal growth is also inhibited by adsorption of the inhibiting substances onto the surface of crystal nuclei. None of the materials studied appears to totally inhibit the phase transformation process (Shefter, 1981).

✱ NB !

1.1.4.6 **Polymorphism**

Polymorphism exists when a compound has the ability to exist in more than one crystalline form, each having a unique packing arrangement. Polymorphs also differ in physical properties such as solubility and melting point.

~~Aguiar et al. (1967) found that the availability of chloramphenicol from chloramphenicol palmitate depended on its polymorphic state. This significantly influences the blood levels obtained during bioavailability studies. Absorption may be influenced by using a more soluble form of chloramphenicol palmitate. The most stable polymorph has the lowest free energy and solubility. All higher energy, more soluble polymorphs transform to the stable form depending on environmental factors, mobility of molecules and structural factors. Therefore, the physical stability of the more soluble polymorph is critical to ensure good dissolution and absorption.~~

The metastable form, having a higher level of free energy and showing greater solubility, will transform to the less soluble, lower energy form upon storage. This transformation significantly alters the dissolution properties of the drug as illustrated by Imaizumi et al. (1980). They demonstrated that the metastable polymorph of indomethacin (form II) had an increased dissolution rate when compared to the stable form (form I) in a 5% methanol aqueous solution at 30°C. The best initial dissolution rate was observed for the amorphous form of indomethacin, indicating that it would show better bioavailability than forms I or II. However, the dissolution rate of the amorphous form became almost the same as that of form II after two hours. This was due to the transformation of the remaining amorphous form to form II during the dissolution process and form II eventually also changed to form I.

1.1.4.7 **Noncrystalline states**

Under certain conditions it is possible to isolate solids in a non-crystalline, amorphous or glassy state. These solids did not have sufficient time to arrange into a three-dimensional pattern, when transformed to the solid state. They usually lack long range order but do exhibit some local order, short range in nature. This state consists only of the pure solid and should not be confused with binary systems such as glass dispersions which involve a drug and carrier in a glassy state. The noncrystalline state is thermodynamically unstable, lacks long-range packing order of the molecules and has a high level of free energy. Poorly soluble drugs may be changed to a glassy state to enhance their solubility. This can be achieved by rapidly precipitating the molecules from a melt or solution. However, these states are unstable and may only be used in exceptional circumstances (Shefter, 1981).

Fukuoka et al. (1987) found that the glassy state of indomethacin had a much higher bioavailability in rabbits than the crystalline form. The poor stability of the amorphous state, however, makes it impossible to use in a dosage form (Imaizumi et al. 1980).

* NB!

1.2 POLYMORPHISM OF INDOMETHACIN

1.2.1 INTRODUCTION

As mentioned in section 1.1.4.6, polymorphism is the ability of any element or compound to exist as more than one distinct crystal species. Different polymorphs of a given compound are, in general, as different in structure and physical properties as the crystals of two different compounds. Solubility, melting point, density, hardness, optical and electrical properties, crystal shape, etc., all vary with the polymorphic form.

In general, it should be possible to obtain different crystal forms of a drug and thus modify the performance properties of that compound. To do so requires a knowledge of the behaviour of polymorphs (Haleblian and McCrone, 1969). For example, the dissolution of a drug may be enhanced by using the most soluble polymorph. However, the most soluble polymorph is often the least stable.

Kaneniwa et al. (1985) showed, using dissolution tests, that the polymorphic form II of indomethacin, which is less stable, gives a better dissolution rate than form I. On the other hand, when a drug is solubilized, as discussed previously, there may be a change in polymorphic state due to the use of solvents (Takayama et al., 1980) or mechanical grinding (Ishizaku et al., 1988). This change may have stability implications. When attempting to solubilize indomethacin, it is thus necessary to be acquainted with the polymorphs of indomethacin and their stability.

1.2.2 CHARACTERIZATION OF THE DIFFERENT POLYMORPHIC FORMS OF INDOMETHACIN

Indomethacin has been noted to exhibit polymorphism (The Pharmaceutical Codex, 1979). Several authors have identified polymorphs of indomethacin and there is much confusion in the literature with respect to the nomenclature of these polymorphs. Kaneniwa et al. (1985) prepared and identified three polymorphs of indomethacin. The α-form was prepared (m.p. 148°C) by a modification of Borka's method (1974) by pouring distilled water into an indomethacin / ethanol solution at about 80°C and filtering off the precipitated crystals. The γ- form (m.p. 154°C) was obtained by recrystallization from ethyl ether at room temperature. The β form (which contains about 0,5 mol of benzene) was prepared by the method of Yamamoto (1968). Allen and Kwan (1969) mentioned form I (m.p. 160°C) and form II (m.p. 154°C). Monkhouse and Lach (1972b) noted two modifications (m.p. 158°C and 152°C). No experimental details, however, were given for the method of preparation of these polymorphs.

In an extensive study, Borka (1974) identified and characterized five polymorphs. They are form I (m.p. 160°C), form II (m.p. 154°C), form III (m.p. 148°C), form IV (m.p. 134°C) and a solvent-containing form (m.p. 90-100°C). Form III could not be isolated in pure form but was distinguished by its appearance and melting point in microscopic preparations in the presence of form II and form IV. Form III has a characteristic brown colour and appears in a very narrow temperature range. Either form II or IV would dominate when trying to isolate form III.

Borka (1974) noted that when indomethacin crystals were grown from various organic solvents, form I or II would be obtained. However, when stoichiometric amounts of solvents remained in the crystalline structure, pseudopolymorphs were formed. These solvent-containing forms have a melting point between 90 and 100°C and are called " form V with solvent content". Similarly, the β form (Yamamoto, 1968) is a pseudopolymorph of benzene-containing indomethacin. This was emphasized by Kaneniwa et al. (1985) who detected benzene using NMR.

When preparing these polymorphs, the use of the correct organic solvent and temperature is very important. Therefore, the confusion that exists is due to the variety of methods and solvents used to prepare the polymorphs. It appears that forms I and II (Borka, 1974) correspond to the γ-form and ∝-form, respectively (Yamamoto, 1968). Since form IV only grows in warm methanol , form III cannot be isolated and the β form is a pseudopolymorph, only the γ(I) form and the ∝ (II) form need to be taken into account when studying the effect of indomethacin polymorphs on the solubility of indomethacin. In this study, the ∝ and γ notation will be used, after Yamamoto (1968).

1.2.3 AMORPHOUS INDOMETHACIN

Borka (1974) prepared an amorphous (glassy) melt of indomethacin which had a melting point of 55-57°C and appeared to be stable for at least 2 months, judging from the physical appearance of the melt. Imaizumi et al.(1980) noted that the amorphous form was unstable in the presence of moisture and at elevated temperatures. ~~Table 1 illustrates 50% transition time of the amorphous form to the crystalline form at various temperatures in the absence of moisture.~~ Crystallization was detected using X-ray diffraction. The transition of the amorphous form to the crystalline form followed first-order kinetics. The logarithm of the degree of crystallinity showed good linearity with respect to time at every temperature. Therefore, the transition rate constant (K) at all temperatures could be calculated. K at 40°C was more than 10 times larger than that at 20°C, indicating that temperature is an important factor influencing the stability of the amorphous form. An Arrhenius plot of K at various temperatures was constructed and, by extrapolation, the value for K and t (indicated by T_{50}) at 10°C were found to be 1.98×10^{-2} day $^{-1}$ and 35.0 days, respectively, indicating that the amorphous form is reasonably stable at low temperatures. Furthermore, the activation energy of transition of the amorphous form to the crystalline form is large (22kcal/mol) and this also indicates that temperature may be an important factor in the stability of amorphous indomethacin.

The stability of amorphous indomethacin at various relative humidities (RH) was studied by Imaizumi et al. (1980). The amount of water absorbed became nearly maximum after 2-3 hours at each RH and then was constant for 6 hours. The maximum amount of water absorbed by the amorphous form increased with increasing RH. The amorphous form changed to form II at 100% RH, to a combination of forms I and II at 89% RH and form I only at both 79% and 69% RH (Imaizumi et al., 1980). The authors postulated that the amorphous form may dissolve well in water at a high RH, accompanied by a super-saturation phenomenon of indomethacin to form nuclei for crystallization. In this case, the amorphous form changes to form II. At lower RH, the amorphous form might only absorb water and nuclei formation would be slow. In this case, the amorphous form changes to form I.

TABLE 1: **TRANSITION RATE CONSTANT K AND 50% TRANSITION TIME (T) AT VARIOUS TEMPERATURES FOR AMORPHOUS INDOMETHACIN (Imaizumi et al, 1980).**

TEMPERATURE (°C)	**K (day^{-1} x 10^{-2})**	**T$_{50}$ (days)**
10	1.98 (a)	35 (a)
20	8.54	8.12
30	22.20	3.12
40	99.80	0.70

(a) This value was obtained by extrapolating the Arrhenius plot

1.2.4 STABILITY OF POLYMORPHS

Kaneniwa et al. (1985) noted that the α form changed to the γ-form when the crystals are suspended in ethanol. Complete transformation took place at 45°C within 18 hours and was determined by using differential scanning calorimetry (DSC). In the presence of 1% of the γ-form as a seed, the transformation to the γ-form was accelerated significantly. At 30°C, complete transformation took place within 50 hours and this transformation time was about half that for the pure ∝-form alone at the same temperature. This indicated that the presence of the γ-form (i.e. form I) as a nucleus is the rate-determining step in the transformation of the metastable ∝ form to the γ-form. The authors also proposed a kinetic mechanism for the transformation of the ∝ form to the γ-form in ethanol.

NB

1.2.5 DISSOLUTION BEHAVIOUR OF INDOMETHACIN POLYMORPHS

Imaizumi et al. (1980) showed, using dissolution tests, that the amorphous form had a better solubility than the polymorphs (the ∝ and γ forms). Dissolution tests were done in a 5% methanol aqueous solution at 30°C. The dissolution rate of the amorphous form was greater than that of the ∝ and γ-forms at the initial stage, indicating that the amorphous form should show better bioavailability. The solubility of the amorphous form became almost the same as that of the ∝ form after 2 hours. According to X-ray diffraction studies, the ∝ form precipitated from the amorphous form at the initial stage of dissolution, and the resulting ∝ form changed gradually to the γ-form. The dissolution rate of the pure ∝ form is also superior to the pure γ form (Kaneniwa et al., 1985). The solubilities of the ∝ and γ forms in distilled water were 0.87 and 0.69mg/100ml, respectively, after 7 hours.

Fukuoka et al. (1987) investigated the crystallization of amorphous (glassy) indomethacin during dissolution using X-ray diffractometry. After standing for 1.5 hours in water, the glass began to crystallize and thereafter crystallization proceeded rapidly. It took 10 hours to reach maximum crystallization and at this stage indomethacin had 50% crystallinity. It was considered that if amorphous indomethacin was dissolved and absorbed rapidly after administration, in vivo absorption may not be influenced by the crystallization of the glass.

1.3 DIRECT COMPRESSION

1.3.1 INTRODUCTION

Direct compression has been used to prepare tablets from single crystalline components such as sodium chloride and sodium bromide. However, not all active ingredients have suitable flow properties and possess sufficient compactibility to be directly compressed. In addition, low dosages of active ingredients (below 50mg) would lead to extremely small tablets. Problems like these have lead to the development of special direct compression vehicles or diluents. Direct compression vehicles must possess both fluidity and compressibility. Spray-dried lactose and microcrystalline cellulose were amongst the first direct compression vehicles that were used. In addition to direct compression vehicles, lubricants, glidants and disintegrants are included in direct compression blends.

Direct compression is the process by which tablets are compressed directly from blends of the active ingredient and suitable excipients which have good flow properties and will form a compact. No pretreatment of the powder blends by dry or wet granulation is necessary (Sheth et al., 1980).

Direct compression is not an easy or a simple process but rather an alternative method of making tablets, which should have cost and stability advantages. When attempting to produce a direct compression tablet from a poorly soluble drug and a solubilizing agent, certain additional factors are important and must be considered. The active ingredient-solubilizing agent complex often possesses a large volume. This complex has to be incorporated into a direct compression blend that will compact into reasonably sized tablets. In this respect, the complex is similar to a large- dose drug. The complex must also not segregate from the other components of the blend.

1.3.2 ADVANTAGES OF DIRECT COMPRESSION WHEN TABLETTING A POORLY SOLUBLE DRUG

Armstrong (1986) considers direct compression to be, amongst others, more economical when compared to wet granulation. Savings are made w.r.t. manufacturing time, labour, fewer manufacturing steps, less equipment and less consumption of power.

The elimination of heat and moisture, during direct compression, has several advantages for solubilized products. During wet granulation these products may undergo polymorphic changes due to the presence of moisture. The use of heat to dry granules of these products may lead to an unfavourable environment which enhances crystal growth and transformation of polymorphic states. Temperature and moisture content are important in the stability of polymorphs (Imaizumi et al., 1980).

When direct compression is used, the disintegration of tablets is optimized. The tablets disintegrate rapidly if a disintegrant is included in the formula and prime particles are produced. Each primary particle is readily available for dissolution as it becomes liberated from the tablet. Dissolution is rapid since the disintegrated particles have a large surface area. Wet or dry granules are agglomerates which retard dissolution. The difference in dissolution rate is especially important when tabletting drug particles solubilized by methods such as solvent depositioning or the coating of particles with a hydrophilic polymer (Johansen and Møller, 1978 and Monkhouse and Lach, 1972a).

Compared to wet granulation, disintegrants in direct compression blends can be used very efficiently. Loss of potency due to the presence of moisture does not occur in direct compression. The chemical stability of the active ingredients is also greater, due to the absence of moisture. Water present in the direct compression diluents is in the form of water of hydration and hydrogen- bonded water and is, therefore, not available for chemical reactions.

After aging, there is no change in the dissolution profiles of directly compressed drugs. This is a major advantage over granulation processes (Sheth et al., 1980).

1.3.3 LIMITATIONS OF DIRECT COMPRESSION

When the active ingredients are present as a low dose, the problem of uniform distribution in the powder blend arises. On the other hand, problems may also arise where the active ingredient is present in high concentrations. If the active ingredient has poor compressibility and fluidity, the resulting mixture may also display these poor qualities. This is an important limitation for bulky solubilized drugs.

The dilution potential of the filler-binder is critical. When tabletting poorly compressible drugs it is necessary that the filler-binder "carry" the drug. The choice of diluent is important to ensure compactibility. This is demonstrated by the dilution potential of microcrystalline cellulose when compared to spray-dried lactose, which has to be present in large proportions in a blend to produce satisfactory tablets.

Thorough blending of all the tablet ingredients is of extreme importance during tabletting by direct compression. This is necessary to ensure uniform tablets, containing a uniform dose. In the case of granulated tablets, once granules of uniform composition have been formed, there is no risk of unblending. However, after the blending of direct compression tablet ingredients, there is a risk of unblending during the further handling of the powder. Therefore, it is important that all the ingredients of the blend have a narrow range of particle sizes. Should particle sizes differ significantly, the range should include fine as well as coarse particles to ensure that all voids are filled. Another approach is that of ordered mixing. The active ingredients and ingredients with the largest particle sizes are mixed initially and then the smaller ingredients are added at a later stage of the mixing process. It can be clearly seen that the particle size of a solubilized drug is critical during the blending and the tabletting process. The densities of the powders should also be uniform. Segregation may be enhanced by the lack of moisture in the blends, causing static charges leading to unblending.

1.3.4 FORMULATION FACTORS AND REQUIREMENTS

1.3.4.1 Compaction and bonding mechanisms

Diluents used in direct compression tablets have a cohesive ability, i.e. they are able to consolidate and aggregate under pressure. The failure of active ingredients to compact into tablets is one of the biggest limitations of direct compression (Armstrong, 1986). Therefore diluents play an important role in the compaction and bonding of a tablet.

Shotton and Obiorah (1975) used an instrumented tablet press to measure the transmission of compression force to the die wall during compression. It was found that diluents that gave a good transmission of compression force to the die wall, e.g. spray- dried lactose, produced good tablets. Poorly compressible substances (phenacetin and acetaminophen) yielded bad conversion from the compression pressure to the die wall pressure (axial pressure transformed to radial pressure). Capping occurred with these substances. Good transmission of force was related to the ability of nearly similar particles to rearrange under pressure, as well as to the elastic properties of the materials.

David and Augsburger (1977) noted that all diluents did not have the same tensile strength under a similar compression force and identical time of compression cycles. Increasing the compression force when tabletting microcrystalline cellulose resulted in stronger tablets. On the other hand, lactose tablets did not show an increase in tensile strength with increasing compression force.

Milosovich (1963) gave an overview of the mechanism of compression of various diluents, based on a hypothesis originally formulated by Train in 1956. Tabletting materials, in a die cavity, that are subjected to increasing pressure undergo repacking initially when the pressure is low. The material in the die undergoes a decrease in volume and densification of the bed occurs through particle movement. Void spaces are filled by migrating particles which must flow past other particles surrounding the spaces. Cohesive forces are overcome and there is maximum contact of particle surfaces. At this stage the particle bed is still loose.

Particles may exhibit two types of behaviour under pressure. Some materials undergo elastic deformation during tabletting. As the pressure on the particles or crystals increases, further rearrangement becomes difficult. Further compression results in particle deformation. Most particles are irregularly shaped and there is a limited area of contact between the particles. An increase in compression pressure increases the pressure at the contact points. The particles may respond to this pressure by deforming elastically. When the pressure is suddenly removed from these particles, the deformation reverses and they return to their original shape. Microcrystalline cellulose behaves in this manner (Marshall, 1986). However, some materials reach an elastic limit or yield point during the normal compression process. When the pressure is high enough, all solid materials will reach an elastic limit. Pressures above the yield point result in deformations that are not immediately reversible upon removal of the pressure and particles are unable to regain their original shape. Therefore non-elastic deformation takes place.

When non-elastic deformation takes place and the shear strength is less than the tensile strength, plastic deformation occurs. This is due to the presence of imperfections in the crystalline lattice called dislocations. The presence of dislocations allows crystal planes to slip and the crystal behaves as though it were a viscous liquid. The crystal acquires a change in shape or a permanent "set". Slipped portions of the crystal fill void spaces and there is close contact between crystals when plastic deformation occurs. The slipped portions are aided by an increase in the amount of dislocations per unit crystal volume or the dislocation density (Milosovich, 1963). Glassy or amorphous materials have no crystalline structure and are very viscous. Under compression they also undergo plastic deformation. Viscous flow takes place when these substances consolidate. Plastic deformation brings the crystals closer together and if they are correctly aligned and subjected to further pressure, the crystal lattices fuse. This is called cold welding or cold bonding . If the lattices of the two crystals are not perfectly aligned, the binding would be weak and strained. Cold welding still occurs and the strained boundary is at a higher energy level, having a higher solubility than the rest of the crystal. If the two lattices are badly aligned, cold welding would not be expected since the strains would be too great.

However, when the shear strength is greater than the breaking strength, non-elastic flow still occurs but the particles fracture in preference to slipping. Cold welding occurs at the contact points where two lattices are correctly aligned. The small fragments fill the air spaces. "Brittle fracture" is said to take place. Compressible sugars (sucrose) exhibit brittle fracture (Marshall, 1986).

All materials will relieve stress to some extent by elastic deformation, plastic deformation and brittle fracture. One mechanism predominates, depending on the lattice structure of the substance.

1.3.4.2 **Diluents**

1.3.4.2.1 **Microcrystalline cellulose (MCC)**

Microcrystalline cellulose (MCC) is one of the most important tablet excipients. It is the direct compression binder that is the most compressible and has the highest dilution potential.

MCC is manufactured from a special grade of wood cellulose. The amorphous cellulose is removed leaving needle crystals after spray-drying. An example of MCC for tabletting is Avicel PH-101 and PH-102. The PH-102 grade consists of larger crystals, having good fluidity and compressibility (Shangraw et al., 1981a)

Reier and Shangraw (1966) noted that tablets consisting of MCC (without any additives) tended to soften and swell after being exposed to humid conditions. However the effect is reversed upon removal of the increased humidities. Elevated temperatures did not affect the tablets. Investigating the mechanisms of compaction, the authors noted that the major binding mechanism is by hydrogen bonding between crystallites. This contributes to the extreme strength and cohesiveness of MCC tablets. Disintegration takes place by the breaking of the intercrystallite hydrogen bonds by the disintegration medium. No separation of components was found during the compression of blends of MCC under production conditions.

During compaction, MCC crystals undergo plastic deformation. MCC crystals possess slip planes and dislocations that undergo deformation. The compact of MCC is strengthened due to the number of clean surfaces brought into contact during plastic deformation (Jarosz and Parrott, 1984).

When used in concentrations of 5-15%, MCC can also act as a disintegrant. MCC has a broad range of particle sizes indicating a high packed density and good covering of other excipients. This leads to a low level of friction. Therefore, no lubricants are needed, except when excipients comprise more than 20% of the formula (Lund and Boylan, 1986).

Lubricants of the magnesium stearate type, have a softening effect on MCC tablets. This softening effect was aggravated when the mixing time of the blend, prior to compression, was increased (Shah and Mlodozeniec, 1977).

1.3.4.2.2 **Spray-dried lactose**

Spray-dried lactose (SDL) is the most widely used and was the earliest available binder for direct compression. SDL contains about 15 % amorphous lactose and 85% ∝-lactose monohydrate (Vromans et al. 1986).

Gunsel and Lachman (1963) compared conventionally processed lactose (lactose USP) with SDL. Four tablet formulations were evaluated and three out of the four formulations that contained SDL exhibited better physical properties than the formulations containing lactose USP. SDL produced harder, less friable tablets that disintegrated more rapidly. There was, however, a notable colour change with the SDL formulae on aging.

Milosovich (1963) reported that a browning reaction of SDL occurs in the presence of basic compounds such as amines, or the combination of their acid salts with alkaline stearate lubricants, e.g. magnesium stearate. The browning reaction was slowed when stearic acid was used in the place of magnesium stearate. However, the absence of catalysts will not necessarily prevent browning. Milosovich (1963) postulated that the browning reaction is due to non-volatile impurities remaining in lactose after spray-drying. The SDL obtained may contain minute inorganic ions and other impurities that cause the browning reaction in the presence of moisture. It was noted that when the amorphous lactose component was not present in SDL, the browning reaction was slower. Meggle, the manufacturers of Tablettose, claim that tablets made with their product show a high degree of colour stability. Tablettose consists of ∝-lactose monohydrate of very high purity with no amorphous lactose.

Castello and Mattocks (1962) have studied the discolouration of tablets containing amine salts and lactose. Results showed that the browning is due to a reaction occurring in the presence of an amine base and not in the presence of a salt. The reaction is accelerated by increasing the temperature and humidity. The release of free base from the amine salt is catalyzed by alkaline lubricants, such as magnesium stearate.

Amorphous lactose was shown (Vromans et al., 1986) to exhibit an increasing compactibility after water sorption, with concomitant decrease in compact thickness. In contrast to crystalline lactose, the tablet pore surface did not change on increasing compaction pressure. In addition, the binding properties of the substance appeared to be very sensitive to magnesium stearate mixing. It was thus concluded that amorphous lactose deforms plastically under load. In comparison, the compactibility of commercially available SDL (which contains about 15% amorphous lactose and 85%α-lactose monohydrate) was hardly affected by moisture uptake and the susceptibility to lubricant mixing was not extravagant. The pore surface area increased with increasing compaction load. It was concluded that the compactibility is to a large extent determined by the amorphous component of the excipient, while the consolidation is determined by the crystalline portion.

SDL has the best flow properties of all the direct compression binders. It contains 5% water of hydration and is non- hygroscopic. In the absence of water of hydration, SDL loses its compressibility. One of the big disadvantages of SDL is its poor compressibility and the fact that it must be present in a concentration of about 80%. It is therefore not effective as a diluent for the direct compression of a high-dose drug which, in itself, is not compressible (Sheth et al., 1980).

1.3.4.3 **Lubricants**

The overall particle size of direct compression blends is less than that of granulated materials. The smaller particles have greater surface areas exposed, resulting in greater interparticulate forces and causing more friction between the particles. Therefore higher concentrations of lubricants are needed for direct compression blends. The amount of lubricant is critical, to ensure adequate lubrication without causing any deleterious effect from excess lubricant. For example, too much lubricant can result in soft tablets (Sheth et al., 1980). Lubrication is necessary to facilitate ejection of the tablet from the die and to prevent unnecessary wear of punches and dies. Lubricants facilitate the rearrangement of the particles in the die during compression.

The effect of lubricants on mechanical strength depends on the bonding mechanism. The strength of a tablet depends on the area of intimate contact between the particles and the adhesive strength over this area. The strongest bonds are formed between clean surfaces. The addition of a lubricant results in a reduction in tablet hardness. The lubricant acts as a physical barrier between the particles of the material which undergoes plastic and/ or elastic deformation. In the case of brittle materials that fragment during compression, new clean surfaces are formed during compression and the lubricant does not interfere as it does for a plastic material. The tablet weakening effect is therefore less pronounced. Studying the influence of lubricant concentration on the tensile strength of tablets, Jarosz and Parrott (1984) determined that brittle materials, e.g. dibasic calcium phosphate, were little affected by the addition of increasing concentrations of various lubricants during tabletting, since new clean surfaces produced by fragmentation are available for bonding. However, lubricants tend to reduce the tensile strength of tablets produced from materials that deform plastically during compression, e.g. anhydrous lactose, aspirin and microcrystalline cellulose. Magnesium stearate, stearic acid, hydrogenated vegetable oil, talc and polyethylene glycol (PEG) 4000, in concentrations up to 8%, were used as lubricants. Of particular interest in this study, was the fact that PEG 4000, as a lubricant, reduced the tensile strength of aspirin and anhydrous lactose tablets in concentrations up to 2%. Above 2% (and up to 8%), PEG 4000 had no significant further influence on the tensile strength. However, with MCC tablets, increasing the concentration of PEG 4000 up to 8% steadily decreased the tensile strength.

Tsumura et al.(1972) used PEG 6000, a water-soluble lubricant, as an ingredient in water-soluble vitamin tablets. The ejection force was measured and the lowest ejection force was obtained with tablets containing PEG 6000 which had a particle size of less than 50 μm. It was concluded that PEG 6000, as a micro particle powder, is an excellent lubricant for direct compression formulations.

Shah and Mlodozeniec (1977) noted that the mixing time of lubricants and excipients had a significant effect on tabletting properties. They found that the ejection force, hardness and disintegration and dissolution times of directly compressed tablets were significantly affected by blending times. Magnesium stearate (1%) was used as a lubricant for spray-dried lactose and microcrystalline cellulose tablets. The results recorded for both tablet types were similar. The hardness of the tablets decreased with increasing blending time. The ejection force recorded for the tablets during compression was reduced with increased mixing due to the greater surface coverage by magnesium stearate, resulting in greater lubrication efficiency. With increased mixing time, the apparent bulk volume of the mixture was reduced. Furthermore, there was an increase in disintegration time after prolonged mixing. The authors proposed a mechanism of surface lubrication for magnesium stearate.

1.3.4.4 **Fluidity**

Fluidity of tablet blends is important to ensure uniformity of die-filling, prior to compression, and a uniform tablet mass. Active ingredients making up less than 5% of a tablet formula may readily be incorporated into a tablet blend using the correct binder. However, when present in large proportions, all substances included must comply with fluidity specifications. Uniformity of the particle size of the components of the formula decreases the potential for segregation (Sheth et al., 1980). When a drug has been solubilized to enhance dissolution it does not always have good flow properties and, when it makes up a large proportion of a formula, the flowability may be affected. Usually, the addition of a glidant becomes necessary.

Ragnarsson et al.(1979) noticed an interaction between fumed silicon dioxide (colloidal silica) and tablet lubricants such as magnesium stearate. The inclusion of magnesium stearate as a lubricant for sodium chloride tablets resulted in the production of softer tablets. A decrease in tensile strength with an increase in magnesium stearate concentration was noted. The ejection force of the tablets from the die was reduced due to the effect of the lubricant. The disintegration time was also retarded. These effects were enhanced with increased mixing times. Shorter mixing times did not influence the lubrication efficiency, but the unwanted effect (retardation of disintegration) was less, due to the poor distribution of magnesium stearate in the blend. However, although the inclusion of fumed silicon dioxide (as a glidant) improved the tablet strength, it did not improve tablet disintegration and had a negative effect on ejection force. Therefore, the authors questioned the use of fumed silicon dioxide to mask the unwanted effects of magnesium stearate.

An increase in the crushing strength of sodium chloride tablets and compressible starch (STA-Rx 1500) tablets (containing magnesium stearate and fumed silicon dioxide) was noted by Lerk et al. (1977) due to the interaction of magnesium stearate with fumed silicon dioxide (Aerosil 200). They proposed that magnesium stearate forms a film around the individual excipients during the mixing process and that this has a negative effect on the binding properties of the excipient. However, the inclusion of fumed silicon dioxide in the blend contributed to the removal of magnesium stearate from the particle surfaces resulting in a reduction of the negative effect of magnesium stearate on tablet hardness. The hydrophobic nature of the magnesium stearate covering the individual particles in the absence of fumed silicon dioxide, resulted in the retardation of the dissolution rate of the tablets tested. Lerk and Bolhuis (1977) noted that the inclusion of fumed silicon dioxide in sodium chloride tablets, with magnesium stearate as lubricant, reduced the retardation of magnesium stearate on dissolution. This result was not supported by the findings of Ragnarsson et al. (1979), who showed a decrease in dissolution rate due to the inclusion of fumed silicon dioxide in sodium chloride tablets. This discrepancy was attributed to different mixing times or intensity of mixing of the tablet blends.

1.3.4.5 **Disintegrants**

The bioavailability of an active ingredient in a tablet is often dependent on the dissolution rate. Disintegration increases the surface area and hastens the dissolution rate. Therefore, rapid disintegration is desirable for poorly soluble drugs that are required to be absorbed rapidly.

Compressional pressure can have an effect on the efficacy of disintegrants. Khan and Rooke (1976) evaluated 7 disintegrants. The effect of compressional force on the disintegration and dissolution behaviour of directly compressed, insoluble dicalcium phosphate dihydrate tablets and wet granulated, soluble lactose tablets was evaluated. The lactose system is of particular interest. Since the dissolution of a soluble system takes place by erosion at the outer surfaces, swelling of disintegrant particles is not expected to play a major role. In this system the disintegration time generally increased with increasing compression pressure, except when sodium carboxymethylcellulose, calcium carboxymethylcellulose, sodium starch glycolate and casein formaldehyde were used as disintegrants; these showed an initial decrease. The dissolution results followed the same pattern as the disintegration results. Cross-linked polyvinylpyrrolidone and cation exchange resins are swelling type disintegrants and are relatively non-adhesive in the hydrated state. Their dissolution efficacy is as a result of swelling. The other disintegrants such as sodium carboxymethylcellulose, calcium carboxymethylcellulose, sodium starch glycolate and casein formaldehyde also rely on swelling to disintegrate, but at low compression pressures (500 and 1000 kg cm^{-2}) there is no significant reduction in dissolution efficiency. The authors postulate that at higher pressures, there is a reduction in pore size, porosity and penetration rate, resulting in a decreased dissolution efficiency of the latter disintegrants.

Rudnic et al. (1981) evaluated eight common disintegrants in a direct compression system of 75:25 calcium phosphate dihydrate/ anhydrous lactose. They noted that even at very low concentrations of disintegrants, significant reduction in disintegration time took place. Of particular interest is sodium starch glycolate and cross-linked polyvinylpyrrolidone that were used at a concentration of 0,25; 0,5; 1 and 2% (m/m) and gave the best results at 2%. The disintegration time for both substances was below 1 minute at a concentration of 2% in the tablets. Disintegrant concentrations above 2% were not tested, since the good disintegration times observed created no need for higher concentrations of disintegrant. Therefore, many of the unwanted effects of a large volume of disintegrant in a formula, such as mass variation, powder flow problems and hardness reduction, may be alleviated by using lower levels of disintegrants, while still achieving significant disintegration.

Fassihi (1986) investigated the mechanisms of disintegration and compactibility of disintegrants in a direct compression system. Tablets containing a variety of disintegrants (sodium starch glycolate, microcrystalline cellulose, croscarmellose sodium and starch) gave practically identical curves for disintegration time vs. compression force, irrespective of disintegrant used. This indicated that compressional force, rather than the physiochemical properties of the disintegrants, dictated the mechanism of action. A mechanism of disintegration was proposed and is illustrated in figure 5.

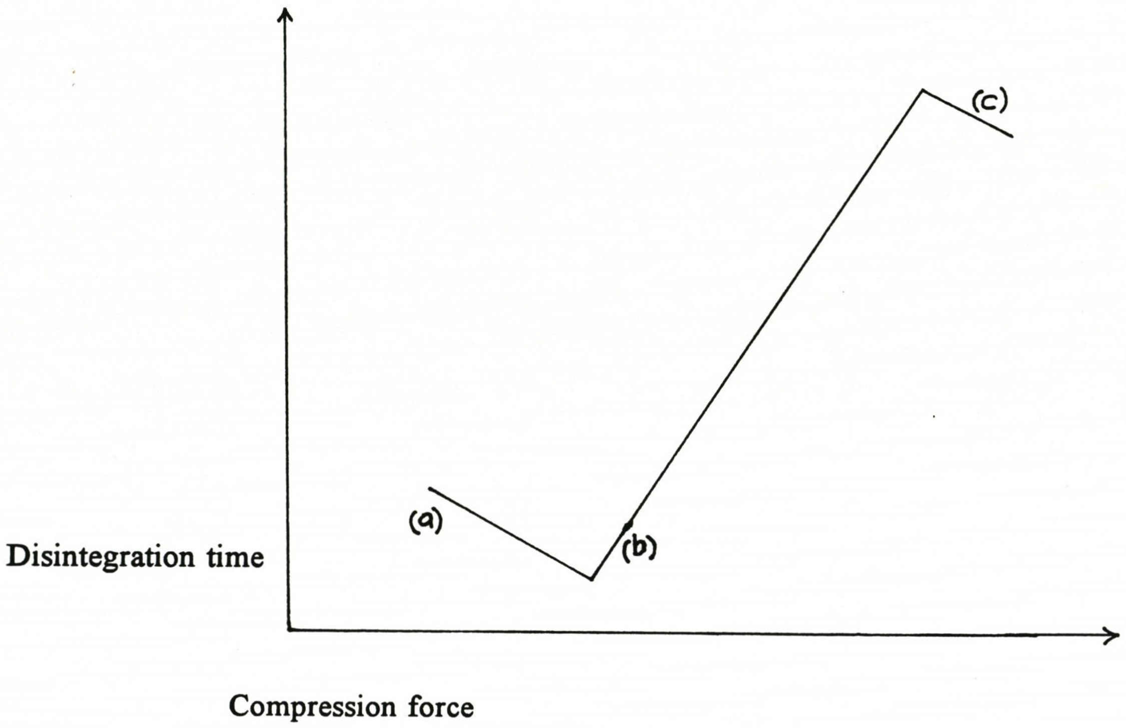


FIGURE 5: **GENERAL MECHANISMS OF DISINTEGRATION** (Fassihi, 1986)

(a) Liquid penetration and swelling.

(b) Wicking (porosity and capillary action).

(c) "Mechanical activation" characterized by

thermodynamic parameters.

At low compressional forces, the degree of porosity is high and water uptake, accompanied by swelling, takes place. At a pressure of 80 MNm^{-2} the degree of porosity decreases slightly, continuous pathways are formed and water can wick into tablets. Wicking is a result of capillary action and there is a resulting decrease in disintegration time. Khan and Rhodes (1974) noted a similar decrease in disintegration time with increased compression.

Washburn (1921) described the influence of water penetration and capillary action, by means of the following equation:

$$V^2 = \frac{2.m.\gamma.\cos \theta.t}{k.\eta} \qquad (6)$$

where m = hydraulic pore radius

γ = surface tension of the penetrating liquid

θ = contact angle between liquid and solid in the pores

η = liquid viscosity

k = constant depending on pore shape

The principles underlined in the Washburn equation (eq. 6) could be applied to the disintegration process. Therefore, liquid penetration into tablets is proportional to the porosity or the mean pore diameter, both of which increase with increasing starch concentration. This has been attributed to the compressibility and low cohesiveness of starch.

At pressures of 120 MNm^{-2} and 160 MNm^{-2}, however, particles are deformed and thus energy rich. When exposed to water, relaxation of the stressed particles gives rise to an exothermic process causing expansion and breakage of bonds ("mechanical activation"). During the compression process, deformation and fracturing contribute to the transformation of mechanical energy into dislocation and distortion energy. The system undergoes an increase in entropy and enthalphy. This state is thermodynamically unstable and the heat of wetting upon disintegration causes entrapped air to expand. The reversible part of the stored energy that can be transformed into other types of energy is responsible for disruption and disintegration at high compaction pressures.

CHAPTER 2

METHODS AND PREFORMULATION STUDIES

2.1 MATERIALS

The following materials were used in the preparation of the various batches of indomethacin products and tablets:

Aerosil 200 (fumed silicon dioxide), donated by Dentapharm CC, Cape Town, SA.

Avicel PH 102, batch no. 2336, supplied by FMC Corporation, Philadelphia, USA.

Explotab, batch no. E2938X, supplied by Edward Mendell Co.,Inc., New York, USA.

Indomethacin, batch no. 48756, supplied by Lennon Ltd., Port Elizabeth, SA.

Kollidon CL (cross-linked polyvinylpyrrolidone), batch no. 553582, donated by BASF Ltd., Johannesburg, SA.

Lactose, Batch no. 35889, supplied by Heynes Mathew Ltd., Cape Town, SA.

Polyethylene glycol 400, batch no. 4763820G, supplied by BDH Chemicals, Poole, England.

Polyethylene glycol 6000 , batch no.245033, supplied by BDH Chemicals, Poole, England.

Starch, batch no. 6526350, supplied by BDH Chemicals, Poole, England .

Tablettose, supplied by Leochem Pty., Ltd., Johannesburg, SA.

2.2 SOLUBILIZATION METHODS

2.2.1 CHOICE OF A METHOD OF SOLUBILIZING INDOMETHACIN

Within the limits previously defined, various methods were available for the solubilization of indomethacin. In the preliminary work, several methods of solubilizing indomethacin were attempted. The products obtained, however, had to be free flowing or be able to be reduced to a free-flowing powder. Methods not giving these results were discontinued, e.g. the glass products made by melting indomethacin with citric acid or various sugars (Summers and Enever, 1976). The preliminary work showed that these products were sticky and not free flowing. Polyvinylpyrrolidone soluble grades, Kollidon 25 and 30, melted with indomethacin also gave sticky products. Methods which involved the use of specialized equipment, e.g. spray-drying, freeze-drying and high-speed mixing were not attempted, due to a lack of equipment.

The methods and materials used are summarized in table 2. Where necessary, the products obtained were ground with the aid of a mortar and pestle and mixed in a cube mixer. Only material with a particle size smaller than 500μm was used. The solubilized forms of indomethacin obtained are henceforth called "products".

TABLE 2: **THE VARIOUS METHODS USED TO SOLUBILIZE INDOMETHACIN:**

METHOD	EXCIPIENT	RATIO OF DRUG TO EXCIPIENT	REFERENCE
Solvent dispositioning	starch lactose	1:9 (10:90g) 1:9 (10:90g)	Johansen and Møller (1978)
Adsorption of a strongly hydrophilic substance	fumed silicon dioxide	9:1 (90:10g)	Monkhouse and Lach (1972)
Solid dispersion	polyethylene glycol 6000 (PEG 6000)	1:3 (25:75g)	Bogdanova et al. (1981)
	cross-linked polyvinyl-pyrrolidone (CL PVP)	1:3 (25:75g)	Takayama et al. (1980) Imaizumi et al. (1983)
Adsorption of an indomethacin solution in PEG 400	fumed silicon dioxide	1:19 (5:95g)	
	talc	1:39 (2,5:97,5g)	

2.2.2 METHODS USED

2.2.2.1 Solvent depositioning

The method used was based on that of Johansen and Moller (1978). The optimum amount of solvent to be used, and the temperature and time for evaporation, were determined empirically to give the most promising products. The amount of indomethacin used, as shown in table 2, was weighed and dissolved in 100 cm^3 of acetone in a 500 cm^3 glass beaker. This was done with the aid of a mechanical stirrer in a vacuum cupboard. During continuous stirring, lactose or starch was gradually added. The mechanical mixer was left stirring, while the acetone was being removed with the aid of the vacuum. After 3 hours, the slurry remaining in the glass beaker was spread out on a drying pan and left overnight in the vacuum cupboard to ensure complete evaporation of the acetone.

2.2.2.2 **Adsorption of a strongly hydrophilic substance**

Using the method described by Monkhouse and Lach (1972a), indomethacin and fumed silicon dioxide were treated in the same way as starch or lactose in section 2.2.2.1 (using acetone as solvent). The amounts and appropriate ratio of indomethacin to fumed silicon dioxide used are given in table 2.

2.2.2.3 **Solid dispersions**

A dispersion of indomethacin in cross-linked polyvinylpyrrolidone (CL PVP) was prepared after the method of Imaizumi et al. (1983). A solution of indomethacin in 100 cm^3 of acetone, containing CL PVP in suspension was prepared. The acetone was evaporated using a rotary evaporator at 40°C. The weight ratio of indomethacin to CL PVP, as well as the amounts of each substance used, are given in table 2.

In a similar way, indomethacin was dispersed in polyethylene glycol 6000 (PEG 6000). The acetone was removed using a rotary evaporator at 70°C. The weight ratio and mass of each substance used are given in table 2.

A combination of the solvent and melting methods for preparing solid solutions, as described in section 1.1.3.4, was used for the indomethacin-PEG 6000 product.

2.2.2.4 Adsorption of an indomethacin solution

Indomethacin powder (6.25%) was dissolved in polyethylene glycol 400 (PEG 400). With the aid of a mortar and pestle, talc or fumed silicon dioxide was gradually added to the indomethacin solution to produce a free-flowing product with the respective weight ratios as given in table 2.

2.3 PREFORMULATION STUDIES

2.3.1 INTRODUCTION

Preformulation studies are performed to maximize the chances of success in formulating an acceptable product and ultimately to provide a basis for optimizing drug product quality and performance. They are also used as a labour-saving device to identify problem areas, in order to avoid them.

Prior to the development of a dosage form, it is essential that the fundamental physical and chemical properties of the drug molecule are determined. However, since well-known materials were used in this study, preformulation testing of this type was not considered necessary. In addition, solubility, intrinsic dissolution rate and dissociation constants are well documented for indomethacin.

Since indomethacin was solubilized and the modified products obtained had different physical appearances, preformulation studies on these products were essential to determine whether they could be tabletted using direct compression. Furthermore, the uniformity of content of indomethacin in the products had to be established to ensure uniform content of indomethacin in the eventual tablets.

Preformulation studies were done in three stages:

a) The indomethacin was tested to see whether it conformed to compendial requirements.

b) The indomethacin products, prepared according to the methods previously described, were submitted to a series of tests to select the most soluble form of indomethacin.

c) The most soluble form was tested to see whether it was suitable for direct compression and whether it was compatible with the adjuvants to be used in the tablet formula.

Throughout the testing procedure, the broad objectives outlined for this study were borne in mind, i.e. that a more soluble, free- flowing form of indomethacin is required, which has an improved bioavailability but which, at the same time, has an acceptable stability and is able to be directly compressed.

2.3.2 TESTS DONE ON INDOMETHACIN

2.3.2.1 Identification

Indomethacin was identified using the tests laid down in the BP (1980). The mean melting point was 161.8°C (n=3). A Mettler apparatus (FP 80) with a Mettler furnace (FP 81) was used. According to the BP, indomethacin melts between 158°C and 162°C. The melting point obtained was that of the γ-polymorphic form. This was confirmed by X-ray diffraction analysis (section 2.3.3.6.2).

The IR spectrum of indomethacin was obtained using a PYE Unicam SP3-200 infrared spectrophotometer. The KBr disc method was used. The IR spectrum is shown in figure 6. The individual peaks at 1226, 1236, 1307, 1478, 1690, and 1714 cm^{-1} correspond with those laid down for indomethacin in The Pharmaceutical Codex (1979).

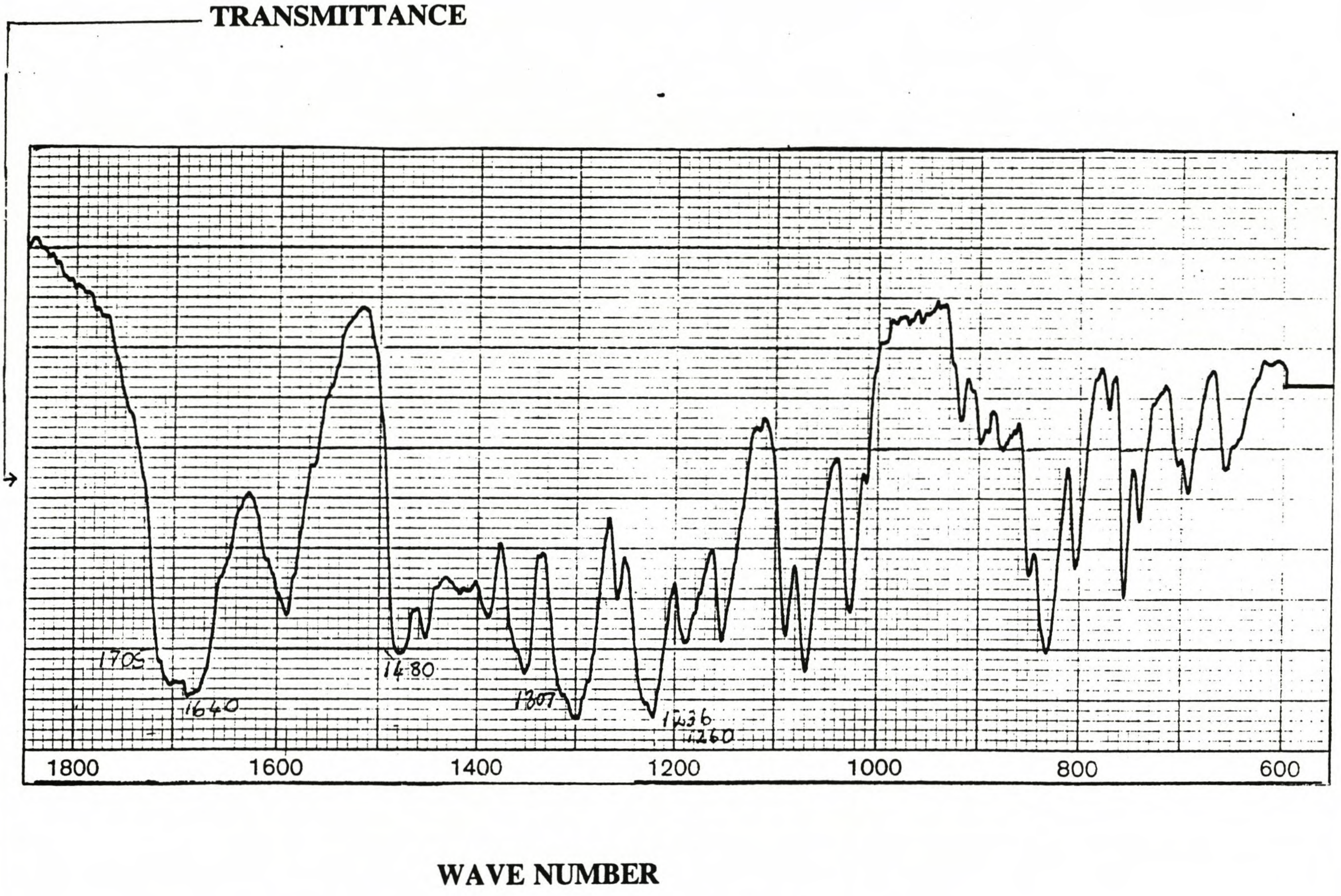


FIGURE 6: **THE IR SPECTRUM OF INDOMETHACIN**

2.3.2.2 Assay of indomethacin

Indomethacin was assayed according to the BP (1980) method and was shown to contain 99.7% of $C_{19}H_{16}ClNO_4$, calculated with reference to the dried substance.

2.3.3 TESTS DONE ON INDOMETHACIN PRODUCTS

2.3.3.1 Assay of indomethacin products for indomethacin content

Apparatus:

Beckman DU-40 Spectrophotometer

Method:

A solution of indomethacin in phosphate buffer (70% 0.066M Na_2HPO_4: 30% O.054M NaH_2PO_4; adjusted to pH 7.2 with phosphoric acid) was prepared and a UV-visible scan was obtained for the 200-800 nm range. Triplicate standard solutions of various concentrations of indomethacin in phosphate buffer were prepared. The absorbance of each solution was read at the wavelength of maximum absorption, i.e. 317 nm. A standard curve of concentration versus absorbance was plotted.

Triplicate samples of powdered indomethacin product, equivalent to approximately 25mg of indomethacin, were weighed out. The powder was placed in a 50 cm^3 glass beaker and dissolved in 10 cm^3 alcohol 90%. The solution was transferred to a 500 cm^3 volumetric flask. Phosphate buffer, used to rinse the glass beaker, was transferred to the volumetric flask which was then made up to volume with phosphate buffer. The volumetric flask was allowed to stand for 10 minutes with frequent shaking. After standing, the contents of the volumetric flask was filtered through a

Millipore filtration unit, fitted with a 0.45 μm membrane filter. The absorbance of the solution was read and the concentration obtained from the linear regression equation of the standard curve (least squares method).

Results:

The mass of each product equivalent to 25mg indomethacin was calculated, i.e. the mass of product needed per tablet. This was necessary to determine whether the product could be incorporated into a reasonably sized tablet (500mg). The results of the assays and the mass equivalent to 25mg indomethacin for each product are shown in table 3.

TABLE 3: THE MASS OF PRODUCT EQUIVALENT TO 25mg INDOMETHACIN

INDOMETHACIN PRODUCT	RATIO (DRUG TO EXCIPIENT)	ASSAY (% IMC) (mean, n=3)	MASS EQUIVALENT TO 25mg INDOMETHACIN
Indomethacin-starch	1:9	11.53	216.82 mg
Indomethacin-lactose	1:9	10.69	233.86 mg
Indomethacin-fumed silicon dioxide	9:1	84.86	29.46 mg
Indomethacin-PEG 6000	1:3	24.16	103.47 mg
Indomethacin-CL PVP	1:3	23.72	105.39 mg
Indomethacin:PEG 400-talc	1:39	2.95	847.45 mg
Indomethacin:PEG 400-fumed silicon dioxide	1:19	5.3	471.69 mg

Discussion:

In an attempt to produce reasonably sized tablets (± 500mg), it can be seen from table 3 that the indomethacin-PEG 6000, indomethacin-fumed silicon dioxide and the indomethacin-CL PVP products have the lowest mass equivalent to 25mg indomethacin. The indomethacin-PEG-talc product, as well as the indomethacin-PEG-fumed silicon dioxide product, have large masses equivalent to 25mg indomethacin. In addition, they are bulky (i.e. they occupy a large volume) and are thus difficult to incorporate into a tablet.

2.3.3.2 Electron microscopic studies

Apparatus:

Hitachi X 650 Scanning Electron Microscope (SEM)

Edward Sputter Coater S 150B

Method:

All the products tested were in powder form and were kept overnight in a vacuum desiccator to ensure that the powders were dry. Prior to viewing the products under the SEM, they had to be gold sputter-coated to ensure conductivity of the products in the SEM. Sputter coating and SEM operations were done according to standard procedures. Electron micrographs were taken of each of the products, as well as the excipients used to prepare the products. The indomethacin:PEG 400-fumed silicon dioxide product was too liquid and thus electron micrographs could not be prepared for this product.

Results:

The electron micrographs of the products and the excipients are shown in figures 7 to 13.

FIGURES 7 TO 13: **ELECTRON MICROGRAPHS OF INDOMETHACIN PRODUCTS AND EXCIPIENTS**

(a) **(b)**

FIGURE 7 **(a) INDOMETHACIN-FUMED SILICON DIOXIDE PRODUCT**

(b) FUMED SILICON DIOXIDE

(a) (b)

FIGURE 8 (a) INDOMETHACIN-LACTOSE PRODUCT

(b) LACTOSE POWDER

(a) (b)

FIGURE 9 (a) INDOMETHACIN-STARCH PRODUCT

(b) STARCH POWDER

(a) (b)

FIGURE 10 (a) INDOMETHACIN-PEG 6000 PRODUCT

(b) PEG 6000 POWDER

(a) (b)

FIGURE 11(a) INDOMETHACIN-CL PVP PRODUCT

(b) CROSS-LINKED PVP POWDER

(a) (b)

FIGURE 12**(a) INDOMETHACIN DISSOLVED IN PEG 400 ADSORBED ONTO TALC**

(b) TALC POWDER

FIGURE 13 MICROCRYSTALLINE INDOMETHACIN POWDER

Discussion:

The use of electron micrographs to study the nature of tablet excipients is well documented (Lund and Boylan, 1986 and Shangraw et al. 1981b). The electron micrographs of the excipients (figures 7b to 12b) used to prepare the solubilized indomethacin products compare favourably with those in the literature (Lund and Boylan, 1986).

The adsorption of fumed silicon dioxide onto indomethacin can clearly be seen in Figure 7(a). The electron micrographs of the lactose and starch products (figures 8(a) and 9(a)), prepared by solvent depositioning of indomethacin onto starch and lactose, respectively, also clearly illustrate that the indomethacin has been deposited onto the excipients. The solubilization of indomethacin using CL PVP and PEG 6000 takes place at a molecular level and no obvious changes could be seen in the electron micrographs of these products, when compared to those of the respective excipients (figures 10(b) and 11(b)). On the other hand, the deposition of indomethacin dissolved in PEG 400 onto talc was clearly demonstrated (figures 12(a) and (b)). As stated previously, the indomethacin-PEG 400-fumed silicon dioxide product could not be used for electron microscopic studies due to its liquid nature. Figure 13 shows an electron micrograph of microcrystalline indomethacin.

2.3.3.3 **Powder flow**

Introduction:

The ability of tablet powders to flow is extremely important during the tabletting process. Uniform tablet mass and content of active ingredients depends on the ability of the material to feed into the dies in a reproducible manner. This is important for granules, as well as powders used for direct compression.

During direct compression, the rate of production necessitates good powder flow in a rotary tablet press. This is necessary to ensure adequate die filling of the tablet blend at a high speed (Armstrong, 1986). Flow rates, as well as particle size differences, give an indication of the ability of a mixture of powders to mix and demix during the tabletting process. Mendell (1972a) stressed the importance of a uniform flow rate throughout the tabletting process. The flow rate of the individual components is an indication of their ability to be used in a tablet formula, but the flow rate of a mixture of components in a tablet formula is important for the production of uniform tablets. Therefore the flowability of tablet formulations were tested prior to tabletting (see section 3.2).

The flow properties of a powder are an indication of the forces acting between solid particles. These forces could be friction, surface-tension, cohesive or Van der Waal forces, electrostatic forces or mechanical forces caused by interlocking particles of irregular shape. Many methods are available to measure the extent of interparticulate forces, thus giving an indication of the extent of flow (Fonner et al. 1981)

Direct methods of measuring flow include hopper flow rate determinations and the use of recording flow meters. The rate at which a powder discharges from a hopper gives an indication of powder flow under production conditions. By dividing the discharged powder mass by the time for complete discharge, a flow rate is obtained which can be used for the quantitative comparison of different powders. A recording powder flow meter measures the discharge of a powder from a hopper or container onto a balance. A chart recorder is used to produce a permanent record of the increase in powder mass with time. Where the balance is digitalised, the powder flow is recorded using a microcomputer (Jordan and Rhodes, 1979). This is the method of choice, since powder components failing to flow may be identified.

Various methods have been used to measure powder flow indirectly, in order to predict the powder flow properties during tabletting. These methods include the use of shear cells, angle of repose measurements, bulk density measurements and the critical orifice diameter measurements. With the aid of a shear cell, the cohesion between the powder particles can be measured. A shear cell consists of two segments in which the powder is packed and a lid is placed on the top segment. The force to shear the bed is measured and, from this data, the cohesive forces in a powder bed may be calculated.

Measuring the angle of repose gives a good indication of powder flow.The coefficient of friction (μ) is numerically equal to the tangent of the angle (ϕ) that the heap or cone of powder makes with the base on which it rests (figure 14).

$$\mu = \tan \phi \qquad (7)$$

$$\tan \phi = \frac{h}{r} \qquad (8)$$

Where h = height of the powder cone

r = radius of the powder cone

The angle, ϕ, is referred to as the angle of repose and gives an indication of the flowability of a powder. The lower the value of ϕ, the better the flow. The theoretical lower limit is 25°.

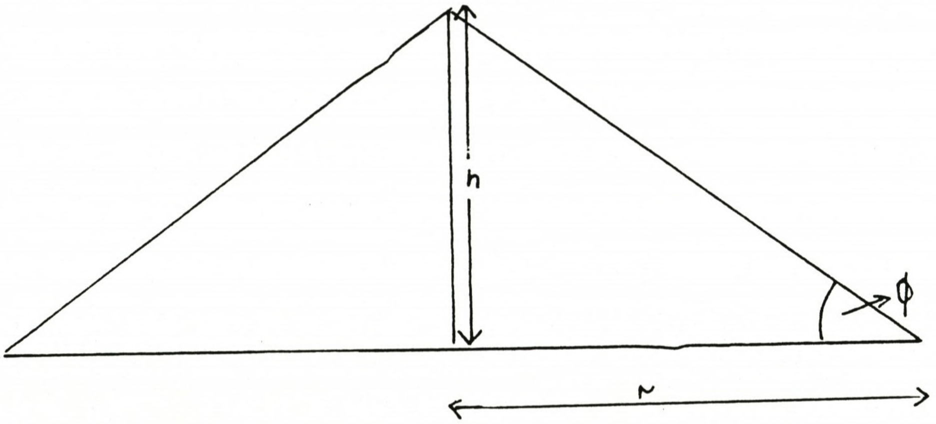


FIGURE 14: ANGLE FORMED BETWEEN CONE OF POWDER AND BASE

The simplest method to measure the angle of repose, is to allow the material to flow through a funnel onto a horizontal surface beneath. The angle of the conical heap gives the angle of repose. However, this method is not reproducible and the cone is distorted due to the falling particles. Several attempts have been made to improve the method, with respect to reproducibility (Staniforth, 1988). The method used in this study involved lifting a glass cylinder, half-filled with powder, using a mechanical device. The powder bed was static. With practice, reproducible results could be obtained.

Apparatus:

The apparatus described by Pather (1989) was constructed. It consists of two plates of perspex, between which is placed a sheet of concentric graph paper. An open-ended glass cylinder with an internal diameter of 23mm and a height of 80mm holds the powder. An oil-filled hydraulic device lifts the glass cylinder smoothly. The apparatus also has a cathetometer to measure the height of the cone of powder.

FIGURE 15: THE APPARATUS FOR ANGLE OF REPOSE DETERMINATION

Method:

The powder was carefully poured into the glass cylinder, until it was approximately half-filled and the powder surface was level with the base of the apparatus. The cylinder was lifted slowly by means of the hydraulic device. The smallest diameter (D_1) and the largest diameter (D_2) of the base of the powder cone were determined, using the concentric circles as a guide. The height (h) of the cone was measured and the angle of repose was calculated from equation 8.

The factor "r" for this equation is given by the formula:

$$r = \frac{D_1 + D_2}{4} \qquad (9)$$

Results:

The angle of repose values of indomethacin products are given in table 4:

TABLE 4: ANGLE OF REPOSE: INDOMETHACIN PRODUCTS

	h (mm)	D_1 (mm)	D_2 (mm)	r (mm)	ϕ	ϕ mean
1	22 21	60 58	60 58	30.0 29.0	36.5 36.2	36.3
2	23 24	56 59	60 57	29.0 29.0	38.4 39.7	39.0
3	22 23	53 56	52 58	26.3 28.5	40.0 38.9	39.4
4	23 23	56 57	56 57	28.0 28.5	39.4 38.9	39.2
5	19 19	57 62	58 58	28.5 30.0	33.5 32.3	32.9
6	20 21	58 58	59 61	29.0 29.8	34.4 35.7	35.0
7	20 21	62 62	56 58	29.5 30.0	34.1 35.0	34.6

ϕ = arc tan h/r (°)

1 = indomethacin-starch product

2 = indomethacin-lactose product

3 = indomethacin-fumed silicon dioxide product

4 = indomethacin-PEG 6000 product

5 = indomethacin-CL PVP product

6 = indomethacin-PEG 400-talc product

7 = indomethacin-PEG 400-fumed silicon dioxide product

Discussion:

Angles of repose above 50° indicate poor flow, while materials having values near the theoretical minimum of 25° flow easily and well. All the indomethacin products possessed fair to excellent flow, as can be seen from their respective angles of repose (33 - 39°) in table 4. The best flow properties were shown by the indomethacin-CL PVP product.

2.3.3.4 **Dissolution tests**

Apparatus

Hanson Dissolution Apparatus (Model 72RL)

Hanson Dissoette Automated Sampler (Model 27)

Choice of a method:

Initially the powders, placed in capsule shells, were tested using the rotating basket method. However, the capsules were trapped in an air bubble inside the basket and floated near the top of the basket. According to Hanson (1982) these results should be ignored. The paddle method (USP method 2) was then used for dissolution testing. The floating capsules were restrained by using a platinum wire coil for each capsule. The coil consisted of a 0.9mm diameter, 10cm long platinum wire turned into a coil big enough to trap the capsule. Although the capsule was prevented from floating in the beaker, this method has been criticized due to the disturbances in flow patterns caused by the platinum loop (Hanson, 1982).

Another disadvantage of the basket method is that the powder, when released from the capsule, tends to form a heap at the bottom of the beaker. To comply with the compendial method, i.e. the USP method, the basket rotates at 100 rpm (method 1) compared to 50 rpm for the paddle method (method 2). However, the rotation of the paddle resulted in better distribution of the powder in the dissolution medium.

Method

A UV-visible scan of indomethacin powder in dissolution medium was run. The dissolution medium consisted of either distilled water or phosphate buffer (70% 0.066M Na_2HPO_4: 30% O.054M NaH_2PO_4; adjusted to pH 7.2 with phosphoric acid). A standard curve of concentration of indomethacin in dissolution medium versus absorbance was plotted. Where excipients were used to form products, a UV-visible scan of indomethacin and the respective excipient was run and a standard curve of concentration of indomethacin, in the presence of the respective excipient, versus absorbance was plotted. The wavelength of maximum absorption in distilled water and phosphate buffer is 317nm. Indomethacin is poorly soluble in water (less than 1 part of indomethacin in 10 000 parts of water) and even less soluble in acid. It was therefore not possible to do dissolution tests in acidic media (e.g 0,1 M hydrochloric acid).

The dissolution test was performed according to the USP paddle method (method 2). The rotation speed of the paddle was set at 50 rpm. The setting-up procedure, the performance of the test and the precautions observed, were all in accordance with the details provided in the USP.

Where necessary, the products were ground, then passed through a 500µm sieve and finally mixed in a cube mixer for 5 minutes. Weighed amounts of powder, theoretically equivalent to 25 mg indomethacin, were filled into empty gelatin capsules (size 1) and subjected to dissolution testing. Physical mixtures of indomethacin powder and the respective excipient, in the appropriate ratios, were also subjected to dissolution testing.

Samples of dissolution medium (5 cm^3) were removed from the flasks at 5, 10, 30, 60 and 90 minutes. The absorbance values of the samples were read at the wavelength of maximum absorption (317nm) and the amount of drug released by each powder sample, after each specific time interval, was determined.

Results:

The dissolution data for indomethacin products 1-7 are given in appendices 1 and 2. The stated percentage of drug released at each time interval is the mean of six values. Using these mean values, composite graphs of the percentage drug released versus time were plotted. These graphs are shown in Figure 16 to 20. Not only are the dissolution profiles of the indomethacin products shown, but also that of microcrystalline indomethacin powder, as well as the profiles of a physical mixture of indomethacin and the respective excipient used for each indomethacin product.

Discussion:

Less indomethacin was released from the fumed silicon dioxide product than from microcrystalline indomethacin (Fig. 16). This could clearly be seen in phosphate buffer and distilled water after 90 minutes. There was no significant difference in the amount of indomethacin dissolved from the physical mixture of indomethacin and fumed silicon dioxide, when compared to the product (after 90 minutes in distilled water).

The lactose product gave a better dissolution profile than that observed for microcrystalline indomethacin in phosphate buffer (figure 17). However, the difference in profiles was not significant in distilled water. The physical mixture of indomethacin and lactose gave more or less the same, or even better, dissolution rates compared to the product. In distilled water, the physical mixture released 15% more indomethacin than the product. Similar results were obtained for the starch product (figure 17) although, in this case, the amount of indomethacin released by the physical mixture after 90 minutes in distilled water (in comparison with the product) was even greater than 15% (45.98% compared to 29%).

The poor dissolution profiles shown for the above products may be attributed to a change in polymorphic state of the indomethacin during the manufacture of these products. It is therefore essential to study the polymorphic states of the different products, in order to clarify the dissolution data observed.

The product obtained by adsorbing a solution of indomethacin dissolved in PEG 400 adsorbed onto either talc or fumed silicon dioxide, released more indomethacin than the indomethacin-PEG 400 solution (figure 18). This result was observed in both dissolution media and shows the significance of increasing the area of solute exposed to the dissolution medium. In this case, it was achieved by spreading the indomethacin PEG 400 solution over the surface of the insoluble talc or fumed-silicon dioxide particles.

As expected, the indomethacin-CL PVP and indomethacin-PEG products gave better dissolution rates than indomethacin powder. In fact, in distilled water (figure 19(a)), twice as much indomethacin was dissolved from the indomethacin-PEG 6000 product, after 40 minutes, when compared to indomethacin powder. The results for the indomethacin-CL PVP product were excellent, showing that 5 times as much indomethacin was released in distilled water, after 40 minutes, when compared to indomethacin powder (figure 19(a)). The indomethacin-PEG 6000 product gave a 5% improvement in dissolution rate in distilled water, after 90 minutes, when compared with the physical mixture. Similarly, there was a 10% improvement in dissolution rate in distilled water of the indomethacin-CL PVP product when compared to the physical mixture. However, in phosphate buffer, there was little difference in the dissolution curves for the indomethacin-PEG and CL PVP products and their respective physical mixtures.

Placing the powders in capsule shells is an accurate method for depositing a small quantity of powder into a dissolution beaker. However, this method does not give a true reflection of how the powders would dissolve when incorporated into a tablet. The slight improvement in dissolution rate of the indomethacin-PEG 6000 products compared to the respective physical mixtures can be explained as follows: In the capsule shell, the physical mixture of the poorly-soluble indomethacin is in close contact with the rapidly-soluble excipient, e.g. PEG 6000. The rapidly-soluble carrier creates a favourable dissolution environment, which enhances the dissolution of the indomethacin. This method of solubilization has been recognized by Chiou and Riegelman (1971). Therefore, the equal dissolution rates observed by the indomethacin-PEG 6000 product and the physical mixture (in phosphate buffer dissolution medium) are probably due to an experimental shortcoming and the observed dissolution profile of the indomethacin-PEG 6000 physical mixture is not a true representation of what would be observed after tabletting , when the indomethacin and solubilizing excipient (PEG 6000), as physical mixtures, would not be in close contact. The cross-linked polyvinylpyrrolidone used to enhance the solubility of indomethacin is not water soluble, but is a strongly hydrophilic substance that is swollen by water and exposes a large surface area (BASF, 1986). It may be postulated that indomethacin adsorbed onto a large surface area enhances the dissolution of indomethacin. The equal dissolution rates observed for the indomethacin-CL PVP product and the indomethacin-CL PVP physical mixture in phosphate buffer, may be similarly explained due to the solubilizing effect of CL PVP.

Figures 20(a) and (b) compare the dissolution profiles of the products in distilled water and phosphate buffer, respectively. The best dissolution profiles, in both dissolution media, were shown by the indomethacin-CL PVP product. There was an approximately 5-fold increase in the amount of indomethacin released in distilled water, after 90 minutes, when compared to microcrystalline indomethacin. In phosphate buffer, the CL PVP product showed a 1,5-fold increase in the amount of indomethacin released, after 90 minutes, when compared to microcrystalline indomethacin. Therefore, the indomethacin CL PVP product shows the most promise for incorporation into an indomethacin tablet.

KEY TO ABBREVIATIONS

IMC AEROMIX	physical mixture of indomethacin and fumed silicon dioxide
IMC AEROSIL	fumed silicon dioxide adsorbed onto indomethacin
IMC PEG AEROSIL	solution of indomethacin in polyethylene glycol 400 adsorbed onto fumed silicon dioxide
IMC CL PVP	indomethacin cross-linked polyvinylpyrrolidone solid solution
IMC CL PVPMIX	physical mixture of cross-linked polyvinylpyrrolidone and indomethacin
IMC LACTMIX	physical mixture of indomethacin and lactose
IMC LACTOSE	indomethacin deposited onto lactose
IMC PEG 400	indomethacin dissolved in PEG 400
IMC PEGMIX	physical mixture of indomethacin and polyethylene glycol 6000
IMC PEG	indomethacin polyethylene glycol 6000 solid solution
IMC POWDER	microcrystalline indomethacin powder
IMC STARCH	indomethacin deposited onto starch
IMC STARMIX	physical mixture of indomethacin and starch
IMC PEG TALC	solution of indomethacin in polyethylene glycol 400 adsorbed onto talc

FIGURE 16 (A)

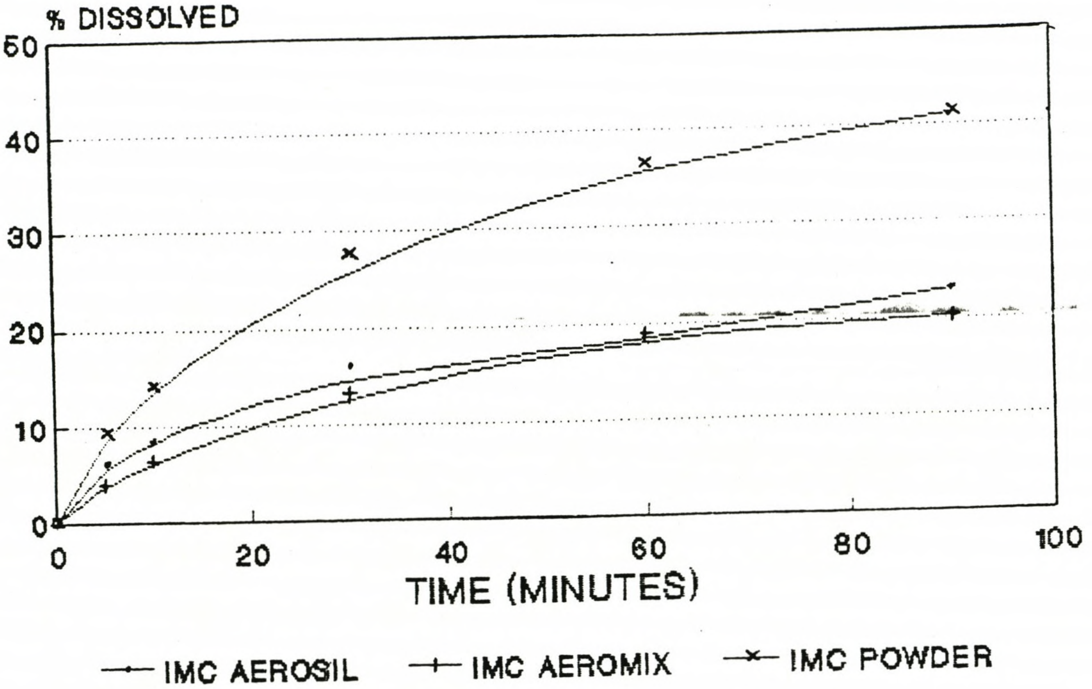


FIGURE 16 (B)

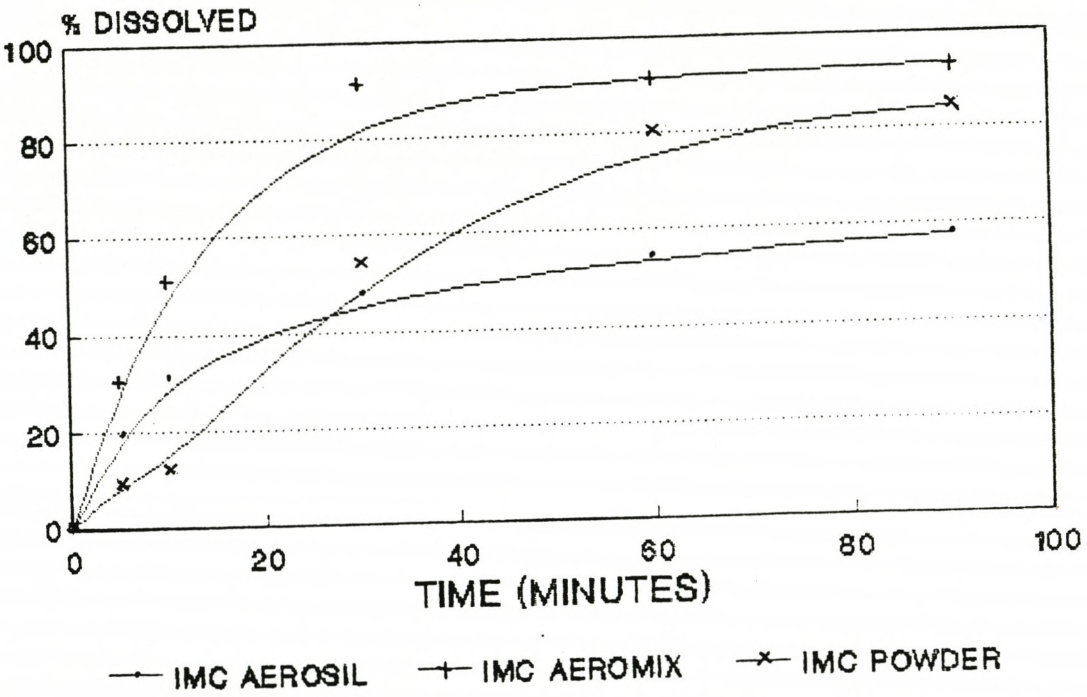


FIGURE 16: DISSOLUTION PROFILE: INDOMETHACIN FUMED SILICON DIOXIDE PRODUCT IN (a) DISTILLED WATER AND (b) PHOSPHATE BUFFER

FIGURE 17 (A)

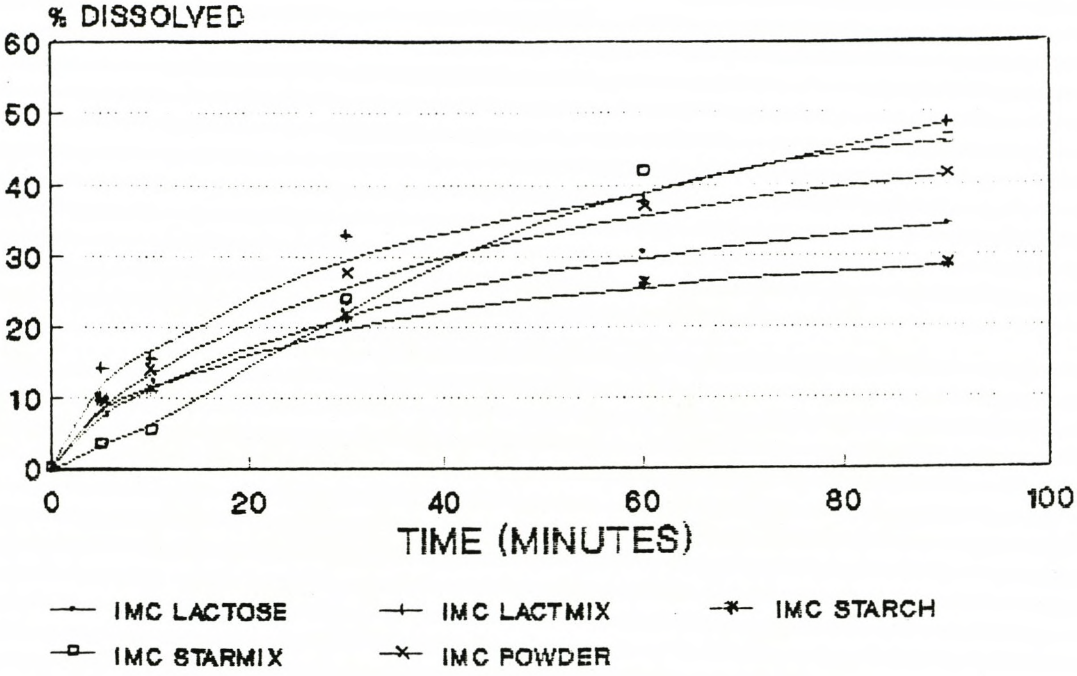


FIGURE 17 (B)

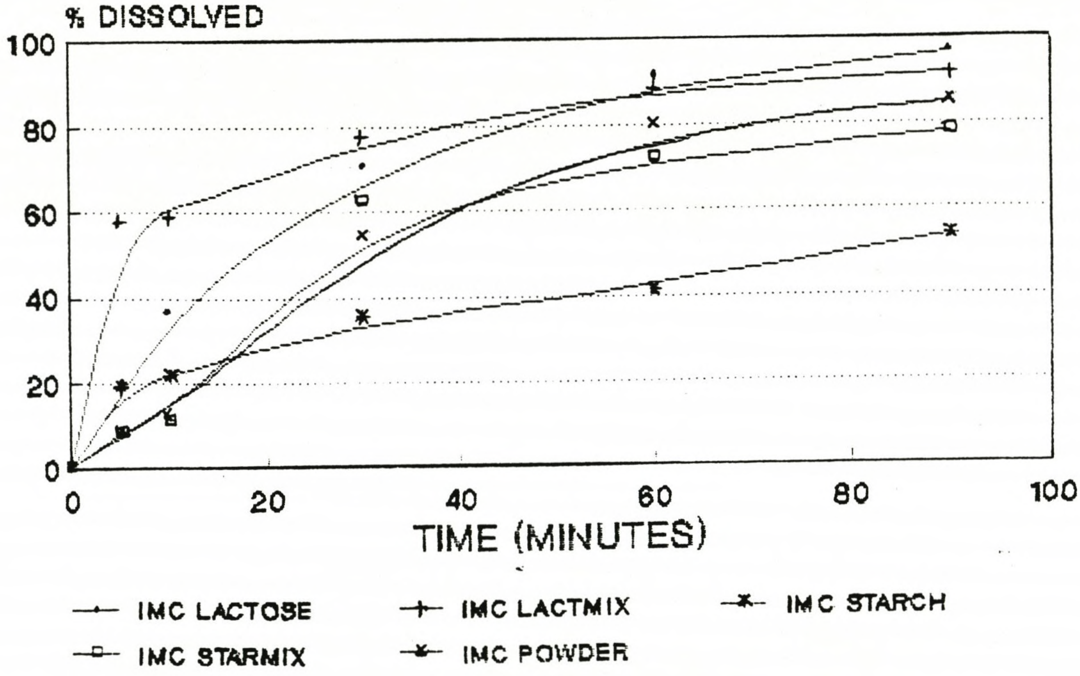


FIGURE 17: DISSOLUTION PROFILE: INDOMETHACIN LACTOSE AND STARCH PRODUCTS IN

(a) DISTILLED WATER AND (b) PHOSPHATE BUFFER

FIGURE 18 (A)

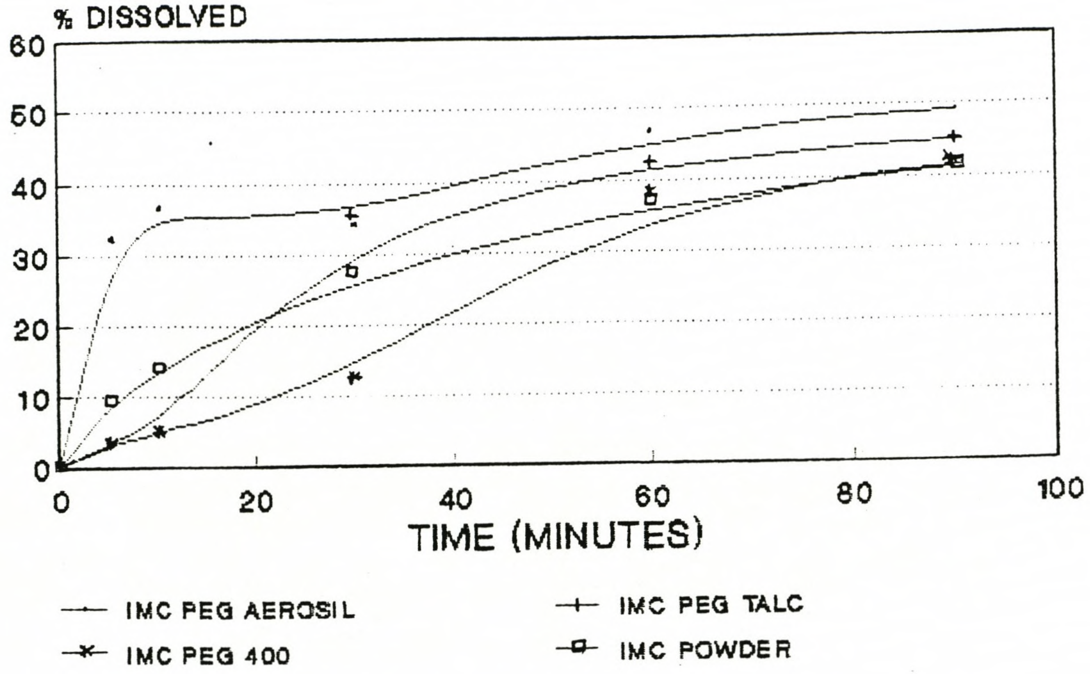


FIGURE 18 (B)

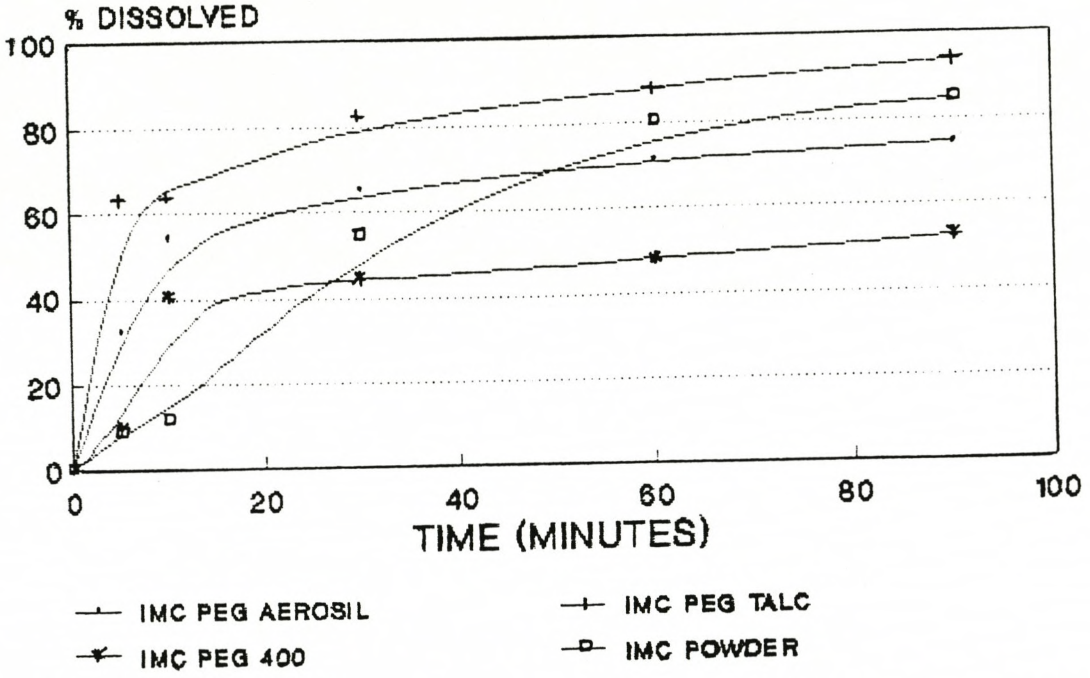


FIGURE 18: DISSOLUTION PROFILE: INDOMETHACIN DISSOLVED IN PEG 400 AND ADSORBED ONTO FUMED SILICON DIOXIDE OR TALC IN

(a) DISTILLED WATER AND (b) PHOSPHATE BUFFER

FIGURE 19 (A)

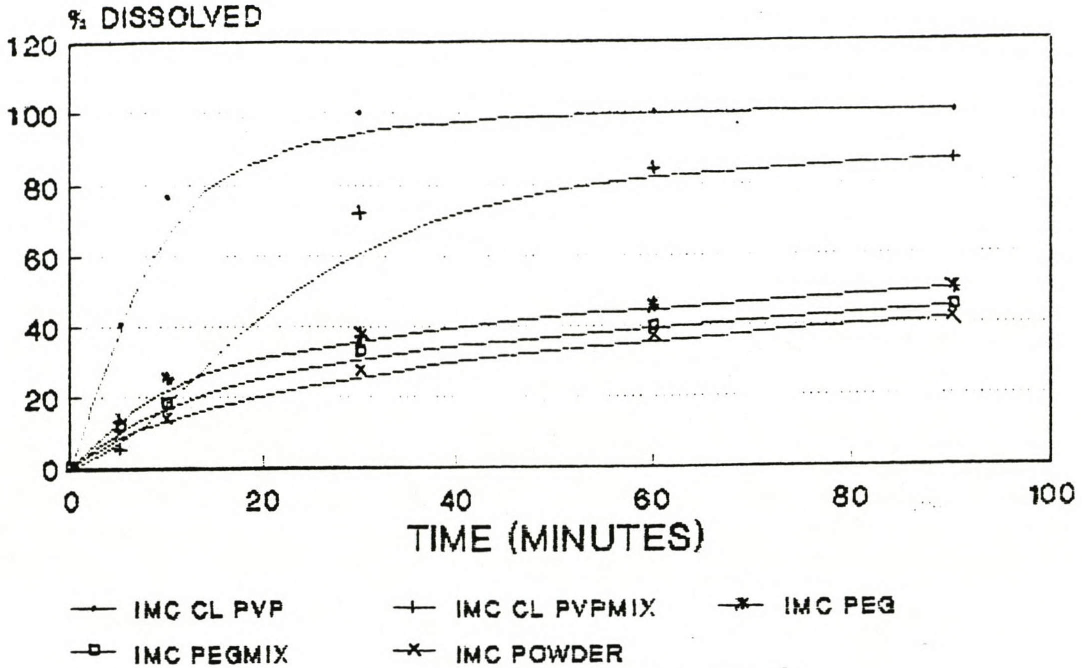


FIGURE 19 (B)

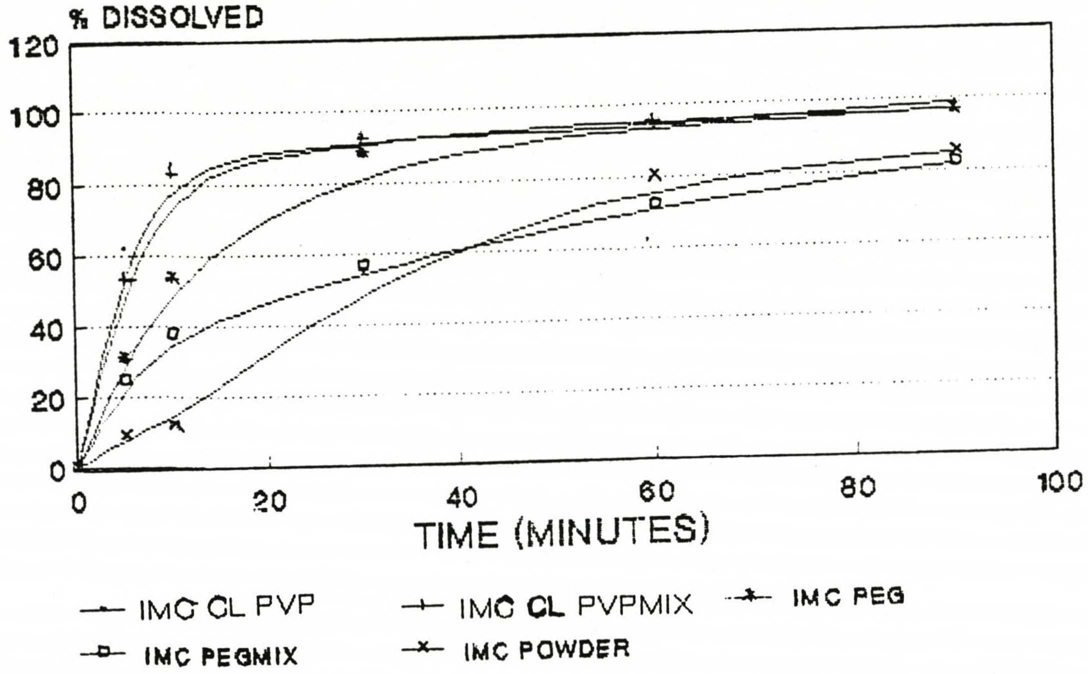


FIGURE 19: DISSOLUTION PROFILE: INDOMETHACIN-POLYETHYLENE GLYCOL 6000 AND INDOMETHACIN-CROSS-LINKED POLYVINYLPYROLLIDONE PRODUCTS IN (a) DISTILLED WATER AND (b) PHOSPHATE BUFFER

FIGURE 20 (A)

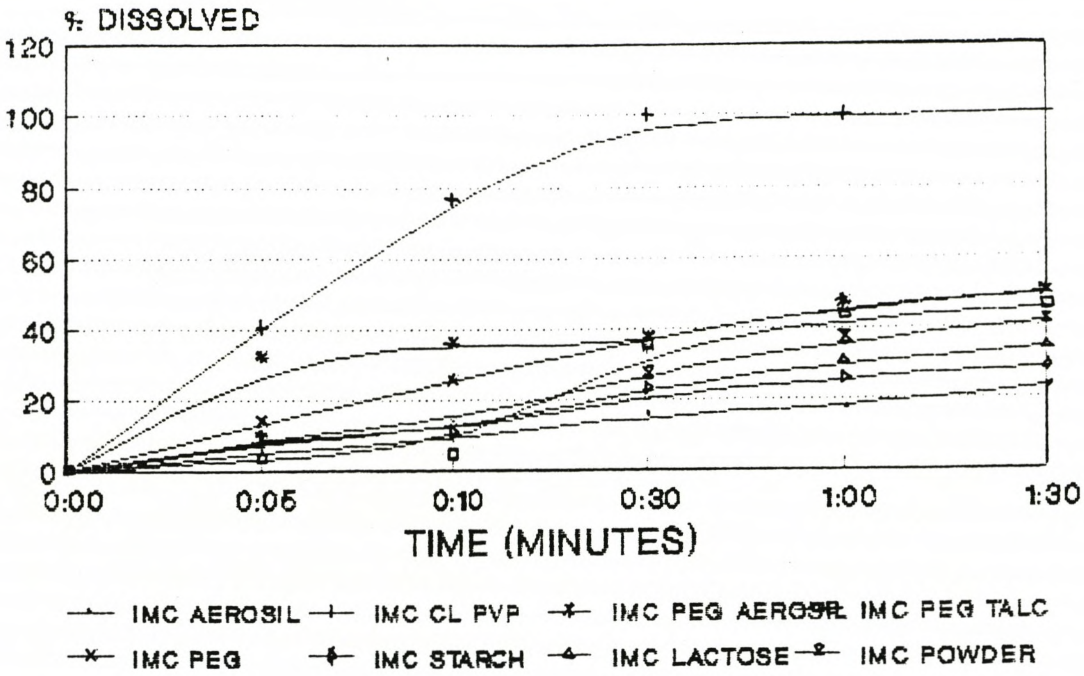


FIGURE 20 (B)

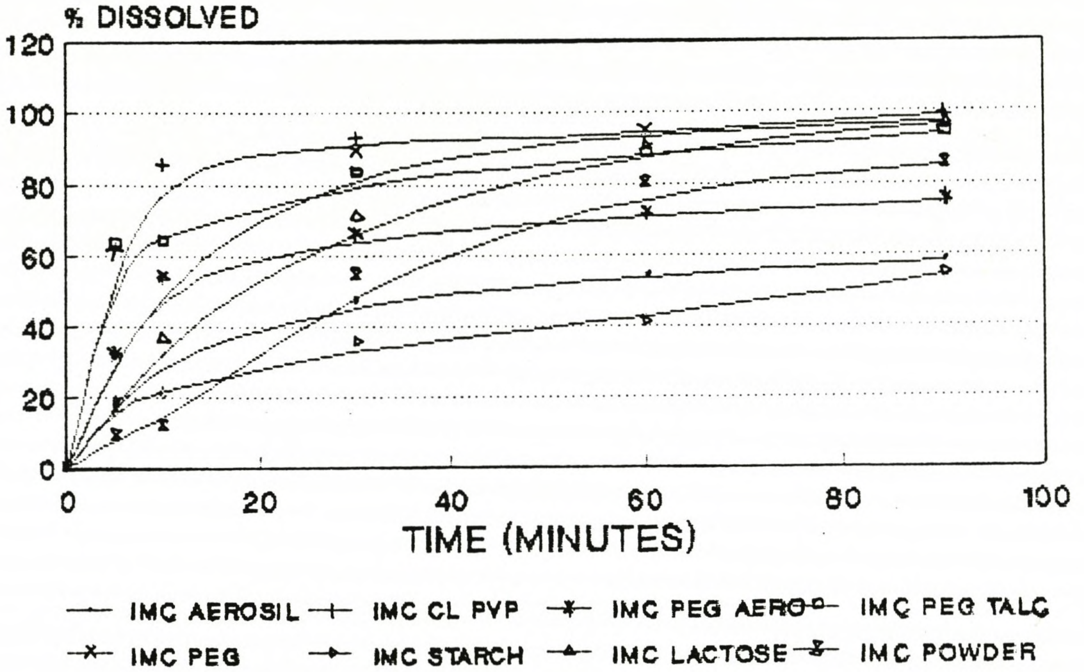


FIGURE 2O: DISSOLUTION PROFILE: A COMPARISON OF THE DISSOLUTION RATE OF INDOMETHACIN PRODUCTS IN (a) DISTILLED WATER AND (b) PHOSPHATE BUFFER

2.3.3.5 **Presence of residual acetone**

Introduction:

Acetone was used as a solvent in the indomethacin products, except for indomethacin-PEG 400 deposited onto talc or fumed silicon dioxide. Although the products obtained were ground, sieved and thoroughly dried, the presence of minute traces of residual acetone could not be ruled out. Residual acetone may affect the chemical stability of the product (Chiou and Riegelman, 1971), as well as favour phase conversion of the particular indomethacin polymorph (Borka, 1974). The ingestion of acetone may also be harmful. However, since the toxic dosage for acetone is 200-400 cm^3 (Medicines Safety Centre, 1991), the primary reason for undertaking this study was the possible chemical instability of the solubilized indomethacin products. Gas-liquid chromatography (g.l.c.) was used to detect acetone in these products.

Apparatus:

Spectraphysics GC 7100 Gas Chromatograph with flame ionizing detector.

A single column was used, packed with Poropak Q (1.5m x 3mm i.d.)

Method:

Sample preparation:

A quantity equivalent to 25mg of indomethacin (i.e. one dosage form) of each of the products to be tested was suspended (in triplicate) in 2ml of distilled water and filtered through a Millipore filtration unit, fitted with a 0.45 μm membrane filter. The filtrates from the indomethacin-starch, -lactose, -fumed silicon dioxide, -PEG and -CL PVP products were then subjected to g.l.c. analysis (group A). For reference, 100 cm^3

standard solutions of 0.1, 0.5, 1 and 2% of acetone in distilled water were prepared (group B). In addition, product samples were prepared as described above, using 0.1, 0.5, 1 and 2% acetone solution, respectively, in the place of distilled water (group C).

G.L.C. Analysis:

The samples prepared were analysed (in triplicate) on the Poropak Q column isothermally at 150°C. The carrier gas was helium and a flame ionisation detector at 300°C was employed.

Results:

The chromatograms of the various dilutions of acetone (group B) are shown in figure 21 (a) to (d). Figure 22 (a) to (e) show the chromatograms of the indomethacin products (group A). Figure 21 is representative of the chromatograms of the indomethacin products prepared from the respective acetone dilutions (group C) and are therefore not shown.

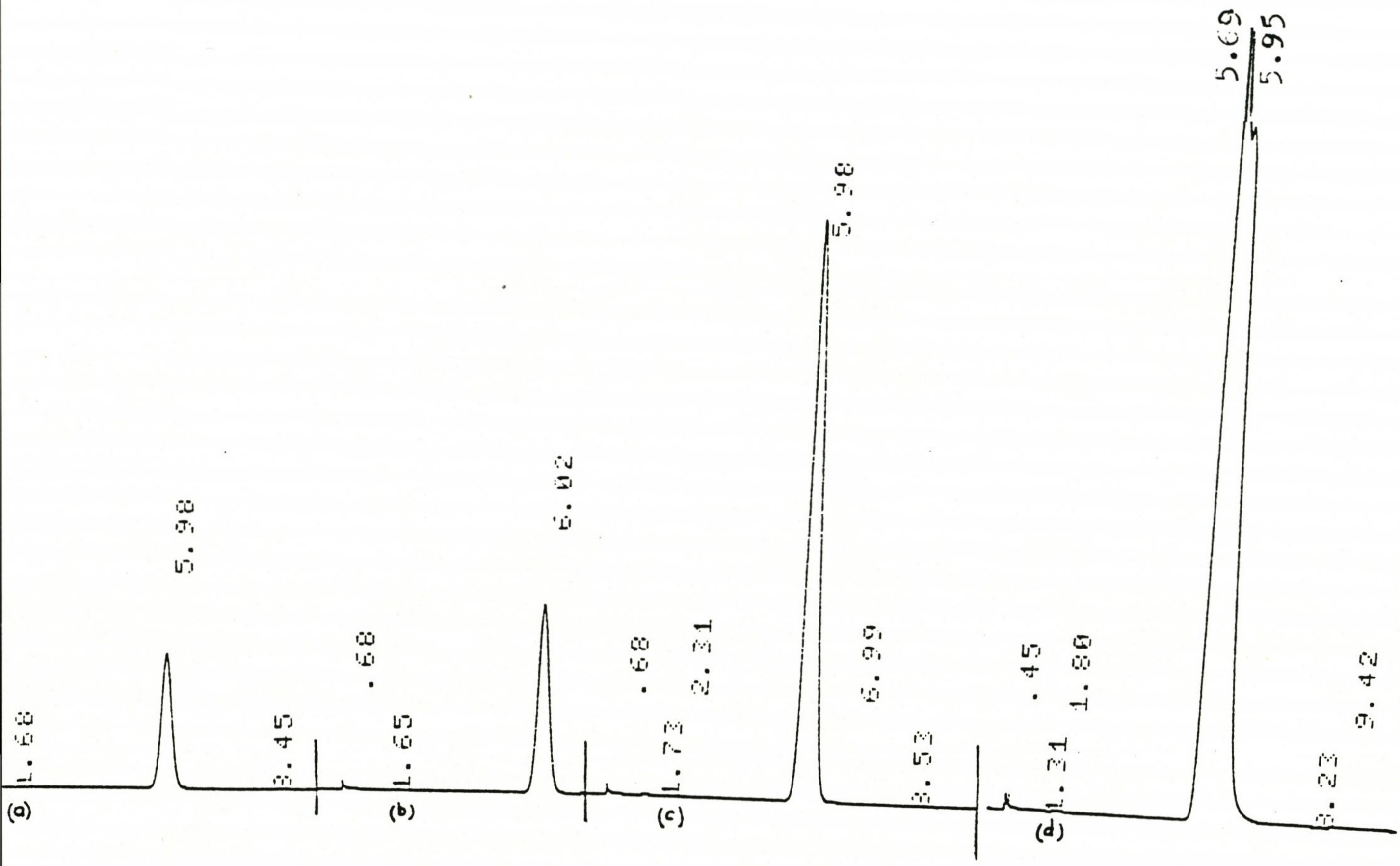


FIGURE 21: THE CHROMATOGRAMS OF VARIOUS DILUTIONS OF ACETONE

(a) 0.1% ACETONE (b) 0.5% ACETONE (c) 1% ACETONE

(d) 2% ACETONE

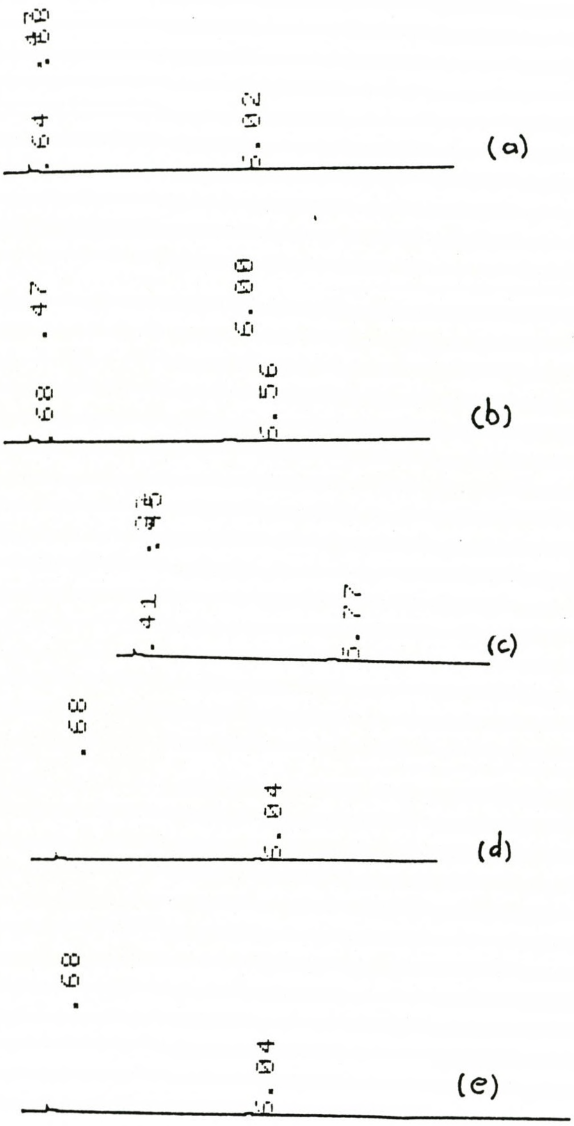


FIGURE 22: THE CHROMATOGRAMS OF INDOMETHACIN PRODUCTS

(a) INDOMETHACIN-STARCH PRODUCT

(b) INDOMETHACIN-LACTOSE PRODUCT

(c) INDOMETHACIN-FUMED SILICON DIOXIDE PRODUCT

(d) INDOMETHACIN-PEG 6000 PRODUCT

(e) INDOMETHACIN-CL PVP PRODUCT

Discussion:

Figure 21 illustrates a unique peak for acetone with a retention time of approximately 6 minutes. The peak area is, as expected, related to the concentration of acetone. Similar chromatograms were obtained for the product samples containing the respective dilutions of acetone. It is obvious from the chromatograms shown in figure 22, that the residual acetone in all indomethacin products is very much less than 0.1% and that for the purpose of this study, the products may be considered to be acetone-free.

2.3.3.6 **Methods used to study polymorphism**

As stated in the literature survey, indomethacin has the ability to exist in more than one polymorphic form. During the process of solubilizing indomethacin, there is the possibility that polymorphic changes may take place. This could have implications for the stability of the solubilized indomethacin products and may affect the dissolution rates of the products.

The indomethacin-lactose, -starch and -fumed silicon dioxide products were subjected to differential scanning calorimetry (DSC) to determine the polymorphic state of the indomethacin present. This method was readily available and easy to use. DSC cannot be used for the identification of IMC polymorphs in PEG because of the formation of a solid solution in the PEG melt (Madhoo and Van Oudtshoorn, 1988). Attempts to use DSC to establish the polymorphic nature of the indomethacin-CL PVP product were not successful. Therefore, powder X-ray diffraction was used to analyze the indomethacin-PEG 6000 and-CL PVP products. Since it was costly to have X-ray diffraction studies done, only those products that could not be analyzed using DSC were subjected to X- ray diffraction studies.

Where DSC was used, the level of excipients ("impurities") for each product was high (e.g. ± 90% lactose for the indomethacin- lactose product). Therefore, accurate quantitative methods could not be used to determine the precise amount of indomethacin polymorphs present. Furthermore, such methods were seen as being beyond the scope of this study.

The products made by indomethacin dissolved in PEG 400 and deposited onto either talc or fumed silicon dioxide consisted of indomethacin dissolved in liquid PEG 400. Since indomethacin is present as a solution, it was assumed that no polymorphic forms existed and these products were therefore not tested.

Borka (1974) and Monkhouse and Lach (1972a) used infra red (IR) spectroscopy to identify indomethacin polymorphs. The most characteristic difference between the pure polymorphs is in the 1700 cm^{-1} region where the CO-bonds shift from polymorph to polymorph. However, due to the high level of "impurities" in the indomethacin products, as mentioned previously, the IR spectrum of indomethacin is obliterated and the polymorphs could not be identified using IR spectroscopy.

Looking at the dissolution tests done in section 2.3.3.4, the PEG 6000 and the CL PVP products appeared to be the most promising for incorporation into an indomethacin tablet. Therefore, these products were subjected to stability testing to see whether polymorphic changes occurred during storage. Samples of each product were subjected to powder X-ray diffraction analysis after storage for 30 days at 37°C.

2.3.3.6.1 **Differential scanning calorimetery (DSC)**

Theoretical background:

Thermal analysis in the broadest sense is the measurement of the physicochemical properties of materials as a function of temperature. Thermogravimetric analysis records changes in sample mass as a function of temperature and time. In differential thermal analysis (DTA), the most commonly used thermal method, the instrument responds to differences in temperature between the test specimen and a reference as it is heated at a uniform rate. However, DSC measures the amount of energy required to keep the sample at the same temperature as the reference. It therefore measures the energy of transition when the sample and reference are heated at a constant rate. When no physical or chemical change takes place, there is neither a temperature change nor the need to input energy to maintain an isotherm. However, when phase changes occur the latent heat suppresses the temperature increase or fall and the change in temperature, or isothermal energy required, registers on a recorder as a result of an electric signal generated by thermocouples. An energy difference is then recorded against the program temperature and a thermogram, as shown in figure 23, is obtained. Since exact heat measurements are essential, the test specimen and the reference material are kept in an identical environment within a temperature-programmable furnace. Crystalline transition, fusion, evaporation and sublimation are obvious changes in state which can be quantified. This makes DSC very versatile and an additional advantage is that the sample size required is only 2-5mg.

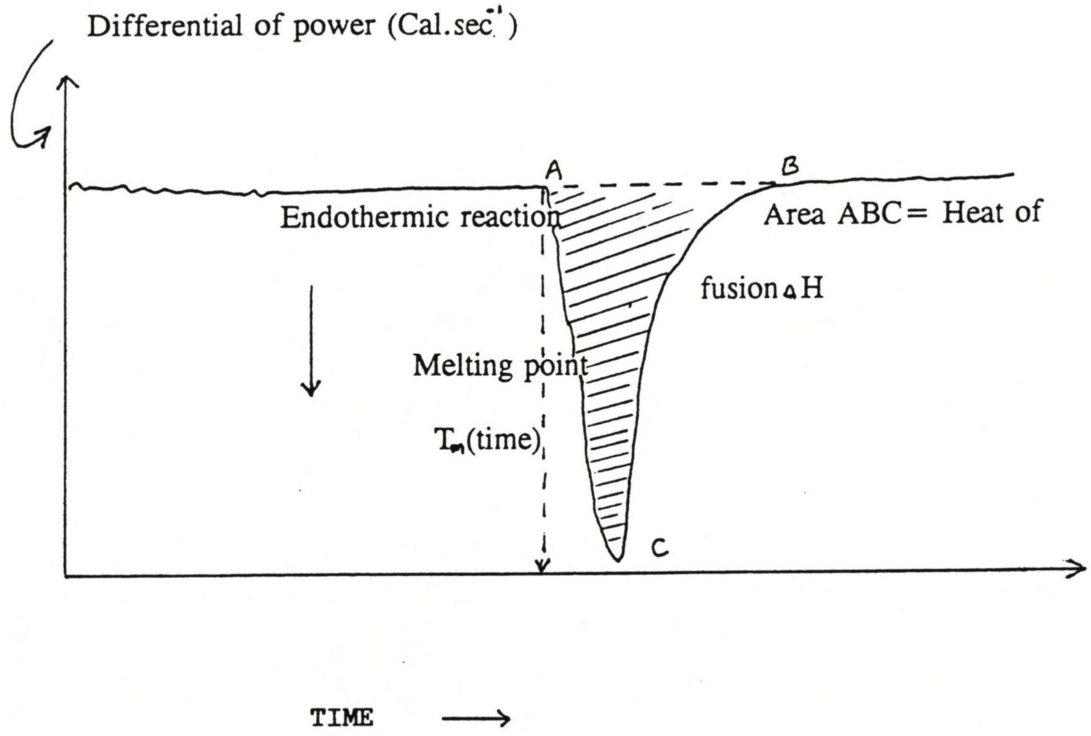


FIGURE 23: A TYPICAL DSC THERMOGRAM

DSC has many applications. It may be used qualitatively for fingerprint comparisons with reference curves or as a screening technique for assessing compatibility of drugs and tabletting excipients (El-Shattawy, 1984). Melting point determinations and the presence of polymorphs of chemicals may also be determined. Quantitatively, it is used to measure the heat of transition (ΔH) when melting, sublimation and glass transition takes place. DSC is also used for eutectic impurity analysis (Brown, 1985 and the USP XIX).

Apparatus:

Mettler FP 80 Central Processor

Mettler FP 85 Thermal Analysis Cell

Perkin Elmer Chart Recorder

Method:

Sample preparation:

Approximately 3mg of powdered indomethacin or indomethacin product was placed in an aluminium crucible and sealed in a sealing press. Since indomethacin does not sublimate easily, the cover of the crucible was pierced to allow free access of the measuring cell atmosphere into the crucible.

Test procedure:

Commercially available indomethacin has a melting point of 158 - 162°C. A starting temperature of 150°C, with a heating rate of 5°C / minute was selected. The end temperature was 170°C. Recording of the melting curve was done according to the procedures described for the instrument. A thermogram was obtained from the chart recorder. Thermograms for the indomethacin-starch, -lactose and -fumed silicon dioxide products, as well as those for the physical mixtures with the respective excipients were obtained.

Results:

The melting curves for the indomethacin products and the physical mixtures with the respective excipients are shown in figures 24 to 26. Using interpolation, the melting points of indomethacin from each melting curve could be determined and are given in table 5.

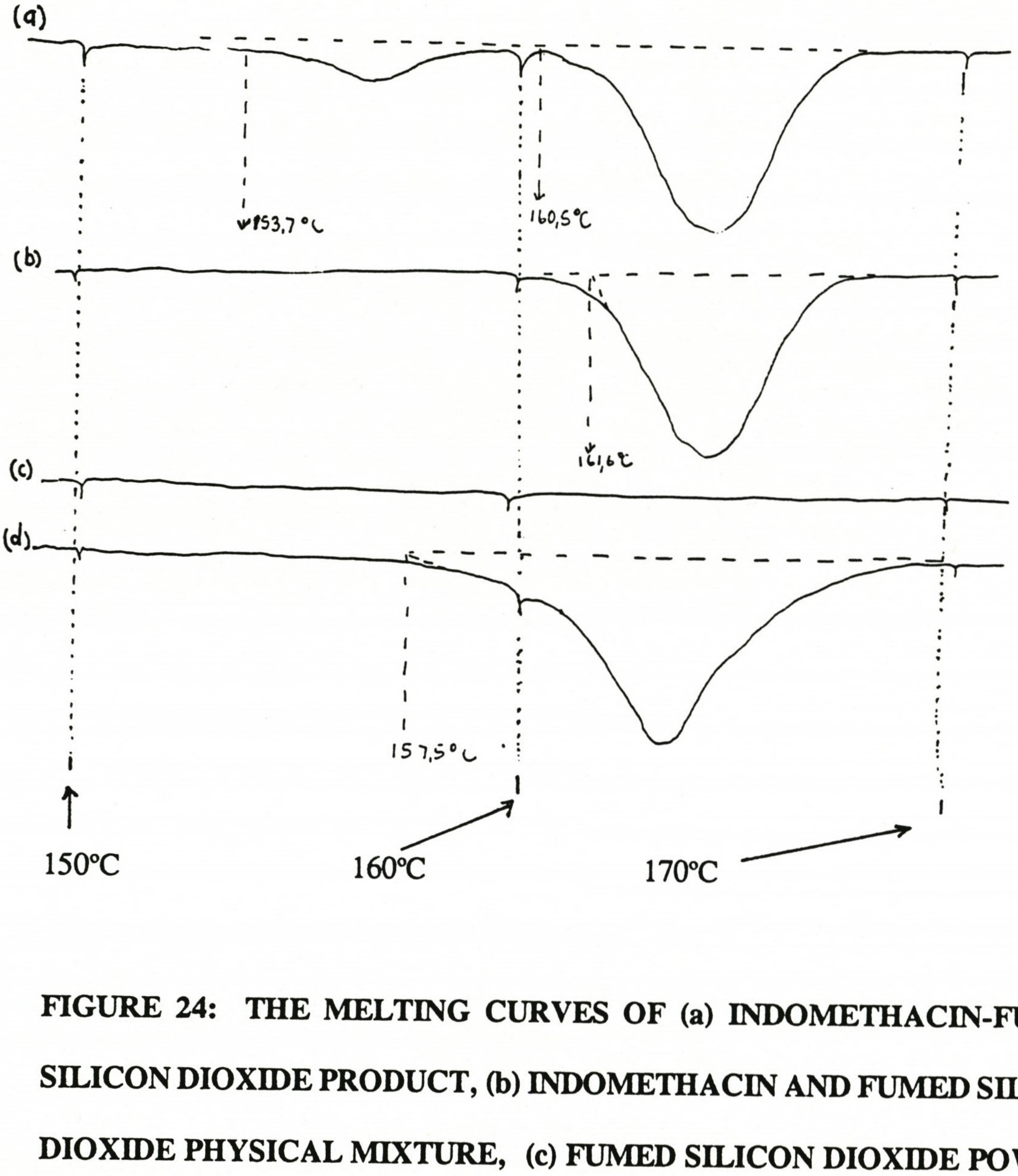


FIGURE 24: THE MELTING CURVES OF (a) INDOMETHACIN-FUMED SILICON DIOXIDE PRODUCT, (b) INDOMETHACIN AND FUMED SILICON DIOXIDE PHYSICAL MIXTURE, (c) FUMED SILICON DIOXIDE POWDER AND (d) INDOMETHACIN POWDER

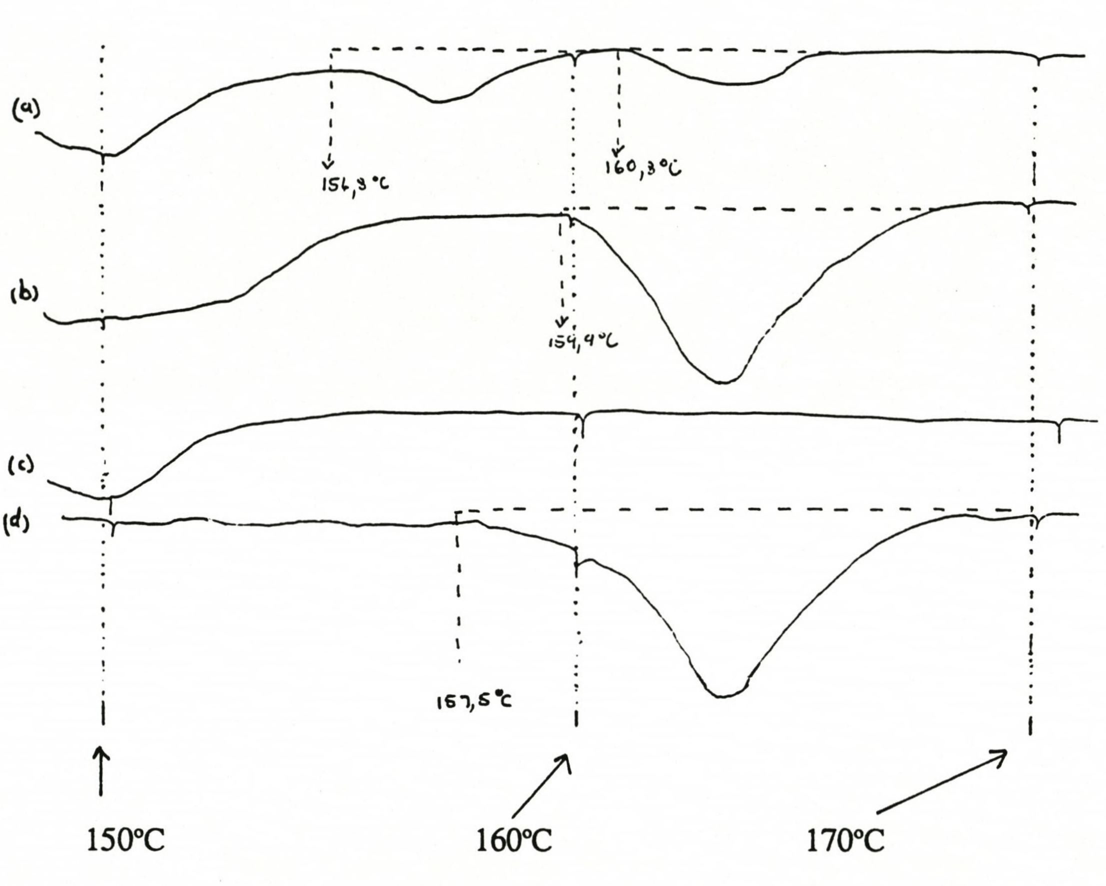


FIGURE 25:THE MELTING CURVES OF (a) INDOMETHACIN-LACTOSE PRODUCT, (b) INDOMETHACIN AND LACTOSE PHYSICAL MIXTURE, (c) LACTOSE POWDER AND (d) INDOMETHACIN POWDER

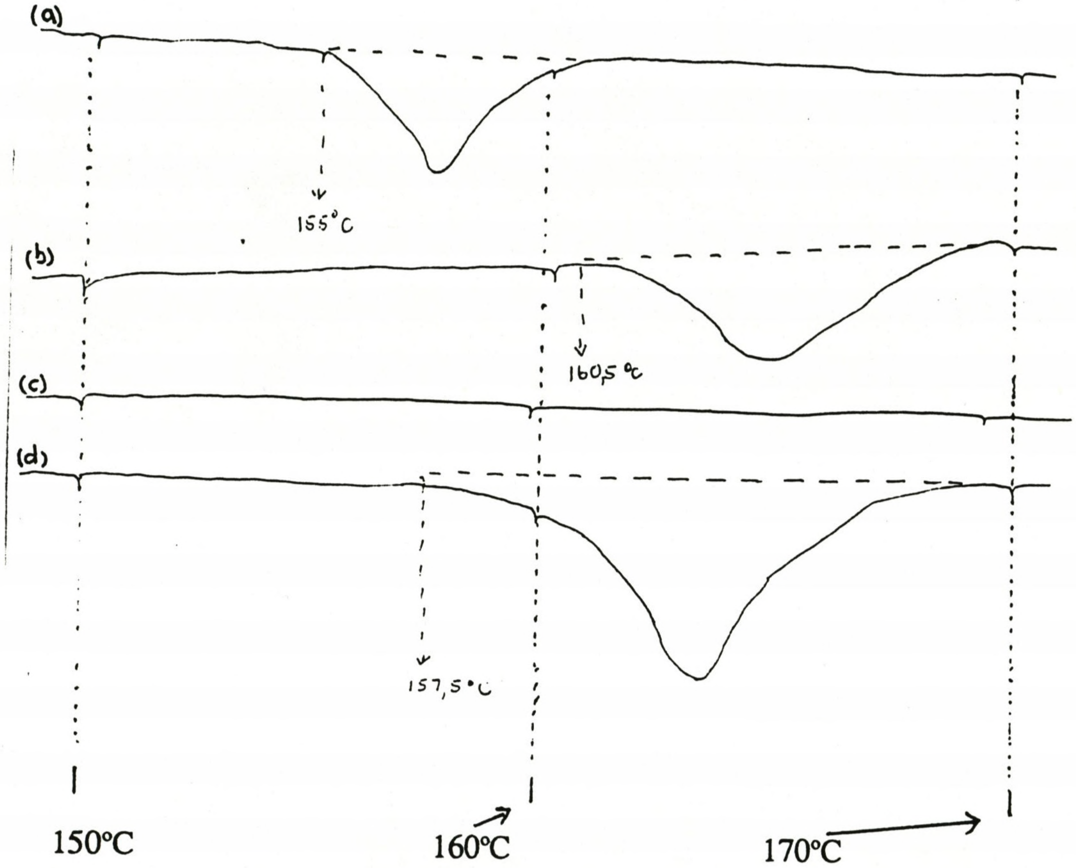


FIGURE 26: THE MELTING CURVES OF (a) INDOMETHACIN-STARCH PRODUCT, (b) INDOMETHACIN AND STARCH PHYSICAL MIXTURE, (c) STARCH POWDER AND (d) INDOMETHACIN POWDER

TABLE 5: MELTING POINTS OF THE VARIOUS POLYMORPHS OF INDOMETHACIN AS DETERMINED FROM THE MELTING CURVES OF THE VARIOUS SOLUBILIZED PRODUCTS AND PHYSICAL MIXTURES TESTED (n=3)

TEMPERATURE (°C)

	∝ FORM	**- FORM**
Indomethacin-lactose product	154.8	160.8
Indomethacin-starch product	155.0	-
Indomethacin-fumed silicon dioxide product	153.7	160.5
Indomethacin powder		157.5
Indomethacin and lactose physical mixture		159.9
Indomethacin and starch physical mixture		160.5
Indomethacin and fumed silicon dioxide physical mixture		161.6

Discussion:

The thermograms of the indomethacin-fumed silicon dioxide and - lactose products each show 2 peaks in the 154°C and 160°C regions. These correspond with the ∝ form and γ-form, respectively, as shown by Borka (1974). Therefore, these products contain both polymorphic forms of indomethacin. The indomethacin- starch product contained only the ∝ form at 155°C, as can be seen from the thermogram. The indomethacin powder gave one peak at 157.5°C, indicating that it consisted of the γ- form. The physical mixture of the respective excipients of the products all showed a peak at ± 160°C, confirming that the indomethacin was of the γ- form and did not change after been mixed with the excipients.

The presence of both polymorphic forms of indomethacin in the indomethacin-lactose and -fumed silicon dioxide products is due to the recrystallization of the products from acetone (Borka, 1974). No explanation can be given as to why the indomethacin-starch product did not also contain the ∝ form. Since none of these indomethacin products gave above average dissolution profiles, no stability tests were done to determine if the polymorphic forms observed were stable.

2.3.3.6.2 **X-ray powder diffraction**

Apparatus:

Phillips PW 1050/70 Automatic X-ray Powder Diffractometer.

Method:

Specimens of each of the indomethacin products or their respective physical mixtures were mounted onto X-ray diffraction plates and individually clamped onto the diffractometer fitted with a monochromator and scintillation counter, with pulse height selections. A PW 2233/ 20 Cu normal focus tube was run at 50 kV and 30mA and was used with 1 divergence and scatter slits. Diffraction patterns (i.e. peak positions and intersections) were recorded on a strip chart, while scanning the sample through a 2θ range of 10° - 60°.

Results:

The X-ray diffractograms for the samples tested are labelled as follows:

A = commercially available indomethacin powder

B = physical mixture of indomethacin powder and PEG 6000

C = physical mixture of indomethacin powder and PEG 6000 kept at 37°C for 30 days

D = indomethacin-PEG 6000 product

E = indomethacin-PEG 6000 product kept at 37°C for 30 days

F = physical mixture of indomethacin powder and CL PVP

G = physical mixture of indomethacin powder and CL PVP kept at 37°C for 30 days.

H = indomethacin-CL PVP product

I = indomethacin-CL PVP product kept at 37°C for 30 days

The diffractograms of the above samples are given in figures 27 to 30.

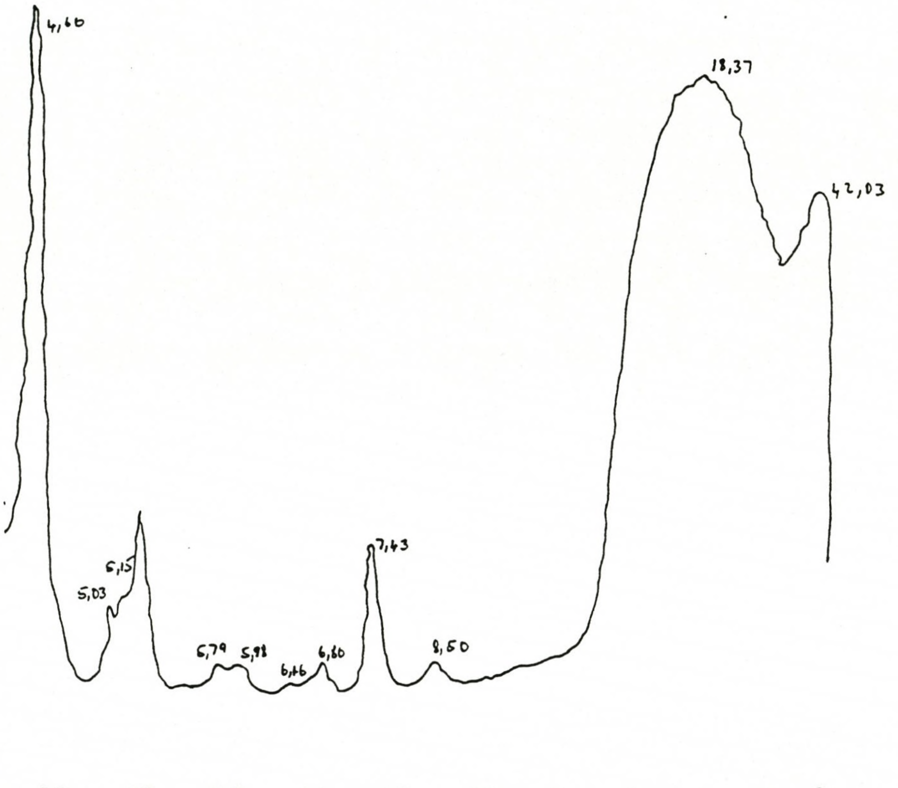


FIGURE 27: THE X-RAY DIFFRACTOGRAM OF INDOMETHACIN POWDER (SAMPLE A)

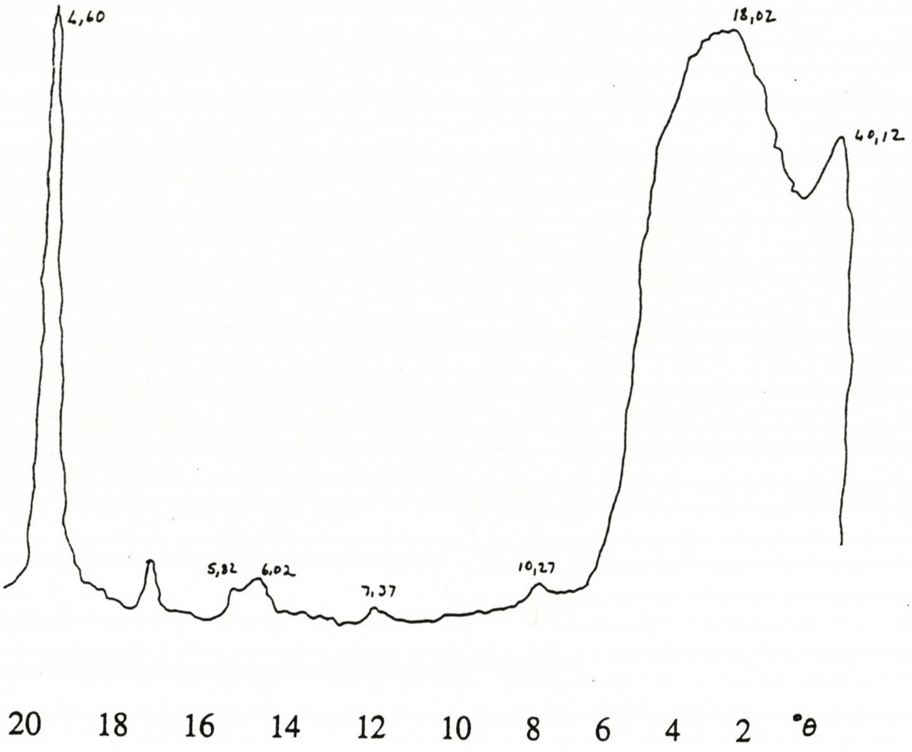


FIGURE 28: THE X-RAY DIFFRACTOGRAM THAT IS REPRESENTATIVE OF SAMPLES B,C,F AND G (A PHYSICAL MIXTURE OF INDOMETHACIN AND AN EXCIPIENT)

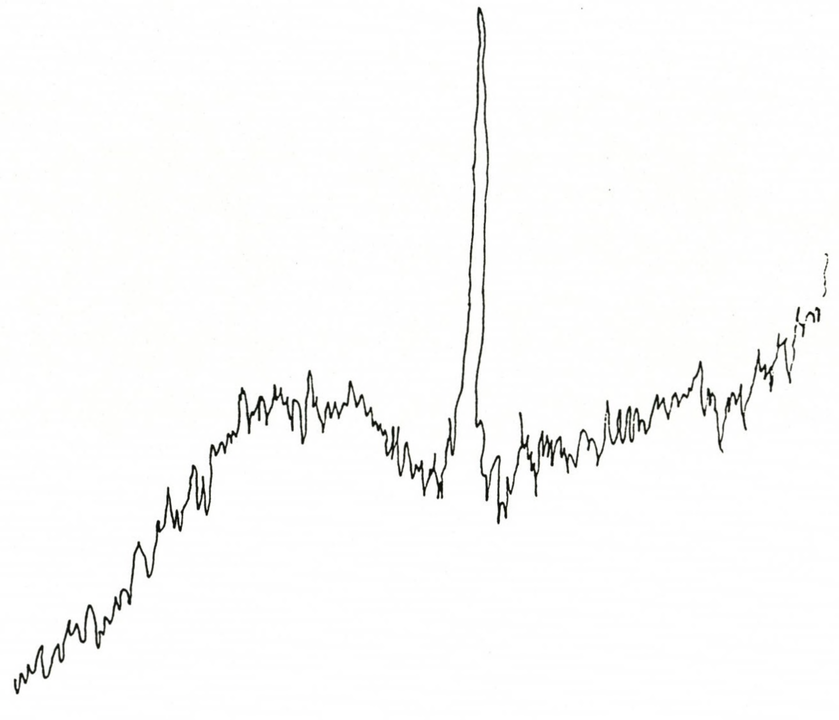


FIGURE 29: THE X-RAY DIFFRACTOGRAM OF THE INDOMETHACIN-PEG 6000 PRODUCT (SAMPLE D)

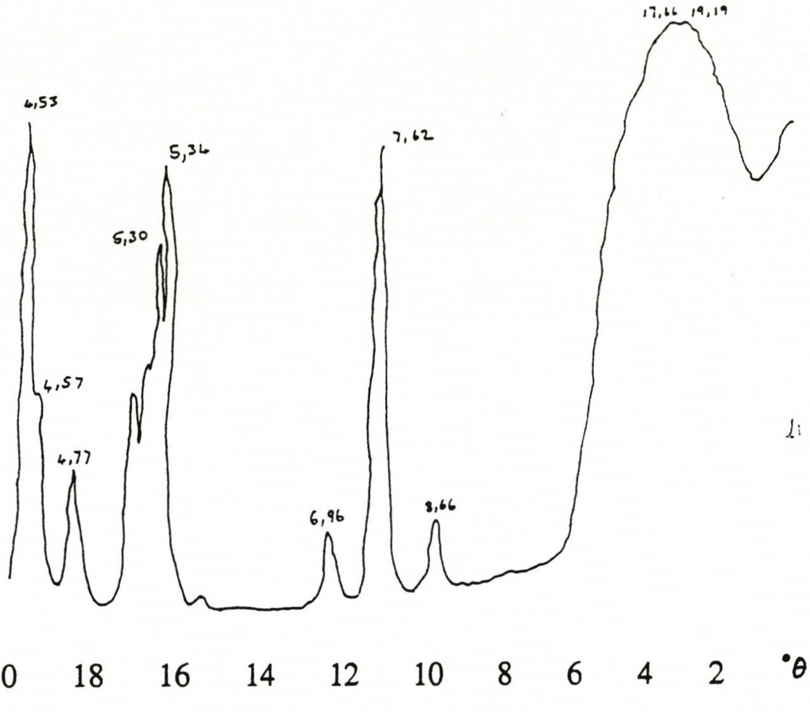


FIGURE 30: THE X-RAY DIFFRACTOGRAM OF THE INDOMETHACIN-CL PVP PRODUCT (SAMPLE H)

Discussion:

The X-ray diffractograms of samples B,C,F and G are identical (figure 28). These samples are physical mixtures of indomethacin and the excipients (PEG 6000 and CL PVP), samples C and G having been subjected to stability testing (kept at 37°C for 30 days). Sample A (indomethacin powder) was also identical to the above samples (figure 27). Samples D and E (figure 29) were identical, but different to samples B, C, F and G. Samples H and I were also identical, but different to the other samples (figure 30).

In an attempt to identify the polymorphs themselves, the diffractograms were compared to those published for the ∝, β and γ- forms by Kaneniwa et al. (1985). Inspection of the latter shows that the polymorphs have unique diffraction peaks in the 2θ ranges of 5-13° and 15-22°. Based on this it appears that samples A, B, C, F and G contain the γ-form and samples D and E, the ∝ form of indomethacin.

The diffractograms of samples H and I are diffuse with no well- defined peaks. This is characteristic of an amorphous substance or a sample in which the particles are extremely fine. Since the particle size of the indomethacin-CL PVP product is in the 100 μm range (see section 2.3.4.1) and the microcrystalline indomethacin produces a diffractogram (figure 30), the latter possibility can be ruled out (Rodgers, 1990).

It may be concluded that no polymorphic changes took place during stability testing of those powders tested. The indomethacin- PEG 6000 and -CL PVP products were stable during storage at 37°C for 30 days (samples C and E). Mixing of indomethacin and the excipients did not result in polymorphic changes (samples B, C, F and G) . The amorphous form of indomethacin in the indomethacin- CL PVP product (sample H) is identical to that in the product prepared by Imaizumi et al. (1983). However, the indomethacin-PEG 6000 product (sample D) contained indomethacin in the α polymorphic form. This is in agreement with the findings of Van Oudtshoorn (1990), who prepared indomethacin suppositories using a hydrophilic base.

2.3.3.7 Conclusion: selection of the most promising solubilized form of indomethacin for incorporation into a tablet

When selecting the most promising solubilized form of indomethacin, it is essential to keep the broad objectives, as previously outlined (section 2.3.1) in mind.

Looking at the dissolution profiles of the indomethacin products prepared, the indomethacin-crosslinked polyvinylpyrrolidone (CL PVP) product gave the best dissolution profile in distilled water and phosphate buffer. After 60 minutes, more than 90 % of the indomethacin had dissolved in both dissolution media. The angle of repose is very favourable for the indomethacin-CL PVP product (32,9°), indicating good flow properties. Therefore, no serious flow problems were anticipated during tabletting. Furthermore, the amount of indomethacin-CL PVP product equivalent to 25 mg of indomethacin powder is 105,39mg. This amount can easily be incorporated into an average sized tablet of ± 500mg. X-ray powder diffraction studies confirmed that the indomethacin-CL PVP product was the only solubilized product that contained amorphous form of indomethacin. As shown by Imaizumi et al. (1980), the amorphous form gives the best dissolution profile of all the polymorphic forms. The successful use of CL PVP to stabilize indomethacin in the amorphous form corresponds with the results obtained by Imaizumi et al. (1983). The powder X-ray diffraction studies also indicated that the amorphous form of indomethacin in the indomethacin-CL PVP product remained stable after storage at 37°C for 30 days. This agrees with the work done by Imaizumi et al. (1983). For the above reasons, the indomethacin- CL PVP product is considered to be the most promising for incorporation into a tablet.

2.3.4 TESTS DONE ON THE BEST INDOMETHACIN PRODUCT

2.3.4.1 Particle size

Powders with different particle sizes have different flow and packing properties. Tabletting relies on the volumetric fill of equipment. The method chosen should reflect the surroundings in which the particles will be handled and processed. The range of expected particle sizes to be measured is also an important consideration.

The indomethacin-cross-linked polyvinylpyrrolidone product to be tested is a dry powder and was expected to have a particle size range between 100 µm and 1000 µm. Therefore, sieving is the method of choice. It is a simple and cheap method and the expected particle size range did not necessitate the use of sensitive methods such as the Coulter Counter, laser-scattering or electron microscopic determinations.

Apparatus

A set of Endecott's Brass Sieves, ranging from 63 μm to 1400 μm, with a top lid and a bottom collection pan.

Endecott's Test Sieve Shaker.

Method

The entire batch of indomethacin-cross-linked polyvinylpyrrolidone product was placed on top of the set of sieves. The sieves were placed onto the collection pan, covered with the lid, clamped in the test sieve shaker and shaken for 15 minutes. After completion of shaking, the product remaining on each sieve and the bottom collection pan was weighed. Two batches the of product were subjected to sieve analysis (n = 2).

Results

The mass of product remaining on each sieve is given in table 6. From this data a particle distribution curve was drawn, as shown in figure 31.

Discussion

A representative sample of the powder should be tested and the sampling technique used is important. However, in this case, the entire batch was tested and therefore special sampling procedures were unnecessary.

Using sieving as a method for particle size analysis has several restrictions. There is a need for caution during the procedure, because electrostatic forces result in the particles clinging together. A too high humidity causes agglomeration of particles. Larger particles tend to block the sieve apertures, stopping smaller particles from moving through. Therefore, the use of a shaker is important. In addition, it is important to decide on a time limit for sieving. Particles larger than 1.4mm in diameter were discarded (23.72 %).

The particle sizes of the other tablet ingredients were obtained from the literature and are shown in table 7. The powders had more or less the same particle size ranges and serious flow problems in the direct compression formulae were not foreseen. Since the particles of the powders used in the formulae are not ideally spherical in shape, nor even in size, a glidant was incorporated to create a close to ideal situation. The significance of using a glidant was previously discussed in section 1.3.4.4.

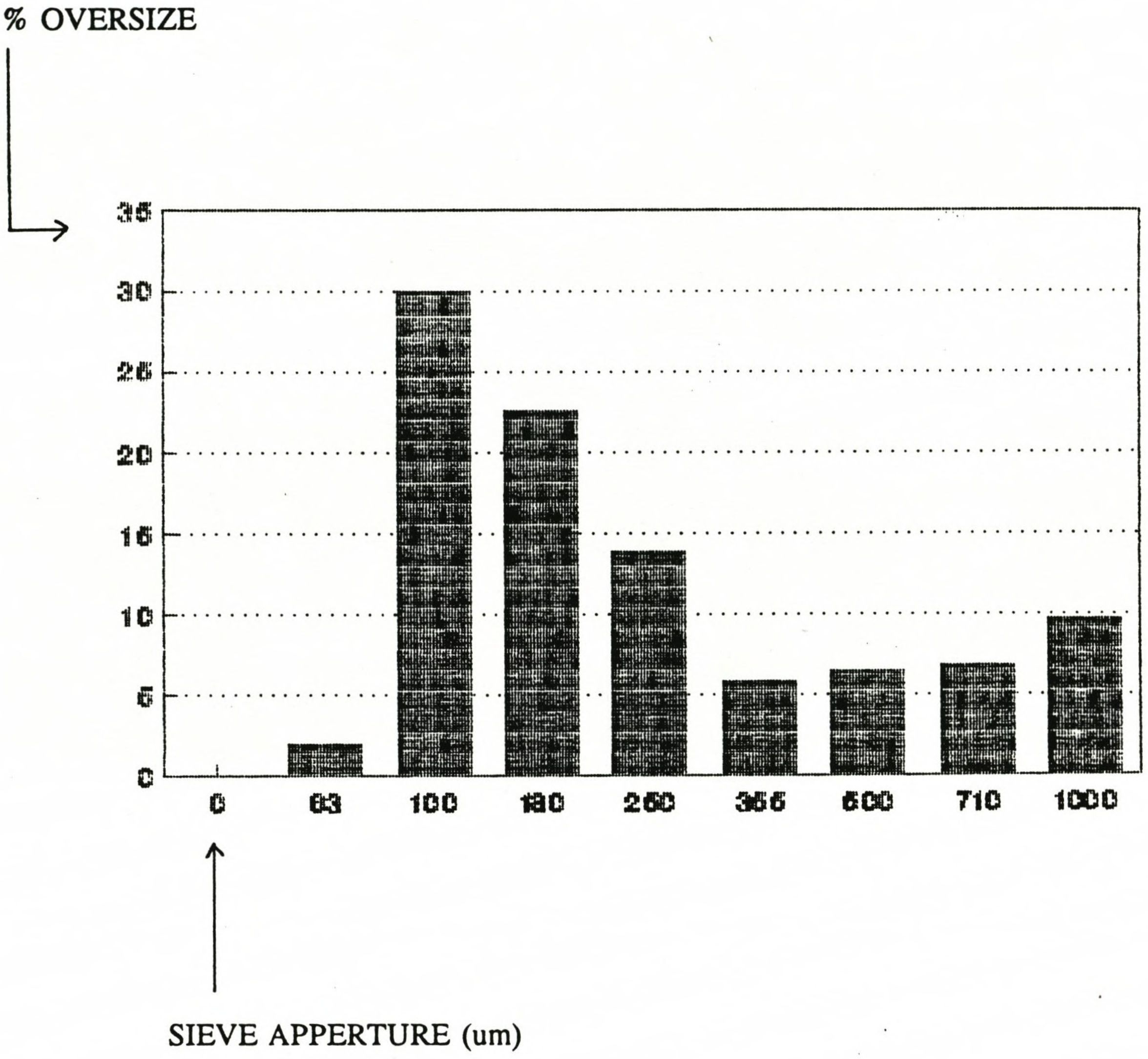
TABLE 6: PARTICLE SIZE DISTRIBUTION OF THE INDOMETHACIN-CROSS-LINKED POLYVINYLPYRROLIDONE PRODUCT (n = 2)

SIZE (μm)	PERCENTAGE
> 1000	9.71
> 710	6.72
> 500	6.54
> 355	5.78
> 250	13.93
> 180	22.48
> 100	29.98
> 63	2.02
< 63	2.68

TABLE 7: PARTICLE SIZES OF ADJUVANTS USED IN TABLET FORMULAE

ADJUVANTS USED	AVERAGE PARTICLE SIZE
Polyethylene glycol 6000	< 90 μm
Fumed silicon dioxide	12 nm
Tablettose	Spheres averaging 630 μm
Explotab (sodium starch glycolate)	Microfine powder
Avicel (microcrystalline cellulose)	100 μm

FIGURE 31: PARTICLE SIZE DISTRIBUTION OF INDOMETHACIN-CROSS LINKED POLYVINYLPYRROLIDONE PRODUCT



2.3.4.2 **Moisture content**

Introduction

The amount of moisture present in tablet excipients can have an influence on the compression capability of the excipients. When the amount of moisture present on the powder surfaces is just sufficient to fill the remaining voids in the bed, an increase in compression force will result in a decreased porosity with water being squeezed out onto the surface of the tablet. This expelled moisture may act as a lubricant at the die wall. Too much moisture may cause the material to stick to the punch surfaces. Too much moisture may also cause flow problems prior to compression. Too little moisture produces poorly formed compacts or tablets which cap easily.

Apparatus

Moisture Balance (Mettler PE 160) with an Infrared Heating Unit (Mettler, LP 15)

Method

Approximately 1g of powder was sprinkled onto the surface of the aluminium pan of the balance. The exact mass was noted. The infrared heat source was set at " 4 " and left on for 30 minutes. This setting corresponds to a temperature of approximately 80°C. The final mass reading was taken and the moisture content was determined from the formula:

$$\text{Percentage moisture content} = \frac{\text{Mass of moisture}}{\text{Final mass of sample}} \times \frac{100}{1} \qquad (10)$$

where mass of moisture = initial mass of sample - final mass of sample

Results

The moisture content values obtained are given in table 8.

TABLE 8: MOISTURE CONTENT OF THE PROPOSED TABLETTING COMPONENTS

	INITIAL MASS (g)	FINAL MASS (g)	MOISTURE CONTENT (%)	MEAN %
Indomethacin-CL PVP	0.97	0.9	7.77	8.23
	0.99	0.91	8.70	
Microcrystalline cellulose	1.01	0.99	2.02	2.51
	1.03	1.00	3.00	
Tablettose	1.03	1.02	0.98	0.97
	1.03	1.04	0.96	

Discussion

The infrared heating source is very efficient and drying was much faster than in a conventional oven. Equilibrium moisture content was reached long before the 30 minute period was over. Spray- dried lactose and microcrystalline cellulose contained low levels of moisture and are in accordance with results reported in the literature (Lund and Boylan, 1986 and Meggle). All grades of PVP have high moisture levels, at low relative humidities, i.e. 17% water at 40% relative humidity (BASF, 1986). The indomethacin-CL PVP product is therefore expected to have a high relative moisture content (the ratio of indomethacin to CL PVP is 1 :3 in the product prepared). It is possible that this moisture level may influence the tabletting characteristics.

2.3.4.3 **Density**

Introduction

Bulk density measurements are an indirect method used to characterize powder flow. The bulk density (ρ_B) of a powder is a characteristic of the powder, rather than that of the individual particles. This is given by the mass, m, of powder occupying a known volume, V, according to the relationship ρ_B = m/V kg.m^3.

The bulk density of a powder is differentiated from the particle density or true density of its component particles. The powder contains interparticulate pores, while individual particles are an entire solid. Therefore, a powder can have a single particle density, but several bulk densities, depending on the packing of the powder bed and the amount of voids in the bed. The bulk density is reduced when the particles in the pack consolidate. When a reduction in bulk density occurs, there are greater interparticulate forces and arching of the powder takes place. Therefore the powder is more resistant to flow.

One method of predicting how a powder may consolidate, is to tap down the powder in a measuring cylinder by means of a constant velocity cam. A change in packing volume occurs when the void spaces are diminished. The initial bulk density is reduced after a specific time to the final tapped density. The change in volume is expressed as the loose volume (V_{loose}) reduced to the packed volume (V_{packed}). Using these volumes, Carr (Staniforth, 1988 and Bavitz and Schwartz, 1974) calculated the percentage compressibility of a powder. The expression gives a direct measure of the potential arch or bridge strength. The percentage compressibility is calculated according to equation 11.

$$\% \text{ Compressibility} = \frac{D_{packed} - D_{loose}}{D_{packed}} \times \frac{100}{1} \qquad (11)$$

Carr concluded that there is a relation between powder flowability and percentage compressibility. This relationship is summarized in table 9.

TABLE 9: CARR'S INDEX AS AN INDICATION OF POWDER FLOW PROPERTIES

% COMPRESSIBILITY	FLOW DESCRIPTION
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Poor
28-35	Poor
35-38	Very poor
> 40	Extremely poor

From equation 11, it can be seen that a large difference between tapped and bulk density results in a high compressibility index and poor powder flow. In addition it may be concluded that, taking the bulk density into account, the size of the final dosage form can be predicted. Powders with a low bulk density tend to give relatively small tablets.

Apparatus

The apparatus was constructed by Pather (1989), based on the idea of Neumann (1967). It has a platform on which a measuring cylinder is clamped. When the motor is operated, a specially cut cam raises the platform gradually and smoothly to a maximum height. Further rotation of the cam causes the cylinder to drop 1cm under the influence of the combined mass of the platform, the cylinder and its contents.

Method

Agglomerates were broken up by sieving. 100g of each of the powder samples tested was carefully poured into a 250 cm^3 glass measuring cylinder. A glass funnel was used for pouring the powder, so that the surface of the powder in the measuring cylinder was level. The volume of the powder was read (V_{loose}). The motor was operated at 100 rpm for 12,5 minutes (1250 revolutions). Afterwards the volume was read again (V_{packed}). The loose density (d_{loose}) was determined from the equation:

$$d_{loose} = \frac{m}{V_{loose}} \qquad (12)$$

The packed density (d_{packed}) was determined from the equation :

$$d_{packed} = \frac{m}{V_{packed}} \qquad (13)$$

The compressibility index was determined using the following equation:

$$\text{Compressibility Index} = \frac{d_{packed} - d_{loose}}{d_{packed}} \qquad (14)$$

Results

The packed and loose densities and compressibility indices are shown in table 10.

TABLE 10: PACKED AND LOOSE DENSITIES AND COMPRESSIBILITY INDEX

PARAMETER	TABLETTOSE	MICROCRYSTALLINE CELLULOSE	INDOMETHACIN CL PVP PRODUCT
Loose density (g/cm^3)	0.4651	0.3472	0.3700
Packed density (g/cm^3)	0.7042	0.4182	0.3115
Percentage Compressibility (%)	8.37	15.98	5.85

Discussion

The apparatus used in the determinations is simple and effective. Results are also consistent and reproducible. It is important that the powders that are compared have the same mass, because the mass of the powder used provides, to a large extent, the packing force.

According to the Carr index (% compressibility), the indomethacin- CL PVP product shows excellent flow properties and no serious flow problems were anticipated. The same applies to Tablettose, the proposed tablet excipient. Microcrystalline cellulose falls in the 'good' category but, due to its hygroscopic nature, care must be taken when handling it under tabletting conditions, in order to eliminate flow problems such as bridging. The measurement of the bulk densities gives an indication of the ability of the powders to pack down in the die cavity. Due to the low bulk densities of the powders, it can be expected that relatively thin tablets will result.

CHAPTER 3

TABLETTING AND THE EVALUATION OF TABLETS

3.1 DEVELOPMENT OF AN INDOMETHACIN TABLET FORMULA

Initially it was arbitrarily decided on formula 1 (table 11) for the production of indomethacin tablets. In formula 1, indomethacin is in its solubilized form, i.e. indomethacin-CL PVP. The largest proportion of the formulation is taken up by the filler-binders, i.e. microcrystalline cellulose (MCC) and spray-dried lactose. Fumed silicon dioxide acts as a glidant, PEG 6000 act as a lubricant and sodium starch glycolate is a disintegrant. The ingredients that make up the largest proportion of the tablet formula, i.e. indomethacin-CL PVP product and Tablettose, did not show any flow problems during the preformulation studies. However, the angle of repose gives no indication and the compressibility index little indication, of the compactibility of the powder blend. An attempt to produce tablets using formula 1 was unsuccessful. A very large compression force was necessary to produce a tablet, resulting in capping. Furthermore, there was picking on the breakline of the tablet surface. The appearance of the tablets was not only unsatisfactory, but the compression force needed to compress the tablets resulted in damage to the tablet punches.

The amount of Tablettose in the formula was reduced and replaced by MCC. It is well known that MCC has a good compressibility (Shangraw et al. 1981a). By means of trial and error, the amount of MCC was gradually increased, as shown in formulae 2, 3 and 4 (table 11), until tablets of satisfactory physical appearance were produced. No capping or sticking occurred with formula 4 and therefore, this formula was considered to be the most promising for the production of indomethacin tablets.

TABLE 11: COMPOSITION OF FORMULAE 1-4

	FORMULA 1	**FORMULA 2**	**FORMULA 3**	**FORMULA 4**
Indomethacin CLPVP	19.43	19.43	19.43	19.43
PEG 6000	2.00	2.00	2.00	2.00
Fumed Silicone Dioxide	1.00	1.00	1.00	1.00
Tablettose	76.57	56.57	46.57	36.57
Microcrystalline Cellulose	-	20.00	30.00	40.00

TABLET MASS = 500mg

3.2 TABLETTING OF THE MOST PROMISING FORMULA

Apparatus

Erweka Cube Mixer

Manesty Tablet Press (type F3), fitted with 12.7 mm diameter flat punches (breakline on top punch)

Angle of Repose Tester , as described previously.

Method

Three batches of formula 4, as shown in table 11, were weighed (batches 4a, 4b and 4c). Each ingredient was sieved and added independently to the cube mixer and premixed for 10 minutes. Fumed silicon dioxide was sieved, weighed and added to each batch in the cube mixer. Mixing was continued for a further 2 minutes. The mixer was stopped occasionally, to remove the powder adhering to the sides of the mixer. The mixed powders of each batch were tabletted at a hardness level of ± 70 Newtons, each tablet having a mass of approximately 500mg. Prior to compression, portions of the mixed powders were used to determine the angle of repose, as described previously.

Results

The results of the angle of repose tests for batches 4a to 4c are given in table 12.

TABLE 12 : ANGLE OF REPOSE: MIXED POWDERS OF BATCHES 4a, 4b AND 4c.

	BATCH 4a		BATCH 4b		BATCH 4c	
h (mm)	16	14	15	14	14	15
D^1 (mm)	63	66	68	67	63	64
D^2 (mm)	64	67	67	69	65	66
r (mm)	31.75	33.25	33.75	34.00	32.00	32.5
Θ = arc tan h/r (°)	26.74	22.83	23.96	22.38	23.62	24.77
Θ mean (°)		24.78		23.17		24.19

Discussion

The flow properties of the tablet batches tested were found to be good and the angle of repose values, in each case, were well below the theoretical maximum of 50°. Therefore, no serious flow problems were anticipated and uniform tablet die fill should result in tablets having a uniform mass. The flow properties also indicate that fumed silicon dioxide, as a glidant, is effective.

The absence of sticking and picking from the tablet surfaces, indicates that the formulation possesses sufficient anti-adherent properties. Although magnesium stearate has been used widely as a lubricant, it is hydrophobic and has been known to retard the dissolution rate (Shah and Mlodozeniec, 1977). Since the dissolution rate of the indomethacin tablets had to be enhanced, a water soluble lubricant such as PEG 6000 (less than 90 μm) was used, as proposed by Tsumura et a[1]. (1972). PEG 6000 was milled using a mechanical mortar and particle sizes less than 90 μm were separated by sieving with a test sieve shaker.

Sodium starch glycolate is effective as a disintegrant at low concentrations (Rudnic et al., 1981). Although the microcrystalline powder itself is known to have poor flow properties, the inclusion of 1% sodium starch glycolate in the formula had no adverse effects on its flow properties.

By using a combination of MCC and Tablettose, the advantages of the good compressibility of MCC (Shangraw et al., 1981a) and the excellent flow properties of Tablettose (Sheth et al. 1980) are combined.

3.3 **QUALITY CONTROL**

It is important to know if the tablets conform to certain minimum standards of quality and, therefore, Hardness, Friability and the BP Uniformity of Mass Tests were performed. The durability of the tablets was established. An assessment of content uniformity was also made. One of the most important evaluations of quality is dissolution testing. This is an in vitro method to establish the effectiveness of the dosage form.

3.3.1 **UNIFORMITY OF MASS TEST**

Method

Twenty tablets from each batch were randomly selected and individually weighed. The mean tablet mass of each tablet was determined and the BP Uniformity of Mass Test was applied. The coefficient of variation (C.V.) was also determined, using the formula:

$$C.V. = \frac{S.D.}{\text{Mean mass}} \times \frac{100}{1} \qquad (15)$$

Results

The results of this test are given in table 13.

TABLE 13: UNIFORMITY OF MASS: FORMULAE 4a, 4b and 4c

	MASS OF TABLET (mg)		
FORMULA	4a	4b	4c
1	511	499	510
2	474	482	520
3	510	498	521
4	516	496	524
5	535	474	514
6	470	497	533
7	535	492	509
8	538	502	507
9	498	472	523
10	483	500	518
11	522	511	510
12	498	500	518
13	508	491	520
14	516	502	523
15	520	489	521
16	533	486	507
17	506	499	524
18	518	500	509

19	492	500	514
20	535	494	533
Mean	511.0	494.2	517.9
(±S.D.)	± 20.3	± 9.6	± 7.8
5% of mean	25.3	24.7	25.9
10% of mean	51.1	49.4	51.8
5% range	485.8-536.3	470.0-519.4	492.0-543.8
C.V. (%)	4.0	2.0	1.5

5% range: (mean - 5%) - (mean + 5%)

Discussion

All three batches tested were within the BP limits for uniformity of mass. As can be seen from the angle of repose values, the formulae showed good flow properties and this was confirmed by the uniform rate of die filling, resulting in the production of tablets of uniform mass. Considering the coefficient of variation (C.V.%), tablets from formula 4a were above the 2% acceptable limit for variation in mass. This could be attributed to the sampling method used initially. Tablets were sampled throughout the tabletting process of the batch. However, towards the end of the tabletting cycle, slightly lighter tablets were produced due to there being less powder in the hopper, leading to incomplete fill of the die cavity. Samples of formulae 4b and 4c were taken in the middle of the tabletting process of these batches and their C.V. values are below 2%.

3.3.2 **HARDNESS TEST**

The hardness test was performed, using a Pharma Test (type PTB 301) Hardness Tester, at least 24 hours after production of the tablets, to allow for stress relaxation.

Results

The results, which are the mean of at least 3 tests per batch, are given in table 14.

Discussion

The tablets produced showed little hardness variation. This is confirmed by the low standard deviation values. Using proper machine settings, tablets of the same hardness could be produced repeatedly.

TABLE 14: FRIABILITY, DURABILITY AND HARDNESS OF FORMULAE 4a, 4b AND 4c TABLETS

FORMULA	MEAN HARDNESS (Newtons) (± S.D)	FRIABILITY (%)	DURABILITY (%)
4a	71.66 ± 1.52	0.10	0.55
4b	75.33 ± 1.52	0.23	0.64
4C	76.33 ± 2.51	0.11	0.37

3.3.3 FRIABILITY TEST

The friability test is performed to determine the ability of tablets to be handled without chipping, cracking or breaking. If tablets tend to cap, higher friability values will then be observed.

Apparatus

Erweka Friabilitator

Method

Twenty tablets were dusted to remove any loose powder and were then weighed. The tablets were placed in the plexiglass drum of the apparatus. The apparatus was operated at 25 rpm for 4 minutes. After removal from the drum, the tablets were again dusted and weighed. The percentage loss in mass was determined.

Results

The results are given in table 14.

Discussion

The friability test is not an official test, but it is used widely to evaluate tablets (Carstensen, 1977 and Graf et al., 1979). Mass loss due to friability is satisfactory if it is less than 1%. All the batches tested had friability values well below 1% and thus the tablets should not be damaged during normal handling conditions.

3.3.4 **DURABILITY TEST**

The durability test is a more stringent test used to evaluate tablets, to see whether they would be damaged during normal handling conditions.

Apparatus

Erweka Friabilitator, fitted with a special plexiglass drum to test durability.

Method

Twenty tablets were dusted to remove any loose powder and were then weighed. The tablets were placed in the plexiglass drum of the apparatus. The apparatus was operated at 25 rpm for 15 minutes. After removal from the drum, the tablets were again dusted and weighed. The percentage loss in mass was determined.

Results

The results are given in table 14.

Discussion

As is the case with the friability test, the durability test is not official. It is used to test tablets under stringent handling conditions. A mass loss less than 2% is acceptable. The tablets tested were all within the specified limits.

3.3.5 CONTENT UNIFORMITY

Apparatus

Beckman DU-40 Spectrophotometer

Millipore Filtration Unit (250 cm^3)

Method

A solution of indomethacin was prepared in phosphate buffer (70% 0.066M Na_2HPO_4 : 30% O.054M NaH_2PO_4; adjusted to pH 7.2 with phosphoric acid) and a UV-visible scan was obtained for the 200-800 nm range. Triplicate standard solutions of various concentrations of indomethacin in phosphate buffer were prepared. The absorbance of each solution was read at the wavelength of maximum absorption, i.e. 317 nm. A standard curve of concentration versus absorbance was plotted.

Twenty tablets from each batch were accurately weighed and powdered using a mortar and pestle. From each batch, a mass of powder equivalent to one tablet (i.e. the average mass per tablet of 20 tablets) was weighed and added to 10 cm^3 90% ethanol in a 50 cm^3 glass beaker. The residue in the glass beaker was left for 10 minutes with frequent stirring and filtered through the Millipore filtration unit fitted with a 0.45 μm hydrophobic filter. The 50 cm^3 beaker was washed with phosphate buffer and the washings were also filtered through the filtration unit. The filtrate was transfered to a 500 cm^3 volumetric flask and made up to volume with phosphate buffer. Absorbance of the solution was read and the concentration obtained from the linear regression equation of the standard curve (least squares method). Each batch was assayed in triplicate.

Results

Table 15 shows the results of each batch of tablets assayed.

TABLE 15: DRUG CONTENT OF VARIOUS BATCHES OF INDOMETHACIN TABLETS

BATCH	DRUG CONTENT (mg)
4a	25.17
4b	24.75
4c	26.09

Discussion

Although the BP describes an assay for indomethacin capsules, no official method is given for indomethacin tablets.

The fumed silicon dioxide, PEG 6000 and sodium starch glycolate used in the formula were present at low concentrations and did not interfere with the absorbance of the indomethacin at the wavelength used. The microcrystalline cellulose, being insoluble in the phosphate buffer, was removed during the filtration process and also did not affect the absorbance of indomethacin. The spray-dried lactose used in the formula is readily soluble in phosphate buffer and was not found to interfere with the absorbance of indomethacin at 317 nm. Indomethacin is poorly soluble in water, i.e. less than 1 in 10 000 (Reynolds, 1982) ; therefore, 90% ethanol was used to dissolve indomethacin.

The drug content of all the batches is close to the formula content of 25mg and is within the usually accepted limit of 95 to 105%. Tablets 4a and 4c contained slightly more indomethacin than the formula content. This is probably due to the fact that the batches had an average mass slightly in excess of the tablet formula mass.

A linear relationship between concentration and the extent of UV-light absorption was found within the concentration range studied. The linear regression coefficient (r), obtained by the least squares method, was 0.99. This indicates that Beer's law is obeyed within this concentration range.

3.4 THE RELATIONSHIP BETWEEN TABLET HARDNESS AND COMPRESSION FORCE

Apparatus

Erweka Cube Mixer

Manesty Tablet Press (type F3) fitted with a 12.7mm die (breakline on the top punch) and a hydraulic pressure control mechanism

Pharma Test (type PTB 301) Hardness Tester

Method

The powders as specified in formula 4 were mixed and tabletted, as described previously in section 3.2. The tablets were compressed at different punch pressures. The pressures were regulated by a hydraulic pressure regulating mechanism, termed by the manufacturers as an "overload release mechanism", which was set up and used according to the manufacturer's instructions (Manesty). The "overload release mechanism" enables the machine to be set at any predetermined load and is actually a means of regulating the punch pressure. If one attempts to compress tablets with a greater pressure than that set on the pressure gauge (by inappropriate hardness adjustment settings of the machine), the "overload release mechanism" comes into play and only the pressure set on the hydraulic pressure indicator will be applied. The production of tablets that are very hard is thereby prevented. The maximum pressure applied by the overload release mechanism is shown on the hydraulic pressure indicator and on a graduated scale, the load indicator. The machine was set to produce tablets of a specific hardness and mass. If the hardness at which the machine is about to compress, exceeds the maximum pressure set on the hydraulic pressure indicator, the "overload release mechanism" comes into operation. This is noted by deflection of a machine component, the lower regulating collar.

By trial and error, the appropriate setting at which the tablets could be produced using the desired compression pressure (as shown on the hydraulic pressure indicator) was noted on the arbitrary hardness scale of the machine. At each applied force of the overload mechanism of the tablet to be compressed, the locking and adjusting handles of the tablet hardness regulating mechanism were set to cause only slight deflection of the lower regulating collar (indicating that the tablets were not compressed too hard). The crushing strength of the tablets at the point of just perceptible deflection was noted. Various pressures were set and the crushing strength of the tablets compressed was measured.

Results

The results are given in table 16. A graph was plotted of the compression force versus the tablet hardness, at the respective compression force. This graph is shown in figure 32.

Discussion

The ideal is to use an instrumented tablet press, used in conjunction with a computer, to evaluate the forces involved during the compression of tablets. Compression behaviour was initially evaluated using strain gauges, fitted to tablet machine punches. However, using the "overload release mechanism" of the tablet press, an indication can be obtained of the compression force during tabletting.

The graph of compression force vs. tablet hardness is more or less a straight line, which goes through the origin. The relationship between the tablet hardness and compression force of Tablettose and MCC, respectively, was obtained from the literature (Sheth et al., 1980) and is also indicated in figure 32. It is apparent that the compression profile of the mixture of Tablettose and MCC lies between those of the individual components. Tablettose and MCC are present at a concentration of 36.57% and 40%, respectively, which is approximately a ratio of 1:1 (equal parts). The linear relationship of the mixture of the two binders and the two individual components is graphically also intermediate, with the slope of the profile of the mixture exactly in-between those of the individual components.

In addition to the compression profile obtained, the exact machine settings can be read from table 16 to obtain a tablet at a specific compression force having a known hardness.

TABLE 16: THE RELATIONSHIP BETWEEN TABLET HARDNESS AND COMPRESSION PRESSURE

OVERLOAD (TONS)	MACHINE SETTING	HARDNESS (NEWTONS)
0.5	23.5	25.32
1.0	24.0	46.66
1.5	24.0	45.00
2.0	24.0	58.00
2.5	26.0	137.13
3.0	26.0	164.66

Each hardness value is the average of 3 determinations

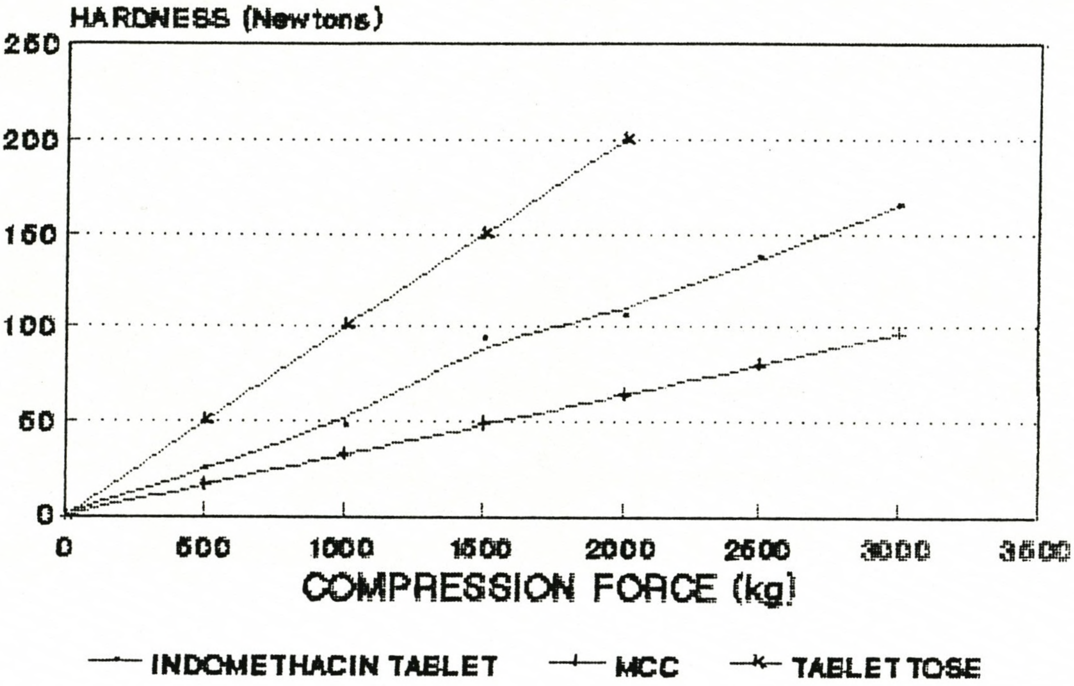


FIGURE 32: THE RELATIONSHIP BETWEEN COMPRESSION PRESSURE AND HARDNESS OF INDOMETHACIN TABLETS

3.5 DISSOLUTION TESTING

The dissolution of a drug from a tablet dosage form is often the rate determining step in the bioavailability of the drug. By doing dissolution tests, an in vitro indication is given of drug release and, thus, the effectiveness of the dosage form. Dissolution tests were done in two stages: a) the dissolution profile of the most promising formula and the influence of disintegrants on the dissolution rate were determined; and (b) the influence of compression force on dissolution rate was determined.

All the tablets produced were also subjected to the BP Disintegration Test. However, the presence of sodium starch glycolate as a disintegrant resulted in disintegration times that were too fast (less than 20 seconds) for comparative evaluation. Therefore, dissolution testing is necessary to quantitatively evaluate the various batches of tablets produced.

3.5.1 THE DISSOLUTION RATE OF THE MOST PROMISING FORMULA AND THE INFLUENCE OF DISINTEGRANTS ON THE DISSOLUTION RATE OF THE TABLET

Apparatus

Hanson Dissolution Apparatus (model 72RL)

Hanson Dissoette Automated Sampler (model 27)

Method

As described previously, a standard curve of various concentrations of indomethacin in phosphate buffer (70% 0.066M Na_2HPO_4 : 30% O.054M NaH_2PO_4, pH = 7.2) and distilled water, respectively, was plotted.

TABLE 17: COMPOSITION OF FORMULAE 4 TO 7

	% (m/m)			
	FORMULA 4c	**FORMULA 5**	**FORMULA 6**	**FORMULA 7**
Indomethacin (25mg)		5.00		5.00
Indomethacin-CL PVP product	19.43		19.43	
Cross-linked PVP		14.43		
fumed silicon dioxide	1.00	1.00	1.00	1.00
PEG 6000	2.00	2.00	2.00	2.00
Sodium starch Glycolate	1.00	1.00		1.00
Tablettose	36.57	36.57	36.57	36.57
Microcrystalline Cellulose (Avicel PH 102)	40.00	40.00	40.00	40.00

Additional tablets were produced according to formulae 5, 6 and 7 and, together with formula 4c, these were subjected to dissolution testing. In table 16, it was observed that compression at 1.5 tons gave tablets of an appropriate hardness. Therefore, these formulae were compressed at a compression force of 1.5 tons and the resulting tablets had a tensile strength of ± 90 N. Commercially available indomethacin capsules (Indocid$^{(R)}$) were also subjected to dissolution tests. The dissolution tests were performed according to the USP paddle method (method 2). The setting up procedure, the performance of the test and the precautions observed, were all in accordance with the details provided in the USP.

Samples of dissolution medium (5 cm^3) were removed from the flasks at 2, 4, 10, 30 and 60 minutes. The absorbance values of the samples were read at the wavelength of maximum absorption (317nm) and the amount of drug released by each tablet at the specific time intervals was determined.

Results

The dissolution data for indomethacin tablets (batches 4c, 5, 6, 7) and indomethacin capsules are given in appendices 4 and 5. The stated percentage of drug released at each time interval is the mean of six values. Using these mean values, composite graphs of the percentage drug released versus time were plotted. These graphs are shown in figure 33.

FIGURE 33 (A)

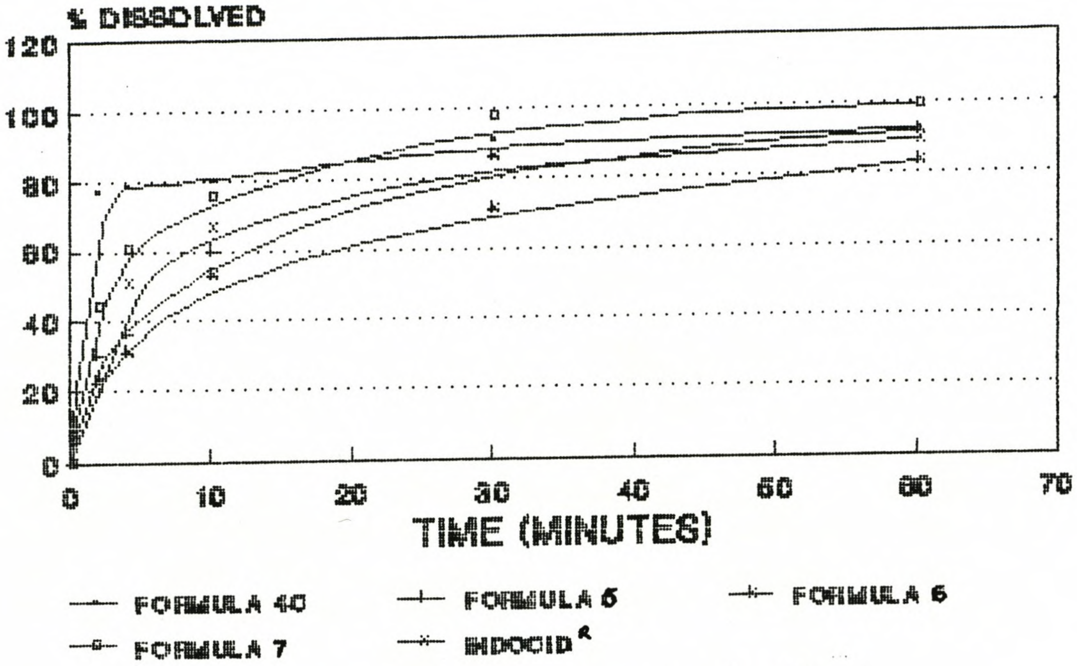


FIGURE 33 (B)

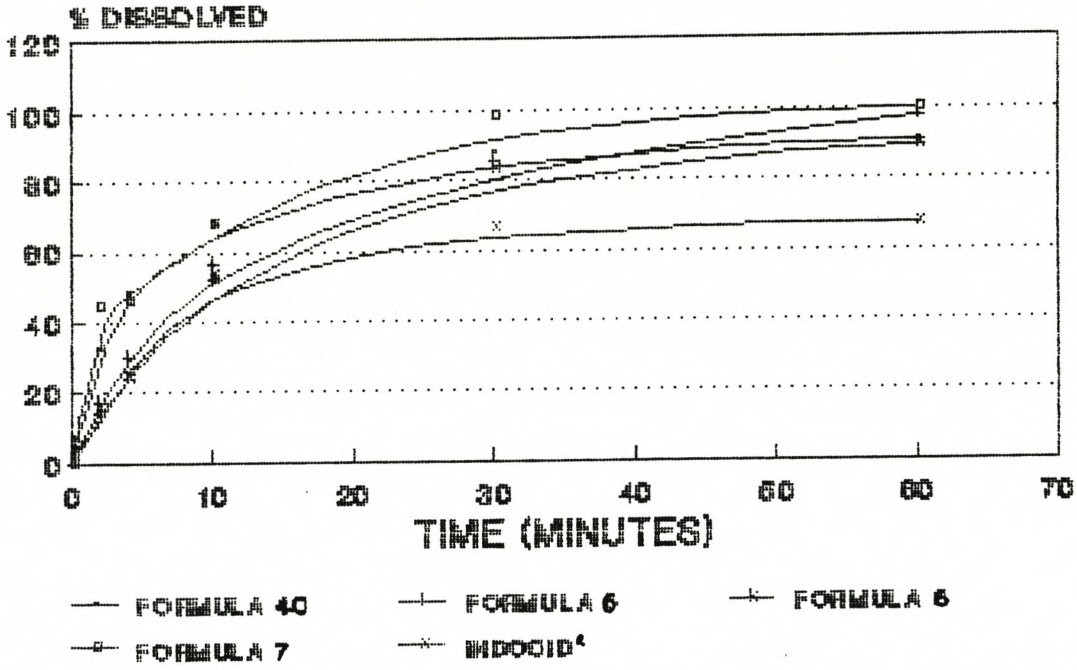


FIGURE 33: THE DISSOLUTION PROFILES OF INDOMETHACIN TABLET BATCHES 4c, 5, 6 AND 7 IN (A) PHOSPHATE BUFFER AND (B) DISTILLED WATER

Discussion

The dissolution tests on the tablets were done in a similar manner to those for the indomethacin products in section 2.3.3.1. This enabled the comparison of the dissolution profiles of the tablets with that of the indomethacin-CL PVP product. The indomethacin formula 4c tablets showed a marked increase in dissolution rate in phosphate buffer, when compared to the commercially available indomethacin capsules (Indocid$^{(R)}$). Within 10 minutes, 1.5 times as much indomethacin had dissolved from the tablets when compared to the indomethacin capsules. A similar increase in dissolution rate was noted in distilled water, when tablets of formula 4c and the capsules were compared.

The effectiveness of the solubilized indomethacin-CL PVP product may be illustrated by comparing tablets made of a physical mixture of indomethacin and cross-linked PVP (formula 5) with formula 4c. After 10 minutes, 1.33 times more indomethacin was released from formula 4c than from the physical mixture of formula 5 (in phosphate buffer). This observation was also noted in distilled water.

The effectiveness of the disintegrant may be illustrated by excluding sodium starch glycolate from formula 6. Poor disintegration produced results equivalent to those of the physical mixture of indomethacin and CL PVP (formula 5) in phosphate buffer. In distilled water, formula 6 gave an even worse profile than that of formula 5. An interesting observation was made when CL PVP was excluded from the formula (as in formula 7). In both dissolution media, the dissolution rate was decreased when compared to the physical mixture of indomethacin and CL PVP in formula 5. This illustrates the influence of CL PVP as a disintegrant used to enhance dissolution rate, although, in this study, it was used primarily to solubilize the indomethacin .

3.5.2 THE INFLUENCE OF COMPRESSION FORCE ON DISSOLUTION RATE

Apparatus

Hanson Dissolution Apparatus (model 72RL)

Hanson Dissoette Automated Sampler (model 27)

Method

Batches of formula 4 i.e. batches 4d, 4e, 4f and 4g were tabletted at various compression forces, as described previously. The compression force used, as well as the tablet hardness determined after compression, for each batch is shown in table 18.

TABLE 18. THE COMPRESSION FORCE AND HARDNESS OF BATCHES 4d, 4e, 4f AND 4g

BATCH	4d	4e	4f	4g
Compression Force (Tons)	0.5	1.0	1.5	2.0
Hardness (Newtons)	25.3	45.6	93.2	105.3

(The tablet hardness at each compression force is the average of 3 determinations)

Dissolution tests were performed on batches 4d, 4e, 4f and 4g in a similar way to that described in section 3.5.1. Samples of dissolution medium (5 cm^3) were removed from the flasks at 5, 10, 30, 45 and 60 minutes. The absorbance values of the samples were read at the wavelength of maximum absorption (317nm) and the amount of drug released by each sample, at the specific time intervals, was determined.

Results

The dissolution data for indomethacin tablets, batches 4d, 4e, 4f and 4g, are given in appendix 6. The stated percentage of drug released at each time interval is the mean of six values. Using these mean values, composite graphs of the percentage drug released versus time were plotted. These graphs are shown in figure 34.

Discussion

The same precautions and dissolution test procedure, as described previously, were adhered to. In phosphate buffer, there was a difference in the dissolution rates of tablets compressed at different compression forces. The biggest difference was shown by the tablets tabletted at 500 kg (batch 4d). There was 10% more drug released from batch 4d after 20 minutes than from any of the other batches. Batches 4e, 4f and 4g showed a decrease in dissolution rates when compared to their respective increasing compression forces. However, the differences between the dissolution profiles of the latter three batches is very small. Since the tablets compressed at 500 kg have a good physical appearance, higher compression forces were not considered to be necessary. Furthermore, at a compression force of 500kg, optimum dissolution is obtained and there are thus no advantages to be gained by using a higher compression force for tabletting.

FIGURE 34

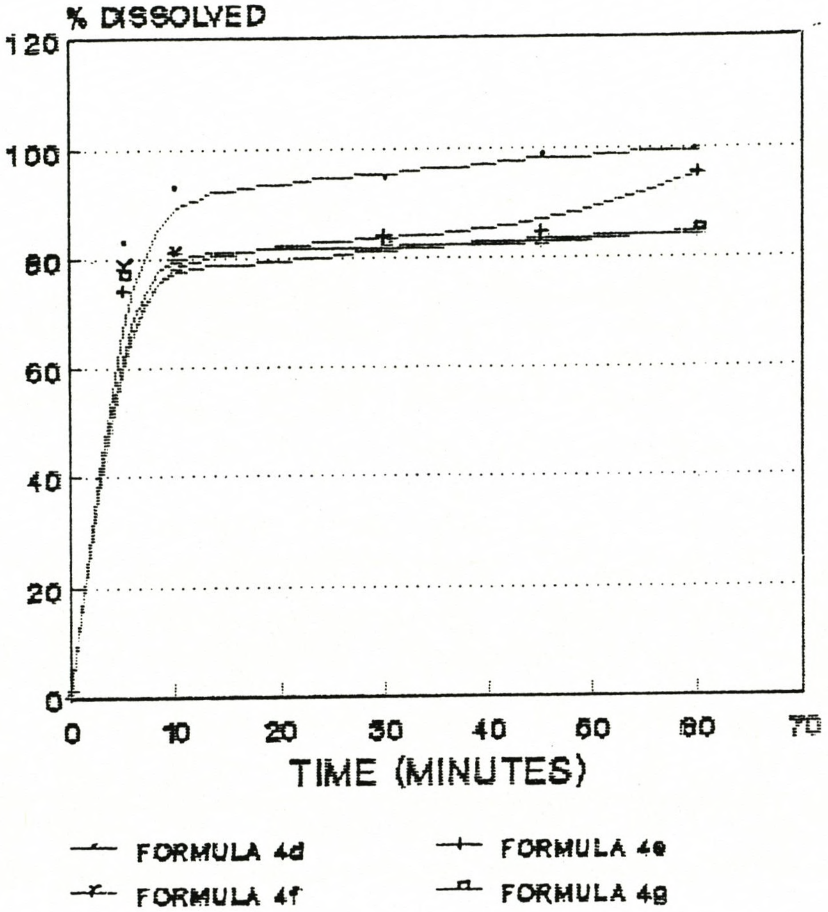


FIGURE 34: **THE DISSOLUTION PROFILES OF BATCHES 4d, 4e, 4f AND 4g IN PHOSPHATE BUFFER**

3.6 QUALITY CONTROL OF STORED PRODUCTS

Method

Tablets of formula 4c were placed in 3 separate, constant-temperature drying ovens at 40°C, 60°C and 80°C for 30 days (henceforth called batches 4h, 4i and 4j, respectively). Another batch of tablets of formula 4c was kept in a humidifier (75% relative humidity) at 37°C for 30 days (batch 4k).

After the storage period, the tablets were tested for uniformity of mass, durability, friability and hardness. Dissolution tests were also done. These tests were done in accordance with the methods previously specified in sections 3.3. and 3.5. The results were compared with those from tablets kept at room temperature (25°C) for the same period (control group, batch 4l).

Results

The results of the uniformity of mass tests are given in table 19. Table 20 shows the friability, hardness and durability of the tablets tested. The dissolution data for the various batches of indomethacin tablets are given in appendix 7. The stated percentage of drug released at each time interval is the mean of six values. Using these mean values, composite graphs of the percentage drug released versus time were plotted. These graphs are shown in figure 35.

TABLE 19: **UNIFORMITY OF MASS :BATCHES 4h TO 4l**

MASS OF TABLET (mg)

BATCH	4h	4i	4j	4k	4l (control)
1	541	498	534	554	533
2	519	522	527	553	510
3	544	519	530	552	520
4	544	523	530	530	521
5	546	487	524	553	524
6	516	509	524	551	524
7	535	520	511	551	509
8	542	510	531	550	507
9	533	522	523	542	523
10	513	522	535	549	518
11	510	504	511	548	510
12	518	501	523	550	518
13	525	496	491	551	520
14	529	518	525	551	523
15	512	501	523	553	521

16	510	498	528	552	507
17	516	499	526	552	524
18	496	516	526	554	509
19	531	512	516	555	514
20	530	511	526	553	533
Mean	525.0	509.4	523.2	550.2	517.9
(±S.D.)	± 14.1	± 10.8	± 9.9	± 5.5	± 25.9
5% of mean	26.3	25.5	26.2	27.5	25.9
10% of mean	52.5	50.9	52.3	55.0	51.8
5% range	498.5- 551.3	484.0- 534.9	497.0- 549.4	522.7- 577.7	492.0 543.8
C.V. (%)	2.7	2.1	1.5	1.0	1.5

5% range: (mean - 5%) - (mean + 5%)

TABLE 20: FRIABILITY, DURABILITY AND HARDNESS OF BATCHES 4h TO 4l.

FORMULA	MEAN HARDNESS (Newtons)	FRIABILITY	DURABILITY
4h	75.00 ± 3.60	0.26%	0.16%
4i	55.33 ± 2.64	0.04%	0.27%
4j	33.66 ± 2.08	0.57%	2.01%
4k	44.66 ± 2.08	0.97%	0.14%
4l	76.33 ± 2.51	0.11%	0.37%

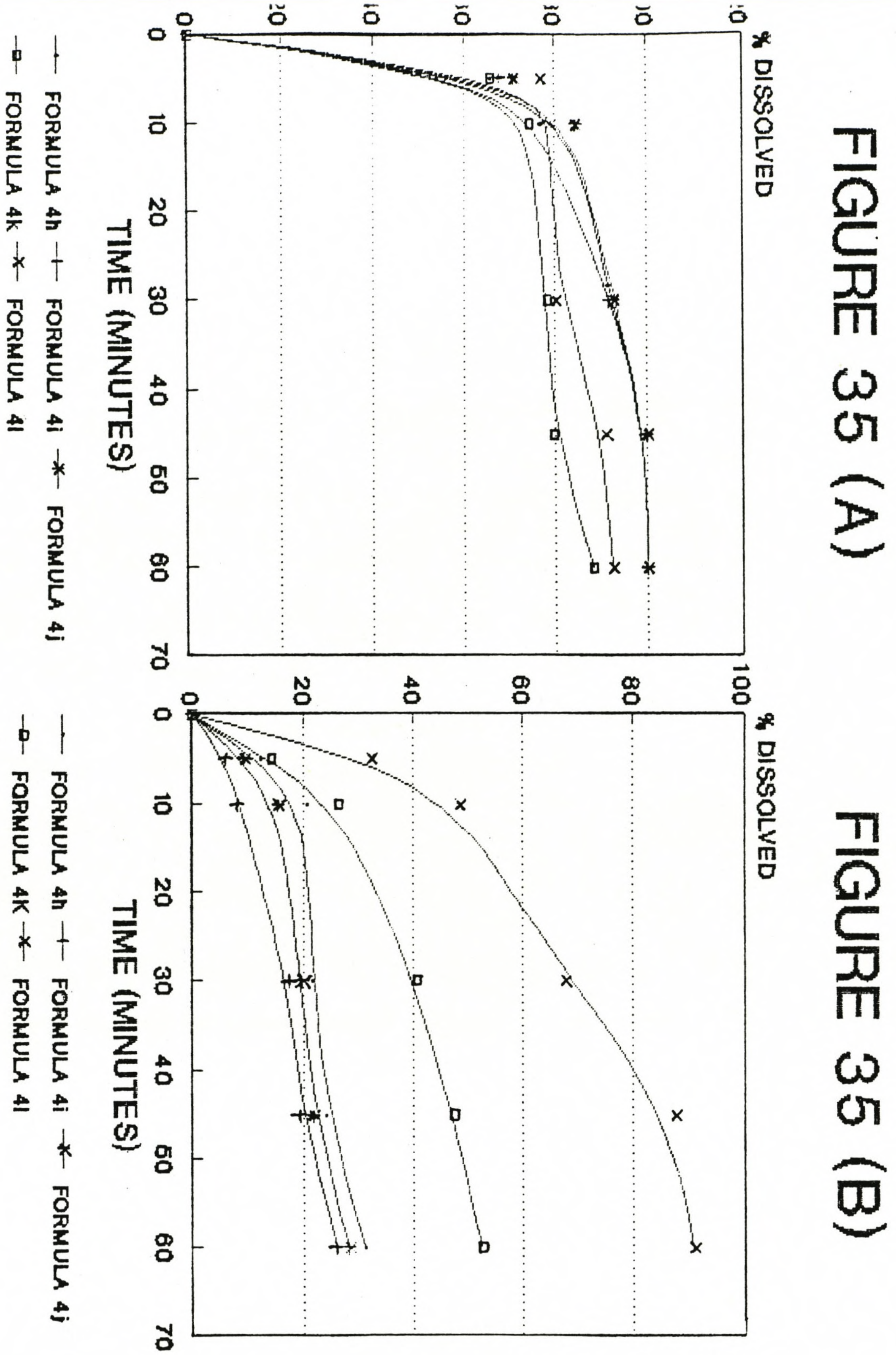


FIGURE 35: THE DISSOLUTION PROFILES OF BATCHES 4h, 4i, 4j, 4K AND 4l IN (A) PHOSPHATE BUFFER AND (B) DISTILLED WATER

Discussion

The physical appearance of the tablets kept at elevated temperatures was good and the tablets had the same size and colour as those of the control group (tablets kept at 25°C). Discolouration due to the presence of Tablettose was not detected and is in accordance with the claims of the manufacturer of Tablettose (Meggle), although spray-dried lactose has been reported to cause discolouration (Milosovich, 1963). However, the tablets kept at an elevated humidity appeared swollen, with rough surfaces. No colour changes were noted for these tablets.

The masses of the all the tablets tested were within the 5% range of variation, as specified in the BP. However, the tablets kept at 40°C and 60°C, did not adhere to the more sensitive statistical parameter, the coefficient of variation (C.V.), having values of more than 2%. Since the tablets were taken from the same batch, i.e. formula 4c, this mass variation could be attributed to the effect of storage on the tablets.

The friability and durability of the tablets tested were within the limits specified previously and this indicates that the tablets should not be damaged during normal handling conditions.
The result of the durability test on the tablets kept at 80°C is marginally above the specified limit of 2% (2.01%).

There is a decrease in hardness observed for the tablets stored at increased temperature. However, as seen from the durability and friability tests, the decreased hardness did not have an influence on the handling capability of the tablets.

The dissolution tests done in phosphate buffer on formulae 4h to 4k compare favourably with that done on the control, formula 4l. The dissolution profiles of formulae 4h, 4i and 4j (tablets kept at 40, 60 and 80°C, respectively) are practically identical and are slightly better than that of the control group, formula 4l. The influence of humidity on tablet stability can be seen in the reduction in dissolution rate of formula 4k.

However, there is a marked decrease in the dissolution profile for all the batches tested in distilled water, when compared with the control, batch 4l. While the decrease is not so marked for formula 4k, the curves for formulae 4h, 4i and 4j are well below that of the control group, formula 4l. Although no definite pattern can be observed, the results of the dissolution tests done in distilled water show a marked decrease in the dissolution rates of tablets when kept at elevated temperatures. Except for a decrease in tablet hardness, the results of the other tests (friability, durability and uniformity of mass) were within the prescibed limits and no reasonable explanation can be given as to why the dissolution rate decreased upon storage at elevated temperatures.

3.7 OVERALL CONCLUSION

The thesis objectives, as outlined previously, have been met. Indomethacin tablets were produced using direct compression. These tablets had a dissolution profile indicating that the indomethacin had been effectively solubilized. The solubilized indomethacin-CL PVP product chosen for tablet production possessed good flow properties and had a small bulk volume, which simplified its ability to be used in direct compression.

Cheap and simple methods were used to effectively solubilize indomethacin. However, a change in the solid-state properties is accompanied by changes in the polymorphic state of indomethacin - a factor which could have an effect on the stability of the solubilized product. This emphasizes the need for a thorough knowledge of the polymorphs of indomethacin and necessitates the use of X-ray diffraction- and DSC-studies. Although these studies were elementary, distinct conclusions could be made from the results obtained. The dissolution tests, powder flow studies and powder density determinations were the most critical tests performed to assess whether the product obtained was suitable for incorporation into a directly compressed tablet.

The choice of an indomethacin tablet formula was done by trial and error. Although 4 different formulae (formulae 1-4) were subjected to powder flow and bulk density studies, no indication could be obtained as to whether the tablets would form a compact. Therefore, each formula had to be compressed to see whether a good compact was possible. The formula eventually selected, formula 4c, adhered to the normal quality control tests laid down for tablets.

A conventional approach was used to formulate the directly compressed tablets. The formula, apart from the active ingredient (indomethacin-CL PVP), comprised a filler-binder, glidant, lubricant and disintegrant. However, the use of CL PVP to solubilize indomethacin, resulted in a simplification of the formula through the use of multifunctional ingredients. Although the CL PVP was ostensibly the solubilizing agent, it also acted as a disintegrant.

The study of the relationship between tablet hardness and compression force (section 3.4) was useful for the prediction of tablet hardness. By using the appropriate machine settings, tablets of the correct hardness could be produced. Furthermore, the relationship between tablet hardness and dissolution rate was established, enabling the production of tablets that were hard enough to be handled without compromising the dissolution rate of these tablets.

Although dissolution testing as a compendial requirement is an acknowledged method to establish in vitro drug availability, the ideal would be to evaluate the biological availability using in vivo animal studies in order to establish whether or not a relationship exists. Since dissolution tests could not be done in acidic media, due to the poor solubility of indomethacin, and since indomethacin is absorbed in the gastro-intestinal tract (with areas like the stomach having an acidic environment), in vivo studies are necessary in order to validate the dissolution results obtained in this study.

Arising out of this study, the following aspects need to be investigated:

a) The extent of polymorphism in the solubilized indomethacin needs to be quantified and a mathematical equation established to predict the stability of the polymorphs.

b) The similarity in the curvature of the dissolution curves from the solubilized indomethacin and indomethacin tablets, indicates a mathematical relationship between the dissolution profiles. It would be of interest to determine the kinetic order of drug release and whether there is a relationship between the dissolution profiles, as expressed by the Higuchi law.

c) In vivo bioavailibilty studies need to be done and the possibilty of a dosage reduction of a readily available, solubilized form of indomethacin needs to be investigated (as suggested by Bogdanova et al., 1981), with the view to reducing the possible side effects of the drug.

d) The question whether solubilized indomethacin could be formulated as a dispersible tablet, as is the case with some of the other anti-inflammatories currently available on the market, also needs to be answered.

It may, thus, be concluded that it is possible to produce indomethacin tablets using direct compression. However, although a study of the pharmaceutical aspects is an important component in the formulation of a product, other fields of pharmaceutical research are necessary to meet the statutory requirements in order to market a product and to ensure its safety, efficacy and quality.

ABSTRACT

Indomethacin is an anti-inflammatory analgesic with antipyretic properties. Indomethacin is currently only available as a capsule dosage form in South Africa. The drug is poorly soluble, its absorption is erratic and it can cause gastro-intestinal irritation. In addition, capsules are generally more expensive to produce than tablets. This study investigates the formulation of indomethacin tablets, in which the drug is present in an apparently more soluble form; this provides an alternate (and, possibly, cheaper) dosage form having an improved bioavailability, a more rapid onset of action and less potential for gastro-intestinal disturbances caused by the accumulation of undissolved drug.

In the literature survey, the factors that cause insolubility of drugs are reviewed. Solid dispersion systems are discussed and a brief overview of other techniques used to improve solubilization is given. Polymorphism of indomethacin is explained and direct compression is discussed with reference to the ingredients used in the tablet formula.

Seven solubilized forms of indomethacin ("products") were prepared. Extensive preformulation tests were done on these products. The products were subjected to powder flow studies and dissolution tests. X-ray powder diffraction and differential scanning calorimetry were used to study the indomethacin polymorphs present in the products. Using these and other criteria, the most soluble, stable and free-flowing form of indomethacin, i.e. the indomethacin-CL PVP product, was chosen for incorporation into a directly compressible tablet. This product was

subjected to particle size, density and moisture content determinations, to evaluate its suitability for direct compression.

Indomethacin tablets were prepared and subjected to standard quality control tests. During dissolution testing, the indomethacin tablets released 1.5 times more indomethacin, after 10 minutes, than the conventional indomethacin capsules. The influence of tablet hardness on dissolution rate was also investigated. In addition, these tablets were shown to be stable after storage.

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CONTENTS OF APPENDICES

APPENDIX 1: DISSOLUTION TESTS DONE IN DISTILLED WATER ON INDOMETHACIN PRODUCTS

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-FUMED SILICON DIOXIDE PRODUCT	IMC-FUMED SILICON DIOXIDE PHYSICAL MIXTURE
5	6.09 ± 2.23	4.03 ± 0.15
10	8.44 ± 1.14	6.37 ± 0.86
30	16.00 ± 2.69	13.22 ± 1.91
60	17.82 ± 4.55	19.00 ± 3.51
90	23.03 ± 3.67	20.06 ± 3.85

TIME (min.)	IMC-CROSS-LINKED POLYVINYLPYRROLIDONE PRODUCT	IMC-CROSS-LINKED POLYVINYLPYRROLIDONE PHYSICAL MIXTURE
5	40.79 ± 19.51	5.42 ± 0.84
10	76.74 ± 20.10	17.05 ± 4.88
30	100.00	72.09 ± 12.27
60	100.00	84.22 ± 14.30
90	100.00	86.08 ± 12.51

TIME (min.)	IMC-PEG 400 SOLUTION DEPOSITED ONTO FUMED SILICON DIOXIDE	IMC-PEG 400 SOLUTION
5	32.31 ± 19.23	3.41 ± 7.15
10	36.36 ± 18.15	4.83 ± 6.65
30	34.16 ± 8.89	12.55 ± 5.38
60	46.92 ± 4.95	37.84 ± 10.22
90	49.25 ± 3.18	41.50 ± 7.92

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-PEG 400 SOLUTION DEPOSITED ONTO TALC
5	3.71 ± 7.15
10	4.83 ± 8.17
30	35.45 ± 7.14
60	42.92 ± 6.45
90	45.01 ± 4.17

TIME (min.)	IMC POWDER
5	9.33 ± 3.20
10	13.91 ± 2.11
30	27.45 ± 4.73
60	36.63 ± 4.35
90	41.25 ± 5.31

TIME (min.)	IMC PEG 6000 PRODUCT	IMC PEG 6000 PHYSICAL MIXTURE
5	14.03 ± 4.63	11.22 ± 9.78
10	25.10 ± 8.30	18.20 ± 10.91
30	37.64 ± 12.42	33.10 ± 13.61
60	45.49 ± 13.01	39.61 ± 12.71
90	49.62 ± 16.37	44.76 ± 13.55

TIME (min.)	IMC-STARCH PRODUCT	IMC-STARCH PHYSICAL MIXTURE
5	9.78 ± 4.30	3.31 ± 1.33
10	11.05 ± 6.40	5.32 ± 1.01
30	21.39 ± 4.99	23.70 ± 3.04
60	26.09 ± 3.49	41.85 ± 8.55
90	28.38 ± 3.36	45.98 ± 8.97

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-LACTOSE PRODUCT	IMC-LACTOSE PHYSICAL MIXTURE
5	8.29 ± 2.31	14.14 ± 7.22
10	11.24 ± 3.94	15.64 ± 6.85
30	23.28 ± 7.05	32.97 ± 7.56
60	30.48 ± 8.51	37.63 ± 8.93
90	34.21 ± 11.36	48.53 ± 10.55

APPENDIX 2: DISSOLUTION TESTS DONE IN PHOSPHATE BUFFER ON INDOMETHACIN PRODUCTS

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-FUMED SILICON DIOXIDE PRODUCT	IMC-FUMED SILICON DIOXIDE PHYSICAL MIXTURE
5	18.84 ± 6.31	30.21 ± 2.81
10	31.42 ± 8.65	51.17 ± 10.42
30	47.95 ± 6.61	91.32 ± 6.75
60	54.40 ± 6.36	91.32 ± 6.75
90	57.77 ± 6.46	93.33 ± 6.01

TIME (min.)	IMC-CROSS-LINKED POLYVINYLPYRROLIDONE PRODUCT	IMC-CROSS-LINKED POLYVINYLPYRROLIDONE PHYSICAL MIXTURE
5	62.08 ± 20.34	53.76 ± 13.25
10	85.45 ± 8.35	83.21 ± 5.12
30	93.04 ± 6.64	92.25 ± 1.94
60	93.53 ± 3.60	95.91 ± 3.19
90	99.00 ± 1.10	97.01 ± 2.60

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-PEG 400 SOLUTION DEPOSITED ONTO FUMED SILICON DIOXIDE	IMC-PEG 400 SOLUTION
5	32.30 ± 4.11	9.83 ± 8.15
10	53.78 ± 5.97	40.55 ± 6.31
30	65.65 ± 6.22	44.60 ± 6.11
60	71.17 ± 6.14	47.92 ± 5.43
90	74.41 ± 7.41	52.47 ± 3.88

TIME (min.)	IMC-PEG 400 SOLUTION DEPOSITED ONTO TALC
5	63.09 ± 14.01
10	63.95 ± 13.54
30	82.71 ± 16.94
60	87.84 ± 9.95
90	93.68 ± 8.65

TIME (min.)	IMC POWDER
5	8.92 ± 3.10
10	11.67 ± 5.67
30	53.99 ± 7.01
60	80.03 ± 11.04
90	84.61 ± 8.34

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	IMC-STARCH PRODUCT	IMC-STARCH PHYSICAL MIXTURE
5	31.23 ± 8.54	24.75 ± 2.19
10	53.15 ± 10.88	37.48 ± 11.45
30	88.44 ± 9.95	56.17 ± 13.48
60	94.50 ± 5.90	71.29 ± 17.33
90	96.86 ± 2.63	81.90 ± 15.81

TIME (min.)	IMC-STARCH PRODUCT	IMC-STARCH PHYSICAL MIXTURE
5	19.01 ± 9.05	8.10 ± 6.30
10	21.36 ± 8.26	10.66 ± 3.39
30	35.26 ± 4.84	61.95 ± 8.52
60	41.52 ± 7.65	71.80 ± 9.99
90	53.83 ± 2.78	77.53 ± 9.75

TIME (min.)	IMC-LACTOSE PRODUCT	IMC-LACTOSE PHYSICAL MIXTURE
5	17.22 ± 10.93	58.09 ± 21.72
10	36.68 ± 13.17	59.07 ± 10.41
30	70.89 ± 11.12	77.74 ± 8.21
60	90.59 ± 6.52	88.58 ± 9.11
90	96.13 ± 3.76	91.52 ± 9.00

APPENDIX 3: DISSOLUTION TESTS DONE IN DISTILLED WATER ON INDOMETHACIN TABLETS

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	FORMULA 4c	FORMULA 5
2	32.34 ± 2.67	16.97 ± 3.55
4	48.25 ± 2.26	29.98 ± 2.10
10	67.72 ± 1.99	56.52 ± 4.15
30	87.79 ± 1.42	85.26 ± 10.96
60	90.81 ± 1.59	97.58 ± 9.71

TIME (min.)	FORMULA 6	FORMULA 7
2	13.92 ± 2.49	44.58 ± 2.31
4	23.73 ± 9.94	45.88 ± 2.29
10	52.29 ± 5.98	69.86 ± 3.26
30	83.49 ± 3.26	98.64 ± 1.21
60	89.51 ± 3.62	99.61 ± 1.04

APPENDIX 4: DISSOLUTION TESTS DONE IN PHOSPHATE BUFFER ON INDOMETHACIN TABLETS

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	FORMULA 4c	FORMULA 5
2	76.92 ± 21.32	29.78 ± 2.00
4	78.91 ± 11.37	36.11 ± 3.20
10	79.99 ± 7.54	59.43 ± 0.08
30	91.05 ± 1.34	86.31 ± 1.71
60	92.16 ± 6.52	91.82 ± 7.71

TIME (min.)	FORMULA 6	FORMULA 7
2	22.39 ± 2.33	44.02 ± 4.33
4	31.27 ± 2.68	60.24 ± 6.60
10	53.11 ± 1.34	75.76 ± 5.30
30	71.23 ± 2.53	97.80 ± 3.27
60	83.31 ± 3.48	99.02 ± 4.59

APPENDIX 5: DISSOLUTION TESTS DONE ON INDOMETHACIN CAPSULES

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	DISTILLED WATER	PHOSPHATE BUFFER
5	26.56 ± 7.71	50.50 ± 6.62
10	53.70 ± 6.73	66.45 ± 5.70
30	66.81 ± 7.32	86.33 ± 6.07
60	67.40 ± 4.71	88.97 ± 4.02

APPENDIX 6: DISSOLUTION TESTS DONE IN PHOSPHATE BUFFER ON INDOMETHACIN TABLETS TO ILLUSTRATE THE INFLUENCE OF COMPRESSION FORCE ON DRUG RELEASE

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	FORMULA 4d	FORMULA 4e
5	82.89 ± 3.68	74.26 ± 5.52
10	92.71 ± 2.34	80.06 ± 3.33
30	94.79 ± 2.12	84.31 ± 5.65
45	98.32 ± 1.57	84.97 ± 3.83
60	99.32 ± 1.01	95.32 ± 3.37

TIME (min.)	FORMULA 4f	FORMULA 4g
5	78.13 ± 4.59	76.19 ± 3.71
10	81.25 ± 3.90	78.13 ± 2.61
30	81.98 ± 2.77	81.10 ± 3.79
45	82.55 ± 2.94	83.66 ± 3.07
60	84.34 ± 3.81	84.66 ± 3.91

APPENDIX 7: DISSOLUTION TESTS DONE IN DISTILLED WATER TO TEST THE STABILITY OF INDOMETHACIN TABLETS

MEAN PERCENTAGE INDOMETHACIN (IMC) RELEASED

TIME (min.)	FORMULA 4h	FORMULA 4i
5	12.26 ± 4.33	6.31 ± 1.33
10	20.41 ± 3.41	8.28 ± 2.32
30	21.42 ± 3.34	17.47 ± 4.82
45	23.97 ± 3.44	19.32 ± 2.73
60	31.06 ± 4.33	26.00 ± 3.37

TIME (min.)	FORMULA 4j	FORMULA 4k
5	9.40 ± 3.77	14.25 ± 2.83
10	15.46 ± 3.46	26.30 ± 2.67
30	19.50 ± 2.68	40.45 ± 4.21
45	21.63 ± 7.31	47.00 ± 4.17
60	28.11 ± 5.22	52.17 ± 7.44

TIME (min.)	FORMULA 4l
5	30.22 ± 2.44
10	45.65 ± 2.27
30	65.33 ± 2.01
45	85.37 ± 1.23
60	88.69 ± 1.99