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POLYETHYELENE GLYCOLS AND DRUG RELEASE

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ABSTRACT

The dissolution rates of several drugs may be increased by incorporation into solid polyethylene glycols[1]. These dispersions are usually manufactured by heating a physical mixture of the drug and polymer to the fluid state and subsequently cooling to room temperature.

The physical structure of both the drug and the polyethylene glycol will be discussed, as these factors may affect the rate of drug release from the dispersions[2,3]. The solid state properties of both components have traditionally been studied by X-ray diffraction and/or by differential scanning calorimetry (DSC). The latter technique has facilitated the use of phase diagrams in the investigation of the melting properties of the dispersions, these usually indicating the presence of eutectics, monotectics, solid solutions or glasses. The application of a further technique, dielectric spectroscopy, in the study of molten and solid dispersions will be described.

The mechanisms by which drug dissolution rate may be enhanced will be described. Furthermore, the kinetics of drug release will be discussed in terms of the non-interactive and interactive models proposed by Corrigan[4].

1. INTRODUCTION

The incorporation of drugs into solid water soluble carriers has frequently been reported to result in an increase in the drug dissolution rate, often leading to an improvement in bioavailability. Such dosage forms are termed "solid dispersions", these being defined as "the dispersion of one or more active ingredients in an inert carrier or matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method"[1]. Alternatively, Corrigan[4] has defined the solid dispersion as a "product formed by converting a fluid drug-carrier combination to the solid state". In practice, the term has become synonymous with oral dosage forms, the carrier usually having a higher water solubility than the drug.

While the usefulness of solid dispersions in the preparation of fast release dosage forms is well established, a number of additional advantages have been reported. These include the possibility of releasing an initial priming dose from a slow release preparation by using a mixture of soluble and insoluble carriers[5]. Furthermore, the stability of the drug may be improved. For example, the hydrolysis of vancomycin may be substantially reduced by formulating the drug as a solid dispersion[6], while a more favourable polymorphic form of nabilone may be stabilised over a two year period on incorporation into polyvinylpyrrolidone (PVP)[7]. The formulation of liquids as solid dispersions is also possible[8]. Furthermore, the relatively low dust levels involved in handling and manufacturing these dosage forms have advantages in terms of safety.

Comparatively few commercial products are available using this technology. This can be ascribed to two factors. Firstly, there have been difficulties in producing a viable solid dispersion dosage form, as the dispersions often exhibit poor handling qualities[9]. There has recently been growing interest in the use of liquid filled hard gelatin capsules[10], involving the use of modified capsule filling equipment. A heated hopper is used to prepare a fluid mix of the drug and carrier, which is subsequently filled into hard gelatin capsules via a heated nozzle

and allowed to cool to room temperature[5]. This technique has been used in the preparation of Vancocin Matrigel (Eli Lilly Ltd.)[6].

The second consideration is the level of understanding of the physico-chemical properties of solid dispersions. The mechanisms behind the reported increases in drug dissolution rate are still a matter of debate. Furthermore, it has frequently been reported that the dissolution rate may alter over a period of time, a process known as ageing[11,12]. While it is usually the case that the dissolution rate decreases with time, increases have also been reported[13]. The mechanisms involved may include changes in the particle size or crystal form of the drug or carrier[1].

The present article will discuss the physico-chemical properties of solid dispersions in terms of their solid state and solution properties. In particular, polyethylene glycol (PEG) solid dispersions will be considered. These polymers have been used extensively as water soluble carriers due to their favourable solution properties, low toxicity, low melting point and low cost. Consequently, it is to these substances that the present article will be largely confined.

1.1 The Manufacture of Solid Dispersions

Solid dispersions may be manufactured by one of three methods. Firstly, the fusion method, which involves heating a physical mixture of the drug and carrier to the fluid state and subsequently cooling to room temperature. However, the conditions used for the fusion process are frequently unstated. For example, the maximum temperature used is often described as the temperature at which the drug appears to melt, this assessment being entirely visual. Chatham[2], however, demonstrated that the temperature of fusion, holding time and cooling rate may have a profound effect on the structure and dissolution properties of trimethoprim dispersions in PEG 4,000.

A number of studies have indicated that the drug does not have to be heated to the liquid state in order to result in an increase in drug dissolution rate. For example, Craig[3] demonstrated an increase in the dissolution rate of nortriptyline

HCl from PEGs, despite using a low temperature fusion method whereby the drug remained in the solid state throughout. Similarly, Chemtob et al[14] compared powdered physical mixes of niclosamide and PEG 6,000 with fusions prepared considerably below the melting point of the drug and also at a temperature corresponding to complete drug dissolution in the carrier. While the higher temperature fusions yielded faster drug release rates than did the other two samples, no clear rank order was seen between the release rate from the low temperature fusions and physical mixes containing various drug concentrations. However, all three systems gave higher dissolution rates than the drug alone.

Increases in dissolution rates compared to the drug alone have also been reported for systems whereby physical mixes of the drug and carrier have been tabletted to form a constant surface area disc[15,16]. A study by Ford and Rubinstein[17] compared the dissolution behaviour of compressed discs of physical mixes of indomethacin and PEG 6,000, discs of dispersions prepared by the melt method and direct compression discs of indomethacin alone. The melt discs gave considerably higher dissolution rates than did the physical mixes, which in turn gave higher rates than the indomethacin alone. Corrigan and Timoney[18], however, showed little difference in release rate from constant surface area discs of dispersions and physical mixes of hydroflumethiazide and PEG 4,000. It may therefore be concluded that it is not always necessary to melt the drug in order to improve the drug dissolution rate, although to do so may result in a greater enhancement in certain cases.

Secondly, the coprecipitation (or, more correctly, coevaporation) method involves dissolution of the drug and carrier in a volatile organic solvent. The solvent is subsequently evaporated, leaving the dispersion as a residue. Lastly, the melting-solvent method involves the dissolution of the drug within a cosolvent, the resulting solution being mixed with the molten carrier. The fluid is then cooled to room temperature. This theoretically allows a molecular dispersion of the drug to be prepared without necessitating the use of heat above that required to melt the carrier.

PEG solid dispersions are usually manufactured by the fusion method, although the coevaporation method (eg. McGinity et al[19]) and, less frequently, the melting-solvent method[20] have also been used. Examples of the polyethylene glycol solid dispersions have been previously reviewed[9] and will therefore not be discussed here. Instead, the present article will be confined to a consideration of two areas central to the study of these systems, namely the solid structure and dissolution behaviour of solid dispersions.

2. THE SOLID STATE PROPERTIES OF DRUG DISPERSIONS IN POLYETHYLENE GLYCOLS

2.1 Methods of Studying Solid Dispersions

While several methods have been used in the examination of solid dispersions, the two most important are differential scanning calorimetry (and other thermal techniques) and X-ray diffraction. Differential scanning calorimetry (DSC) is based on the principle that two pans (one sample, one empty reference) are heated or cooled at a preset rate such that thermal equilibrium is maintained between the two. When the sample undergoes a thermal transition (eg. melting, crystallisation or glass transition), energy must be supplied to one of the pans to maintain this equilibrium. The quantity of energy and the temperature at which it is supplied are both measured. From this information, an indication as to the structure of the sample may be obtained.

The technique offers several advantages over other analytical methods, including the simplicity of operation and the wide variety of samples that may be analysed. DSC may be used to obtain phase diagrams for binary systems and has therefore been applied to the study of eutectic mixtures, solid solutions and glasses, amongst others. Phase diagrams may also be constructed on the basis of the enthalpy of fusion at a particular composition[2,21].

There are also disadvantages associated with the technique. Firstly, the method is invasive and may therefore reflect changes in the sample induced by the

equipment itself. Furthermore, on measuring binary systems, the component with the higher melting point will be analysed when suspended in a melt of the other substance. It is reasonable to assume that the thermal characteristics of a material may be altered under such conditions, in which case care must be taken when relating melting data to the solid structure at room temperature.

Secondly, conditions such as scanning speed, sample weight[22] and particle size[3] may effect the results obtained. It is therefore essential to standardise these conditions when designing the experimental protocol. Finally, many substances are thermolabile and will decompose at or below their melting points, thus preventing useful analysis.

X-ray powder diffraction involves the scattering of X-rays via passage through a powder sample, the resultant beams being detected on a strip of circular film. The distance of the image from the centre of the strip is a measure of the spacing between the crystal planes within the sample. The technique is generally used on a qualitative basis for solid dispersions, involving the comparison of spectra for the drug and carrier alone with that of the dispersion. However, the technique has also been used quantitatively to estimate the degree of crystallinity[23] and crystalline structure[24] of solid disperse samples.

Further techniques that have been employed include IR spectroscopy[25] and solid state NMR[26]. In addition, low frequency dielectric spectroscopy has been used to characterise both the individual components and the dispersions[2,3]. The technique involves the passage of an alternating signal through a sample, causing the dipoles within that material to attempt to realign themselves at the same rate as the fluctuations in the field. Due to local inertia exerted by the immediate environment, a phase lag will develop between the applied field and the response. This lag may be analysed over a range of frequencies in terms of the energy lost and stored by the system. The resultant spectra will therefore contain information concerning the structure of the sample. An additional advantage has been that the dispersions may be studied in both the molten and solid states, thus allowing a greater scope for analysis than is possible with most other techniques.

2.2 The Structure of Polyethylene Glycols

In order to study the structure of a solid dispersion, it is necessary to have an understanding of the morphology of the carrier itself. The structure of polyethylene glycols will therefore be briefly described.

The polyethylene glycols are a series of water soluble synthetic polymers, the repeating unit being oxyethylene ($-OCH_2CH_2-$) with either end of the chain comprising an hydroxyl group. The available molecular weight fractions lie between approximately 200 to several million, the polymers ranging from viscous liquids at room temperature from 200 to 700, semisolids from 1000 to 2000 and wax-like solids from 3000 to 100,000, above which the solids are resinous and form strong thermoplastic films[27]. The molecular weight range used for solid dispersions lies between approximately 3000 to 20,000. The discussion will therefore be limited to the properties of this range of molecular weight materials.

The polymers in this molecular weight range are semi-crystalline, containing both ordered and amorphous components. In the crystalline state, the chains are present as double helices containing approximately 15 monomers within a repeat unit[28,29]. The helices are arranged as plate-like structures (lamellae), from which the hydroxyl end groups are rejected onto the surface[30]. The chains within the lamellae may be extended or folded, the latter being metastable with respect to the former. The lamellae are in turn arranged in spherical structures (spherulites).

In general, the higher the molecular weight of the PEG, the more stable the folded chain form within the lamellae. For example, PEG 10,000 chains may fold up to three times, while PEG 3,000 only exists in the extended or once-folded form[30]. An additional factor determining the degree of chain folding is the thermal history of the material, particularly the cooling rate from the melt[2].

The PEG molecular weight fractions under study have a melting range of approximately 55°C to 65°C, the melting point showing a non-linear increase with chain length[31]. The melting of PEGs has been studied extensively due to the stability of the metastable folded chain forms compared to those of other polymers[30]. Studies using DSC show the folded chain forms of a particular

sample as additional endothermic peaks at temperatures below that corresponding to the stable extended chain form. For example, a study on flash cooled PEG 6,000 showed one peak at 56.1°C corresponding to the once folded chain form, and a second peak at 60.7°C corresponding to the extended chain form[3].

Polyethylene glycols exhibit glass transition temperatures (Tg) over a range of approximately 200-230K, depending on molecular weight and the method of assessment[32]. The relationship between Tg and molecular weight appears to be complex. Faucher et al[33] demonstrated a maximum in Tg at a molecular weight corresponding to PEG 6,000 when using slow-cooled samples, whereas samples quenched in liquid nitrogen showed a direct proportionality between Tg and chain length.

2.3 Proposed Structures of Solid Dispersions

a) Eutectic Mixtures

Eutectic mixtures are formed when two components form a completely miscible melt but solidify on cooling as two phases. These phases may exist as discreet particles of either component or as an microfine mix of both, the melting point of the mix being below that of either pure substance. This is represented by the phase diagram shown in Figure 1.

The formation of the eutectic at two different compositions is described by the lines A-B and C-D. As the temperature is decreased from A to B, the system remains in the molten state until the liquidus cusp meets the solidus line. This point is known as the eutectic point and represents the lowest temperature at which an equilibrium between the liquid and solid binary mixes may exist. On further cooling the system solidifies to form a eutectic mixture.

The morphology of eutectics has been studied in detail, particularly in metallic systems[34]. The two components of a eutectic mixture appear to form microstructures involving interpenetrating crystal forms. For example, both SiO_2 and Al_2O_3[35] and catechol and o-phenylenediamine systems[36] form inter-penetrating plate-like and rod-like structures on cooling from the melt. A possible mechanism

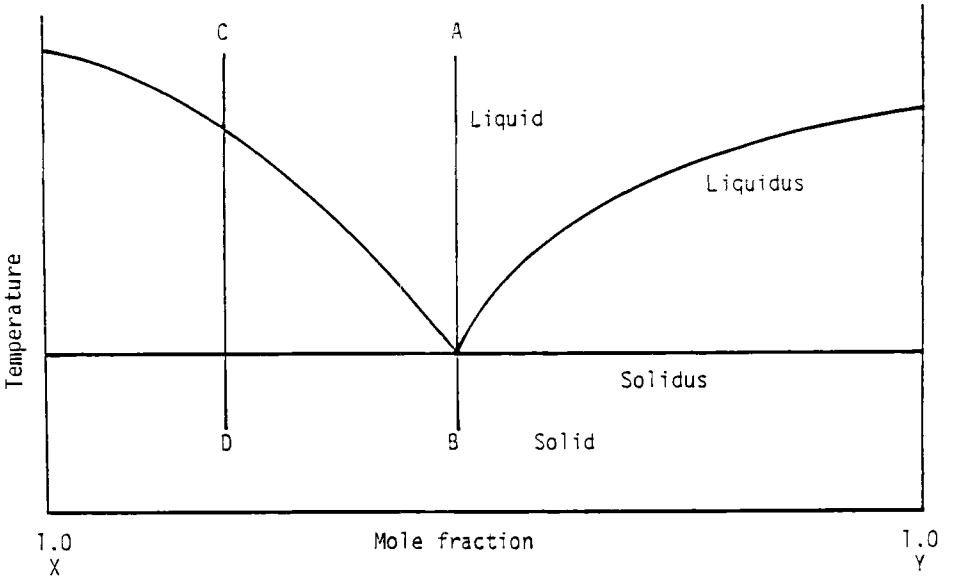


FIGURE 1

Typical Phase Diagram of a Binary Eutectic System

for the generation of eutectics is the formation of heterogeneous clusters of the two components in the melt[37]. On cooling and solidification, the clusters break down to form nuclei of one or other component. As growth proceeds, the surrounding liquid becomes proportionately richer in the other substance. This high concentration of the second component then leads to nucleation, thus forming a new crystal growth face. Growth continues to alternate between the two components until complete solidification occurs.

The crystallisation of a melt at a composition other than that of the eutectic mixture is exemplified by the line C-D. As the temperature is lowered, the liquidus line is crossed, representing the crystallisation of pure X within the melt. As the temperature is lowered further, more solid X is formed and the melt becomes proportionately richer in Y. The process continues until the solidus line is reached, at which point the eutectic mixture is formed.

Several eutectics have been reported in the PEG solid dispersion literature (eg.Ford[38],Mura et al.[39]). However, studies have also found physical mixes of the

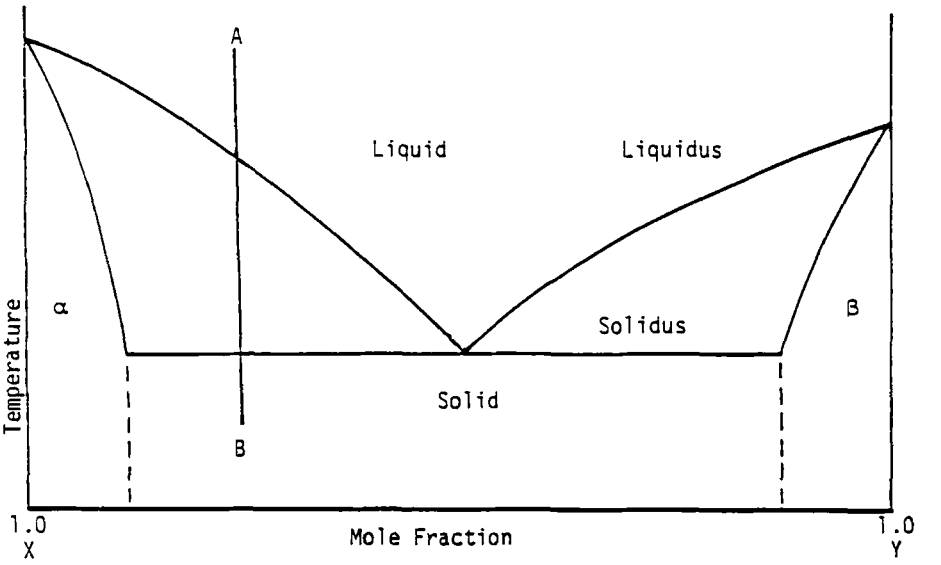


FIGURE 2

Typical Phase Diagram of a Binary Partial Solid Solution

two components to exhibit eutectic melting behaviour, giving almost identical phase diagrams to those of the corresponding dispersions[40,41,42]. This may be due to solid state reactions occurring at the interface between the two components[43]. These studies do imply, however, that eutectic phase diagrams may not necessarily indicate the presence of a eutectic mixture in the original sample.

b) Solid Solutions

Solid solutions represent the mixing of two solids at a molecular level. Such solutions may be classified according to either the miscibility of the two components or else to the crystal form of the solid. The former describes the system as continuous (isomorphous, unlimited, complete), whereby the two components are miscible in all proportions in both the liquid and solid state, or as discontinuous (limited, restricted, partial, incomplete), whereby solid solubility only occurs at certain compositions.

Figure 2 shows an example of the phase diagram of a system exhibiting partial solid solubility. The line A-B represents a typical cooling protocol. Between the liquidus and solidus lines, the system is composed of both solid and melt. However, the system is distinguished from simple eutectics by the solid phase consisting of a solid solution rather than a pure component. The composition of both phases at any temperature can be estimated using tie lines to the liquidus and solidus curves. As the eutectic temperature is reached, the solid consists of the eutectic mix and of pure solid solution α.

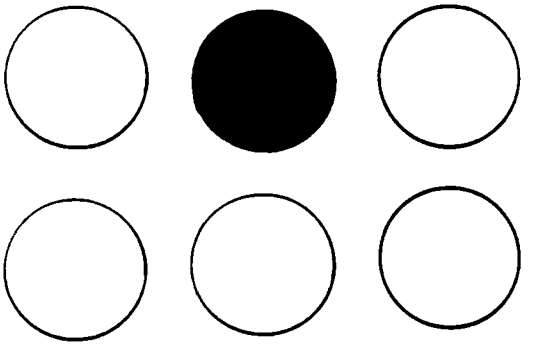
Classification according to crystal form describes the systems as substitutional, whereby the solute replaces an atom or molecule in the solvent lattice, or interstitial whereby the solute occupies the interstitial spaces between solvent molecules. These two categories are illustrated in Figure 3.

In practice, the solid solutions reported in the solid dispersion literature have invariably been discontinuous, as demonstrated by the phase diagrams obtained. However, the distinction between substitutional and interstitial systems is more difficult to ascertain. It is unlikely that substitutional solid solutions can exist between markedly dissimilar molecules[1,44,45], hence any solid solubility between drugs and polymeric carriers is likely to be interstitial due to the size difference between the two components.

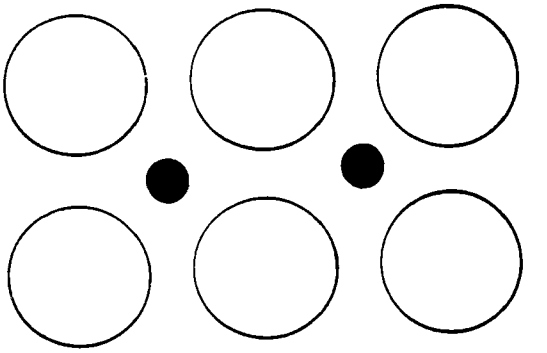
It is possible that the reported solubility of drug molecules in semi-crystalline polymeric carriers represents the dissolution of the drug within the amorphous, rather than the crystalline fraction of the carrier. This has been reported in the chemistry literature for solid solutions of ferrocene in polyethylene[45]. The hypothesis is further supported by the observation that the diffusion of monomeric substances within a semi-crystalline polymer is confined to the amorphous component of the solid[46].

Strictly speaking, eutectic systems must involve some degree of solid solubility, as otherwise the theory predicts that the pure components have two melting points (see Figure 1). However, the extent to which solid solubility occurs in these sytems may be sufficiently small as to be considered negligible.

a) Substitutional solid solution



b) Interstitial solid solution



Dark circles: solute species
Open circles: solvent species

FIGURE 3

Schematic Representation of a Substitutional and Interstitial Solid Solution

c) Glass Solutions and Glass Suspensions

A glass is defined as "a solid having geometrical structure which is characteristic of the liquid state"[47]. Glasses are characterised by the presence of a glass transition temperature, above which the material changes from a brittle solid to a more pliable and rubber-like substance. The magnitude of the effect and the temperature at which it occurs varies between materials and conditions of measurement.

The concept of using glass-forming materials as carriers was introduced by Chiou and Riegelman[48] using griseofulvin dispersed in citric acid. The authors suggested that the griseofulvin effectively existed as a solid solution within the glass. Moreover, they postulated that the dissolution of drugs from glass systems should theoretically be faster than from conventional solid solutions due to the lower lattice energy of the former. Chiou and Riegelman[1] proposed the term "glass suspension" to describe systems whereby drug particles are suspended in glassy solids.

Ford[49] has studied the effect of drug incorporation on the melting, crystallisation and, in particular, the glass transition behaviour of PEG 6,000, with a view to predicting drug dissolution rate and ageing effects.

d) Amorphous Precipitation in a Crystalline Carrier

This category was suggested on the basis of studies on sulphathiazole-urea dispersions[41]. The authors prepared fusions and physical mixes of the two components over a range of concentrations. X-ray diffraction studies on fusions containing 52% w/w sulphathiazole indicated that while the urea was present in a crystalline form, the sulphathiazole showed no diffraction peaks. The authors proposed that the sulphathiazole was present as an amorphous precipitate within the crystalline carrier. A number of additional reports have suggested the presence of similar dispersions, including chlorthalidone and hydrochlorthiazide in pentaerythritol[50] and betamethasone alcohol in PEG 6,000[51]. The drug may also be present in a non-crystalline form when dispersed in an amorphous carrier[52,53].

e) Complex Formation

A number of reports have suggested the formation of a solid-state complex between the drug and carrier. The exact nature of the interaction is frequently unclear, although hydrogen bonding between specific moieties of the drug and carrier molecules has been suggested[7,54]. Solid-state complex formation has been reported for a variety of carriers, including PVP[55], citric acid[56], urea[57], nicotinamide[58] and polyethylene glycols[59].

f) Combination of Systems

The possibility exists that some or indeed all systems may show characteristics of more than one of the above. For example, a drug could theoretically exist in a carrier as both amorphous and crystalline particles. Moreover, it has also been argued[60] that the formation of a eutectic must involve solid state complexation to some extent.

g) Monotectic Systems

Examination of the literature reveals that there is a further solid state category which could be considered to be a separate class of dispersion. Several authors[2,3,25,51,61,62,63,64,65,66] have described phase diagrams whereby the liquidus cusp appears to correspond to the melting point of the pure carrier. The above authors have ascribed such diagrams to the presence of monotectic systems, an example of which is given in Figure 4. Similar diagrams have been reported for polymeric systems[45] and metal alloys[67]. Vasilev[60] has suggested that monotectic phase diagrams occur when the liquid-liquid bonds between two molten components are of comparable strength to those between the higher melting component, whereas with eutectic systems, the bonds between the two is stronger than those of either pure component.

There is some evidence that monotectics represent systems whereby one component is present in the other as discreet crystalline particles, as opposed to eutectics whereby a microfine dispersion of the two components is formed. For example, the monotectic phase diagrams reported for fusions of tolbutamide and griseofulvin in polyethylene glycol 20,000 and polyoxyethylene 40 stearate were

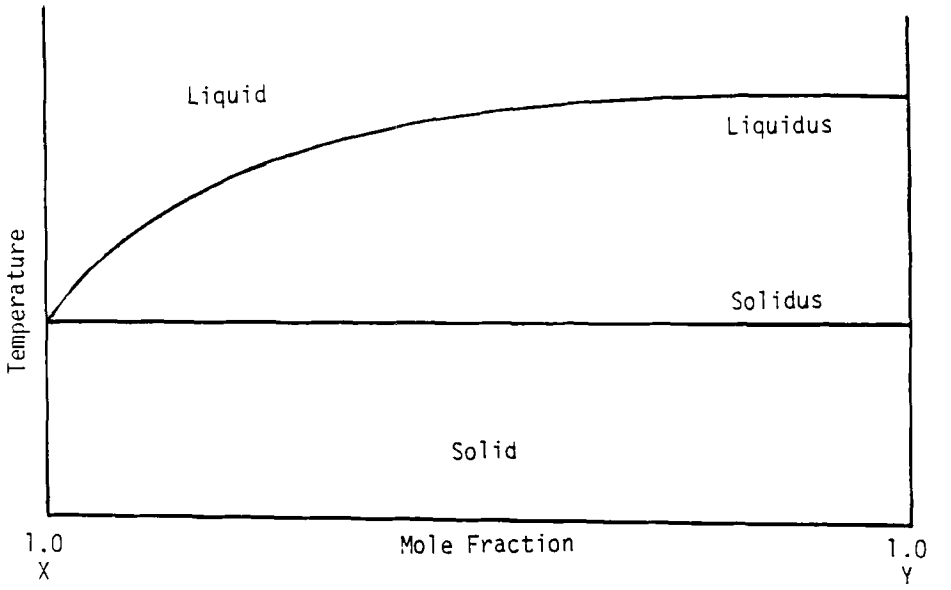


FIGURE 4

Typical Phase Diagram of a Binary Monotectic System

found after heating the physical mixtures to a few degrees above the melting point of the carriers, these being considerably lower than the melting points of the drugs[62]. The drug particles may therefore have remained intact throughout the fusion process.

Hargreaves[51] found monotectic phase diagrams for physical mixes of betamethasone alcohol in PEG 6,000, implying that the lowering of the drug melting point seen at low drug concentrations may not be a reflection of solid state changes to the sample during the fusion process. Venkataram and Rogers[66] reported that electron micrograph studies on griseofulvin-dimyristoylphosphatidylcholine systems showed the drug particles to remain essentially unchanged in appearance before and after coevaporation. The corresponding phase diagram is monotectic in nature. Chatham[2] reported monotectic phase diagrams for dispersions of trimethoprim in PEG 4,000, irrespective of whether the fusion temperature was above or below that required

for complete melting of both components. Craig[3] reported the presence of monotectic phase diagrams for nortriptyline HCl dispersions in a range of polyethylene glycols prepared using a low temperature fusion technique, the drug having remained below its melting point throughout the manufacturing process.

A further implication concerning the presence of monotectics is that on examination of several PEG-drug eutectic phase diagrams reported in the pharmaceutical literature, the eutectic point occurs at very low drug compositions, the liquidus and solidus lines at lower drug contents corresponding to temperatures in the region of 55-65°C. It is questionable whether the thermal techniques used are sufficiently sensitive to pick up the presence of the drug at such low concentrations. Furthermore, the above temperatures may correspond to the melting points of different crystal forms of the PEG, as previously discussed (2.2). This being the case, some of the systems previously reported as eutectics may in fact be monotectics, as the liquidus and solidus lines reported at low drug concentrations may simply correspond to the melting behaviour of the carrier alone. Consequently, the drug particle size within the dispersion may be greater than would be expected, were the system eutectic in nature.

3. DRUG RELEASE FROM POLYETHYLENE GLYCOLS

3.1 Methods of Studying Drug Release

Drug dissolution rates from PEG dispersions have been extensively measured, using either loose powder or constant surface area discs. The reader is referred to the review by Ford[9] for a more specific details of individual cases. Furthermore, a number of studies have been conducted on the dissolution rate of the carriers themselves[2,68,69], thereby allowing more detailed analysis of the dissolution data.

Other methods of studying the solution properties of solid dispersions include measurement of the solubility of the drug in aqueous solutions of the carrier (eg.Najib and Suleiman[25], Shihab et al[70]). In addition, Corrigan et al[71] have

measured drug diffusion rates in order to detect aqueous complex formation between the drug and carrier, in this case sulphathiazole and PVP. Recently, solution calorimetry has also been used, whereby a sample of the dispersion is dissolved in a solvent and the heat change involved in the reaction measured. Najib and Suleiman[25] and Craig[3] have used the technique to study interactions between the drug and carrier during the dissolution process.

3.2 Solution Behaviour of Polyethylene Glycols

Polyethylene glycols are unusual in that their water solubility is considerably greater than closely related polymers such as polymethylene oxide and polytrimethylene oxide, this being ascribed to the steric compatibility of the PEG molecules with the water lattice[46]. They are also soluble in a number of organic solvents, including acetonitrile, chloroform and dimethylformamide, but are insoluble in aliphatic hydrocarbons, diethylene glycol, ethylene glycol and glycerine[27].

On contact with water, particles of PEG swell to form gel-like matrices prior to dissolution. At low concentrations, aqueous solutions of PEGs exhibit Newtonian behaviour, while at concentrations of approximately 20% w/w, elastic gels are formed, at higher concentrations the material becomes semi-solid, the water acting as a plasticiser[27]. There is some evidence that the molecules retain their helical conformation in aqueous solution[72]. Similarly, Huttenrauch and Friche[73] also reported that anhydrous PEG 400 liquid exists in a linear form under ambient conditions. The addition of small quantities of water caused the conformation to change to a helical shape, thereby increasing the viscosity.

A study by Chatham[3] on the dissolution rate of PEG 4,000 indicated that the degree of crystallinity of the PEG may have a significant effect on the carrier dissolution rate, although the extent of chain folding was not found to be of importance in this respect.

3.3 Proposed Mechanisms of Increased Drug Release from PEGs

a) Particle Size Reduction

The Noyes-Whitney equation[74,75] predicts that when a solid dissolves, a diffusion layer is formed at the solid surface, resulting in a concentration gradient from the solid to the bulk solution, such that

$$\frac{dm}{dt} = \frac{DA(C_s-C)}{h}$$

where dm/dt is the dissolution rate, D is the diffusion coefficient, C is the bulk concentration (equal to 0 in sink conditions), C_s is the saturated solubility of the drug in the dissolution fluid and, according to the above model, the concentration immediately adjacent to the solid surface, h is the diffusion layer thickness and A is the area of the solid exposed to the fluid.

As the dissolution rate is proportional to the surface area, decreasing the particle size may lead to a greater drug release rate per unit weight. Therefore, the formation of a eutectic system may result in an increase in dissolution rate due to the drug being dispersed in the carrier as fine crystals[76], the same argument applying to solid solutions, which represent the extreme of particle size reduction[77].

In a thorough study by Sjokvist and Nystrom[78], the relationship between drug particle size within the dispersion and dissolution rate was investigated. The authors concluded that while a relationship was established between particle surface area and release rate, the particle dimensions alone could not fully explain the dissolution rate data and a further mechanism was probably involved.

b) Decreased Aggregation and Agglomeration

The tendency of a drug to form agglomerates or aggregates may be reduced due to the physical separation of particles by the carrier[1]. This is applicable either to systems in which the particle size is very small (and hence the surface energy per unit weight is large) or where the drug is highly hydrophobic. In both cases, agglomeration or aggregation will reduce the surface area exposed to the medium.

c) Particle Wetting

The correlation between wetting and dissolution rate has been discussed by Lippold and Ohm[79], the authors proposing that by wetting the powder, the effective surface area of the drug exposed to the solvent is increased. This will subsequently lead to an increase in dissolution rate, as predicted by the Noyes-Whitney equation. This mechanism has been implicated in the observed increase in dissolution rate of several systems, including reserpine in cholanic acid[80], hydrocortisone in cholesterol esters[81] and acetyl salicylic acid in PEG 6,000[82].

d) Increased Drug Solubility

A number of studies have shown PEGs to increase the equilibrium aqueous solubility of drugs (eg.El-Banna and Abdullah[83], Daabis and Mortada[84]). Hargreaves[51] showed a considerable enhancement in betamethasone alcohol solubility at higher PEG levels, the relationship between the bulk solubility and carrier concentration being non-linear. The author proposed that the drug diffusion layer was likely to contain a similarly high concentration of PEG, which could account for the increase in dissolution rate seen for the dispersions. Similarly, Doherty and York[85] have demonstrated that the inclusion of buffer salts in dispersions may allow control of the pH at the dissolving surface, irrespective of the bulk pH. This study demonstrates the importance of the local environment around the dissolving surface. However, Chiou and Niazi[41] reported that the dissolution rate of sulphathiazole increased in aqueous solutions of urea, even though the drug solubility is decreased by the presence of the carrier[76].

While a number of studies have demonstrated the tendency of PVP to form complexes with drugs in aqueous solution[53,86,87], there have been fewer reports on this mechanism being of relevance to PEG dispersions. However, Guttman and Higuchi[88] have shown PEGs to form association complexes with a number of substances, while Hilton and Summers[89] have suggested that PEGs present in the dissolution fluid of indomethacin/PVP dispersions may compete with the PVP in forming an association complex with the drug. It is therefore possible that the formation of PEG complexes in solution is of relevance to a number of systems.

The drug may also be present in a high energy form within the dispersion. Again, this usually refers to PVP systems, as the tendency of the carrier to inhibit the crystallisation of drugs has been well documented[52,53,90]. The amorphous form, being less thermodynamically stable, is likely to have a greater solubility and hence dissolution rate. Similarly, the formation of metastable polymorphs[1] or an increase in the intrinsic solubility of the drug due to particle size reduction[2] may also result in an increased dissolution rate.

3.4 Kinetic Analysis of Dissolution Behaviour

A further approach to the study of dissolution mechanisms has been to express the release rate data in terms of kinetic models. This method has been thoroughly reviewed[4] and only a brief description will be given here.

In the simplest case, that of a non-interactive system, the model predicts that the drug and carrier are initially considered to dissolve together, until the dissolving surface becomes depleted of one component. The remaining substance therefore forms a porous layer adjacent to the dissolving surface, through which the other component must diffuse before release into the medium can occur. When the carrier is present in excess, the respective dissolution rates per unit area may be given by

$$Gd = (Nd/Nc).Gc$$

and

$$Gc = Dd.Csd/h$$

where Gc and Gd are the dissolution rates of the carrier and drug respectively, Nd/Nc is the weight ratio of the two, Dd is the diffusion rate of the drug, Csd is the solubility of the drug and h is the diffusion layer thickness. The model predicts that the dissolution rate of the drug from the dispersion will not exceed the intrinsic dissolution rate of the drug alone. Moreover, the model implies that at high carrier concentrations the dissolution rate of the carrier is expected to remain constant, irrespective of composition, whereas the dissolution rate of the

drug will increase with concentration within the dispersion until the intrinsic dissolution rate of the drug alone is reached.

In the case of interacting systems, the two components are considered to form a soluble complex, the maximum dissolution rate occurring at a specific critical mixture ratio between the two components. The maximum drug dissolution rate is given by

$$Gd^{max} = (DdCsd + Dcd.K.Csd.Csc)/h$$

where Dcd is the diffusion coefficient of the complex, K is a binding constant, and Csc is the solubility of the carrier. This is in qualitative agreement with the observation that there is frequently a maximum in drug dissolution rate at a specific drug/carrier composition[2,9]. However, while these models are descriptive of a number of systems, they are not universally applicable. For example, PEG systems containing hydroflumethiazide and bendrofluazide exhibited release rates which were higher than predicted by either of these two models[68]. Moreover, there is some evidence that at high carrier compositions, the drug dissolution rate may in some cases be governed by the dissolution rate of the carrier[2,68], resulting in the dissolution fronts of the two components receeding simultaneously. The mechanism behind this carrier controlled dissolution is not yet understood.

CONCLUSIONS

The present article has attempted to describe the considerations involved in the characterisation of PEG solid dispersions. In particular, the importance of studying the properties of the carrier as well as the drug has been highlighted. Indeed, it can be argued that the dissolution behaviour of drugs from PEG dispersions cannot be fully understood unless the solid state properties of these systems have been characterised, although the exact relationship between the solid structure and the drug dissolution behaviour has not yet been established. In

particular, the behaviour of drugs within molten PEGs is poorly understood. This area of study has considerable relevance to the prediction of the solid structure on cooling from the melt. The dielectric technique has been of particular use in this application as it allows the direct study of the drug-carrier systems at any temperature during the manufacturing process. Investigations are also being conducted in our laboratories on the interaction between PEGs and drugs in aqueous systems, with a view to relating this behaviour to that of the dispersions.

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