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Review article

Improving drug solubility for oral delivery using solid dispersions

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Abstract

The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. Although solid solutions have tremendous potential for improving drug solubility, 40 years of research have resulted in only a few marketed products using this approach. With the introduction of new manufacturing technologies such as hot melt extrusion, it should be possible to overcome problems in scale-up and for this reason solid solutions are enjoying a renaissance. This article begins with an overview of the historical background and definitions of the various systems including eutectic mixtures, solid dispersions and solid solutions. The remainder of the article is devoted to the production, the different carriers and the methods used for the characterization of solid dispersions. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Solid solution; Solid dispersion; Eutectic mixture; Amorphous state; Bioavailability; Solubility; Dissolution

1. Introduction

Together with the permeability, the solubility behaviour of a drug is a key determinant of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole and chloramphenicol come immediately to mind. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes–Whitney equation [1,2] provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

The main possibilities for improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but definitely not least, to improve the apparent solubility of the drug under physiologically relevant conditions. Of these possibilities, changes in the hydrodynamics are difficult to invoke in vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the lumenal fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media [3]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.

Table 1 summarizes the various formulation and chemi-

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Table 1
Approaches to improve the solubility or to increase the available surface area for dissolution

I. Physical modifications
Particle size
Micronization
Nanosuspensions
Modifications of the crystal habit
Polymorphs
Pseudopolymorphs (including solvates)
Complexation/solubilization
Use of surfactants
Use of cyclodextrines
Drug dispersion in carriers
Eutectic mixtures
Solid dispersions (non-molecular)
Solid solutions
II. Chemical modification
Soluble prodrugs
Salts

cal approaches that can be taken to improve the solubility or to increase the available surface area for dissolution.

Of the physical approaches, review articles have already been published on the use of polymorphs [4], the amorphous form of the drug [5] and complexation [6,7]. Decreasing the particle size of the compound by milling the drug powder theoretically results in an increase in the available area for dissolution, but in some cases the micronized powder tends to agglomerate, thereby at least partly negating the milling procedure. Presenting the compound as a molecular dispersion combines the benefits of a local increase in the solubility (within the solid solution) and maximizing the surface area of the compound that comes in contact with the dissolution medium as the carrier dissolves. This review is therefore devoted to a discussion of the use of molecular and near-molecular dispersions for the optimization of oral delivery of poorly soluble drugs.

2. Definitions

2.1. Simple eutectic mixtures

No review of solid dispersions would be complete without a brief description of eutectic mixtures, which are the cornerstone of this approach to improving bioavailability of poorly soluble compounds. A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state (Fig. 1). When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comelt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components.

When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug [9,10]. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

2.2. Solid solutions

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions [11] and the dissolution rate is determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude.

Solid solutions can be classified according to two methods. First, they can be classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvendum (substitutional, interstitial or amorphous).

2.2.1. Continuous and discontinuous solid solutions

2.2.1.1. Continuous solid solutions In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

2.2.1.2. Discontinuous solid solutions In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical

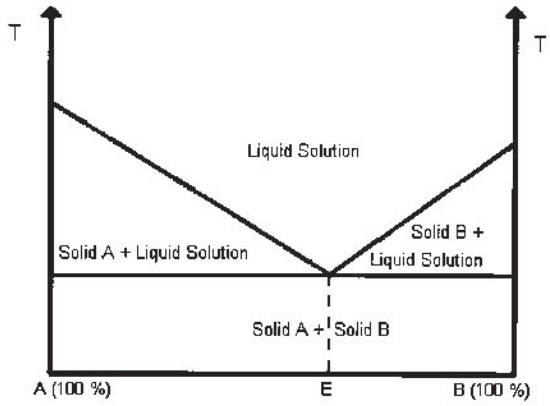

Fig. 1. Phase diagram for a eutectic system (reproduced with modifications from Ref. [8]).

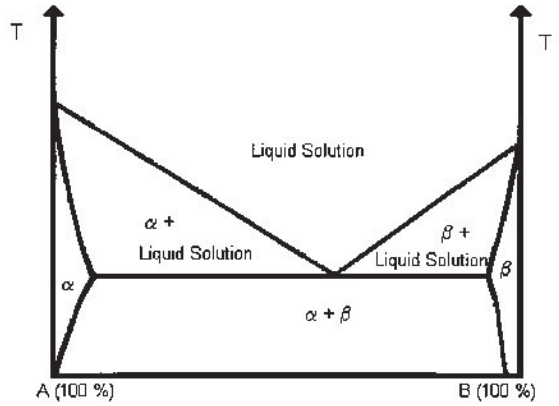

Fig. 2. Phase diagram for a discontinuous solid solution (reproduced with modifications from Ref. [8]).

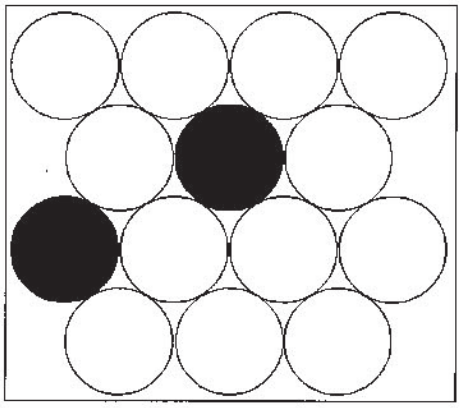

Fig. 3. Substitutional crystalline solid solution (reproduced with modifications from Ref. [13]).

phase diagram is shown in Fig. 2. α and β show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg et al. [11] that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

2.2.2. Substitutional crystalline, interstitial crystalline and amorphous solid solutions

2.2.2.1. Substitutional crystalline solid solutions Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. A substitutional crystalline solid dispersion is depicted in Fig. 3. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules [12].

2.2.2.2. Interstitial crystalline solid solutions In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figs. 4 and 5). As in the case of substitutional crystalline solid solutions, the relative molecular size is a crucial criterion for classifying the solid solution type. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter [14]. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

2.2.2.3. Amorphous solid solutions In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Fig. 6). Using griseofulvin in citric acid, Chiou and Riegelman [16] were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

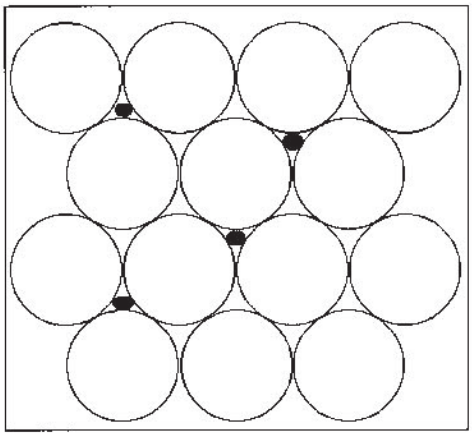

Fig. 4. Interstitial crystalline solid solution (reproduced with modifications from Ref. [13]).

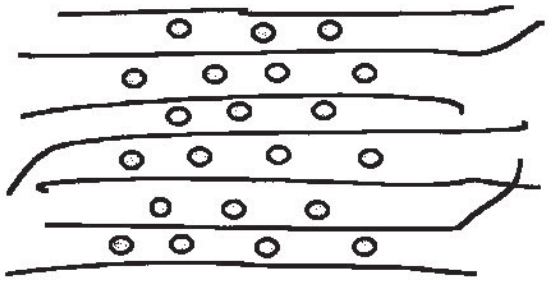

Fig. 5. Interstitial solid solutions of small molecules in the crystalline parts of a polymer (reproduced with modifications from Ref. [15]).

3. Formulation of solid solutions

In the early 1960s, Sekiguchi et al. reported that formulation of eutectic mixtures could lead to an improvement in the release rate and thereby the bioavailability of poorly soluble drugs. Eutectic combinations such as sulphathiazole/urea [9] and chloramphenicol/urea [17] served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier. Both preparations exhibited faster release and better bioavailability than conventional formulations. The explanation offered for this behaviour was that, after dissolution of the urea, a fine suspension of drug particles was exposed to the dissolution medium (or GI fluids) and that both the smaller particle size and better wettability of the drug particles in this suspension contributed to a faster dissolution rate.

The next development was the preparation of solid solutions by Levy [18] and Kanig [19]. In contrast to a eutectic mixture, the dispersed component in a solid solution is molecularly dispersed. In a very informative series of publications, Goldberg [10,11,20,21] discussed the theoretical and practical advantages of solid solutions over eutectic mixtures. The improvement in dissolution characteristics was at first attributed 100% to the reduction in particle size. Molecular dispersion represents the ultimate in particle size reduction [21], and after the carrier has dissolved, the drug is molecularly dispersed in the dissolution medium, i.e. is present in solution form. A further reason for the improvement in the dissolution rate is that the drug has no crystal structure in the solid solution [22]. Therefore, the energy normally required to break up the crystalline structure of the drug before it can dissolve is not a limitation to the release of the drug from a solid solution. After the solid solution has dissolved, the drug is present as a supersaturated solution. In some cases, the carrier may serve to inhibit precipitation of the drug from the supersaturated solution [23–25]. It has also been speculated that, if the drug does precipitate, it will precipitate out as a metastable polymorph with a high solubility compared to that of the most stable form [24,26]. A further way in which a solid solution could enhance dissolution is through improvement of the wettability of the drug [13]. Even carriers that are not surface active, e.g. urea and citric acid, can improve wetting characteristics. Of course, if carriers with surface activity such as cholic acid, bile salts [27], cholesterol esters [28] and lecithin [29] are used, the improvements in wetting can be much greater. Another way in which the carrier can influence the drug's dissolution properties is via direct solubilization or a cosolvent effect.

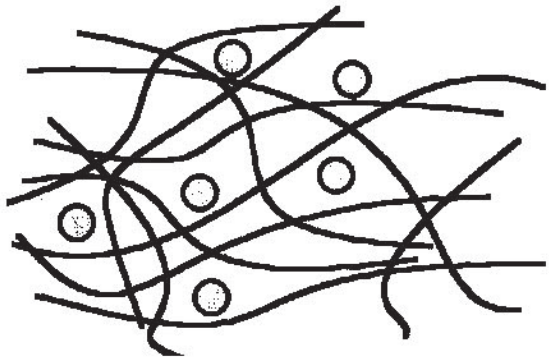

Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

The relationship between the release characteristics of the solid solution and a physical mixture of the two components varies with the drug/carrier combination. For example, the release rate from a solid solution of prednisolone in Cremophore® is almost identical with the release rate from a simple mixture of the two components [30]. A physical mixture of glyburide and PEG 6000 exhibited better solubility and faster dissolution than that of the pure drug [31]. The solubility of paracetamol is greater in urea than alone [10]. However, the solubility of sulfathiazole is adversely affected by mixing with urea [9]. In general, dissolution rates are compared among the pure drug, a physical mixture and the solid solution to assess the benefits of preparing a solid solution.

3.1. Methods for preparing solid solutions

3.1.1. Hot melt method

Sekiguchi and Obi [9] used a hot melt method to prepare simple eutectic mixtures. Sulphathiazole and urea were melted together at a temperature above the eutectic point and then cooled in an ice bath. The resultant solid eutectic was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. Whether or not a molecular dispersion can be achieved depends on the degree of supersaturation and rate of cooling attained in the process. In other words, the process has an effect on the resultant dispersion and can be varied to optimize the product. Sekiguchi et al. [17] and Chiou and Riegelman [16] accelerated the cooling rate by snap-cooling on stainless steel plates. Kanig [19] introduced the variation of spraying the hot melt onto a cold surface. A further

approach is to prepare the solid dispersion by injection molding, as demonstrated by Wacker et al. [32].

An important prerequisite to the manufacture of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important limitation to the hot melt method is the thermostability of the drug and the carrier. If too high a temperature is required, the drug may decompose or evaporate. Of course, oxidative reactions can be avoided by processing in an inert atmosphere or under vacuum, while evaporation can be avoided by processing in a closed system.

Because of these limitations, the solvent method became more popular in the 1970s and 1980s. In recent years, however, the hot melt method has enjoyed a renaissance in the form of hot melt extrusion. Extrusion of moistened powders has been well known in the pharmaceutical sciences for many years [33]. Hot melt extrusion is a very common way of processing plastics in the polymer industry, but Speiser [34,35] and Hüttenrach [36] were the first to adapt the process for pharmaceutical purposes. In recent years, this method has been applied to the manufacture of solid solutions. A scheme of a hot melt extruder is shown in Fig. 7. The drug/carrier mix is typically processed with a twin-screw extruder of the same type used in the polymer industry. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed.

A further alternative for processing thermolabile substances is by hot-spin-melting. Here, the drug and carrier are melted together over an extremely short time in a high speed mixer and, in the same apparatus, dispersed in air or an inert gas in a cooling tower. Some drugs that have been processed into solid dispersions using hot-spin-melting to

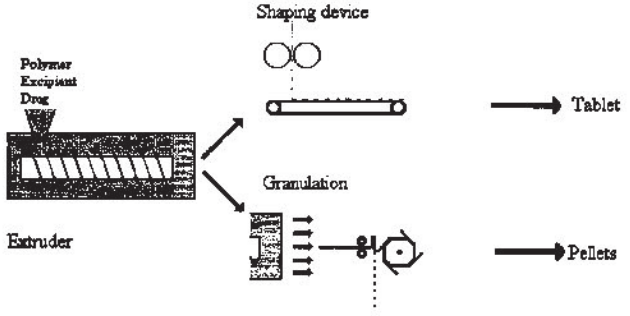

Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

date include testosterone [38], progesterone [39] and dienogest [40].

3.1.2. Solvent method

Until the advent of the solvent method, solid solutions were prepared exclusively by the melting method. Tachibani and Nakumara [41] were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone (PVP). The evaporation method was then taken up by Mayersohn and Gibaldi [42]. By dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent, they were able to achieve a solid dispersion. The release rate of griseofulvin from the solid dispersion was five to 11 times higher than that of micronized drug, depending on the drug/carrier ratio. Bates [43] introduced the term coprecipitates to describe solid dispersions that are manufactured by the solvent evaporation method. Although the term coprecipitate is strictly speaking inaccurate in this case, it is still widely used in this sense today. Simonelli et al. [44] used the term coprecipitate more correctly to describe a solid dispersion of sulphathiazole and PVP that had been precipitated from a solution in sodium chloride by the addition of hydrochloric acid. Solid dispersions and solutions that are manufactured by the solvent evaporation method should really be called coevaporates and not coprecipitates.

An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range 23–65°C [45,46]. The solvent can also be removed by freeze-drying [31] or by spray-drying [47]. It must be remembered that when an organic solvent is to be removed, small variations in the conditions used can lead to quite large changes in product performance. Another point to consider is the importance of thoroughly removing all of the solvent, since most of the organic solvents used have toxicity issues.

With the discovery of the solvent method, many of the problems associated with the melting method were solved. For example, it was then possible to form solid dispersions of thermolabile substances. Likewise, many polymers that could not be utilized for the melting method due to their high melting points (e.g. PVP) could be now considered as carrier possibilities. As a result, for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent-based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions.

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