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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:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = \frac{AD(C_\mathrm{s} - C)}{h}$$

where $\mathrm{d}C/\mathrm{d}t$ 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

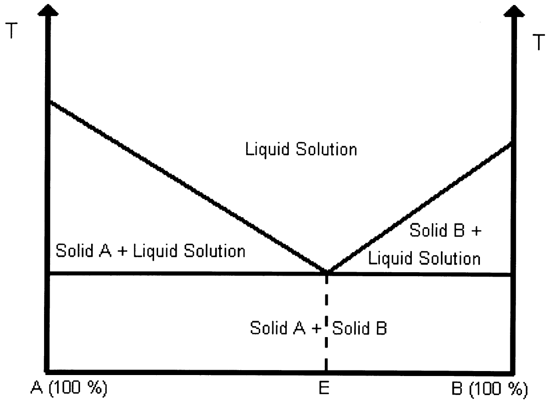

Fig. 1. Phase diagram for a eutectic system (reproduced with modifications from Ref. [8]).

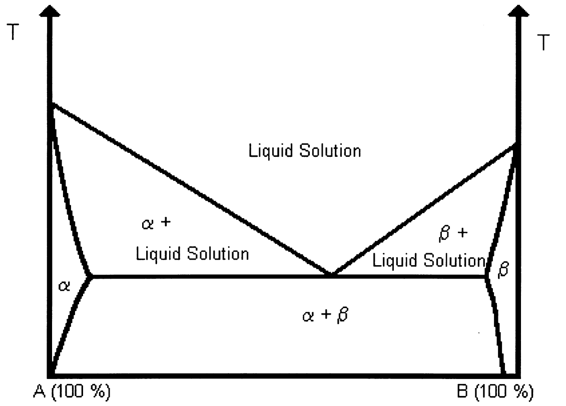

Fig. 2. Phase diagram for a discontinuous solid solution (reproduced with modifications from Ref. [8]).

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.

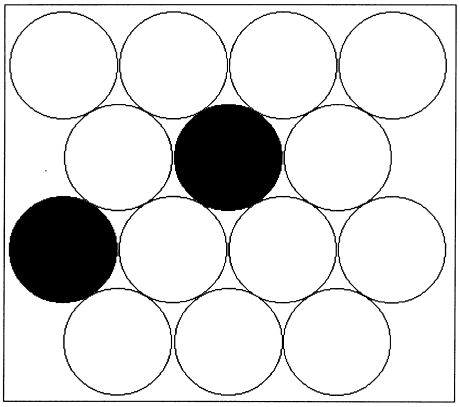

Fig. 3. Substitutional crystalline solid solution (reproduced with modifications from Ref. [13]).

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.

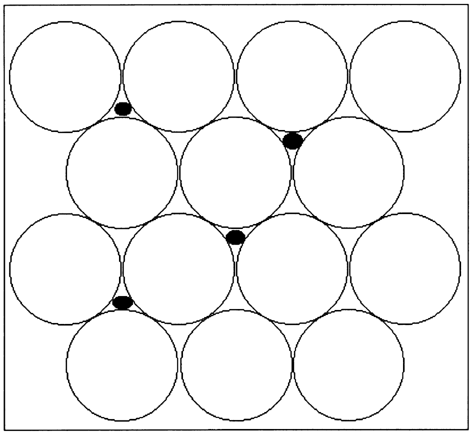

Fig. 4. Interstitial crystalline solid solution (reproduced with modifications from Ref. [13]).

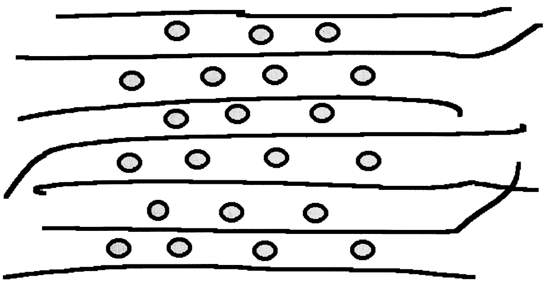

Fig. 5. Interstitial solid solutions of small molecules in the crystalline parts of a polymer (reproduced with modifications from Ref. [15]).

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.

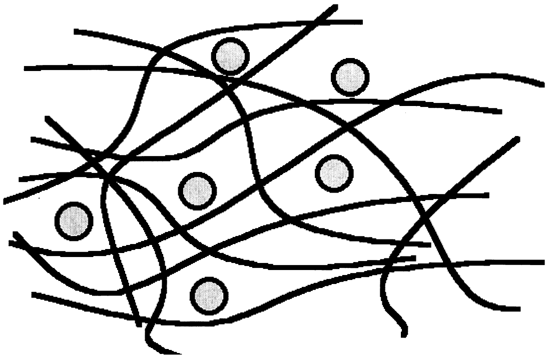

Fig. 6. Amorphous solid solution (reproduced with modifications from Ref. [15]).

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

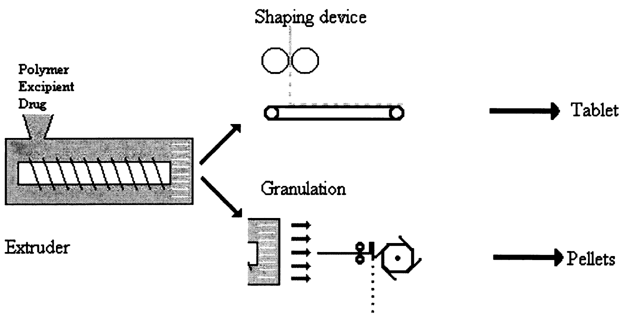

Fig. 7. Scheme of a hot melt extruder (reproduced with modifications from Ref. [37]).

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.

3.2. Carriers

3.2.1. Polyethylene glycol (PEG)

3.2.1.1. General characteristics of PEGs Polyethylene glycols (PEG) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200–300 000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500–20 000 are usually employed. As the MW increases, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800–1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20 000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but decreases with MW. A particular advantage of PEGs for the formation of solid dispersions is that they also have good solubility in many organic solvents. The melting point of the PEGs of interest lies under 65°C in every case (e.g. the m.p. of PEG 1000 is 30–40°C, the m.p. of PEG 4000 is 50–58°C and the m.p. of PEG 20 000 is 60–63°C) [48]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Additional attractive features of the PEGs include their ability to solubilize some compounds [31] and also to improve compound wettability. Even the dissolution rate of a relatively soluble drug like aspirin can be improved by formulating it as a solid dispersion in PEG 6000 [49].

3.2.1.2. Influence of the PEG chain length PEGs of MW 4000–6000 are the most frequently used for the manufacture of solid dispersions, because in this MW range the water solubility is still very high, but hygroscopy is not a problem and the melting points are already over 50°C. If a PEG with too low a MW is used, this can lead to a product with a sticky consistency that is difficult to formulate into a pharmaceutically acceptable product [50]. PEGs with higher MW have also been used with success: products containing PEG 8000 [51] and 10 000 [52] showed enhanced dissolution rates compared to the pure drug.

The importance of the carrier to performance of the solid dispersion was illustrated in a study of 14 different drugs formulated as solid dispersions in PEG 6000 [53]. In this study, Dubois and Ford showed that, when the drug is present in a low drug/carrier ratio ($<2\%$ in the case of phenylbutazone, up to 15% in the case of paracetamol), the release rate is dependent only on the carrier and not on the drug properties. Results with indomethacin showed similar behaviour. Further studies indicated that the release rate is inversely proportional to the chain length of the PEG [54]. Similar results were obtained with etoposide [50] and griseofulvin [16]. However, other studies revealed contradictory behaviour. For example, glyburide release from a solid dispersion in PEG 6000 was faster than from a similar dispersion in PEG 4000 [31]. Possible reasons for the better release from PEG 6000 are that the PEG 6000 was able to dissolve more of the drug than the PEG 4000, leading to a greater percentage drug in the molecularly dispersed form, and that the higher viscosity of the PEG 6000 hindered precipitation of the drug following dissolution of the carrier.

A comprehensive study of phenylbutazone/PEG solid dispersions indicated that the release is dependent on the PEG MW [54]. When the percentage of drug used was low (0.5–2%), the release followed the rank order PEG $1500 > 4000 > 6000 > 20\,000$, at percentages of 3 and 4% the rank order was PEG $1500 > 4000 > 20\,000 > 6000$ and at a 5% loading the order was $20\,000 > 4000 > 1500 > 6000$. Since the rank order could be clearly correlated with the crystallinity of the solid dispersion, the authors concluded that the release is dependent on the extent to which a molecular dispersion can be formed. On the other hand, contradictory results were obtained with chloramphenicol/PEG solid dispersions, for which the rank order of release was PEG $6000 > 4000 > 12\,000 > 20\,000$ [55]. In yet other cases, the MW of the PEG had no influence at all on the release rate. For example, Mura et al. [56] showed that 10% dispersions of naproxen in PEG 4000, 6000 and 20 000 all exhibited similar release.

3.2.1.3. Influence of the drug/PEG ratio The drug/carrier ratio in a solid dispersion is one of the main influences on the performance of a solid dispersion. If the percentage of the drug is too high, it will form small crystals within the dispersion rather than remaining molecularly dispersed. On the other hand, if the percentage of the carrier is very high, this can lead to the complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug. Lin and Cham [57] showed that solid dispersions of naproxen in PEG 6000 released drug faster when a 5 or 10% naproxen loading was used than when a 20, 30 or 50% loading was used. These results could be explained on the basis of X-ray diffraction results, which indicated that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline. However, the upper limit to the percentage carrier that can be employed is governed by the ability to subsequently formulate the solid dispersion into a dosage form of administrable size.

3.2.1.4. Drug/PEG systems Griseofulvin is probably the most studied drug with respect to dispersion in PEGs. Chiou and Riegelman [16] were able to achieve a noticeable increase in the release rate of griseofulvin from solid dispersions in PEG 4000, 6000 and 20 000. The fruit of research with PEG/griseofulvin combinations is the marketed product, Gris-PEG®. More recent studies with griseofulvin and PEGs have focussed on mixtures with various emulsifying agents. Sjökvist et al. [58] introduced small quantities of polysorbate 80, polyethylenedodecylether (Brij® 35), sodium dodecylsulphate (SLS) and dodecylamonium bromide into 10% w/w dispersions of griseofulvin in PEG 3000 and by doing so were able to achieve substantial increases in both the rate and extent of dissolution. Best results were obtained with SLS. Other combination systems, such as a griseofulvin/PEG 6000/talc system [47] could only achieve similar results to that of the two-component dispersion. However, the talc system had the advantages of being easier to process and being less tacky.

An increase in the release rate by formulation as a solid dispersion in PEG 4000 has been observed for many drugs, including oxazepam [59], piroxicam [60] zolpidem [61] and glyburide [31]. In some cases, in vivo data have verified the importance of the increase in release rate to the bioavailability of the drug in question. Arias et al. [62] were able to show that a doubling of the release rate in vitro could be translated into an increase in the diuretic effect of triamterene in rats. A good correlation between release data from solid dispersions of nifedipine in PEG 6000 and the elimination of the drug in urine was documented in human studies [63]. Similarly, a two-fold increase in the release rate of carbamazepine achieved by formulation as a solid dispersion in PEG 4000 and 6000 was translated into an increase in the bioavailability relative to a suspension of the drug and the marketed product, Tegretol® [46]. However, even better results could be achieved with a hydroxypropyl-β-cyclodextrin complex. Norfloxacin/PEG 6000 solid dispersions also produce a moderate increase in bioavailability [64]. Further drugs which exhibit elevated release rates when formulated as PEG solid dispersions include Sr33557, a new calcium antagonist [65], ketoprofen [66], oxazepam [67], nifedipine [68], phenytoin [69], ursodeoxycholic acid [70], fenofibrate [71] and prednisolone [30].

There have also been several studies with PEGs of higher MW. Perng et al. [51] achieved a ten-fold increase in the release rate of an experimental 5-lipoxygenase inhibitor with PEG 8000 using a hot melt method. Studies of coevaporates of ibuprofen with PEG 10 000, with the talc system and with mixtures of the two indicated that the mixture of the PEG with talc produced the best results [52].

3.2.1.5. Problems with PEGs In general, there are few toxicity concerns associated with the PEGs and they are approved for many purposes as excipients. The low molecular weight PEGs do, however, tend to show slightly greater toxicity than those of higher molecular weight [48]. In addition, a great number of drugs are compatible with the PEGs. A few cases have been observed in which the PEG proved to have stability problems during manufacture by the hot melt method. A reduction in the PEG chain length was observed for combinations with disulfiram, furosemide, chlorothiazide and chlorpropamide [53]. Another difficulty can lie in the subsequent formulation of the solid dispersion into an acceptable dosage form. If the dispersion is too soft it can be difficult if not impossible to manufacture a tablet dosage form. This is most likely to occur if a PEG with too low a MW is used or if the drug has a plasticizing effect on the PEG [50].

3.2.2. Polyvinylpyrrolidone (PVP)

3.2.2.1. General characteristics of PVP Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3 000 000. These can be classified according to the *K* value, which is calculated using Fikentscher's equation [72]. Table 2 provides an overview of the relationship between the *K* value and the approximate molecular weight of PVP.

The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (T_g) is high; for example, PVP K25 has a T_g of 155°C [73]. For this reason PVPs have only limited application for the preparation of solid dispersions by the hot melt method. Due to their good solubility in a wide variety of organic solvents, they are particularly suitable for the preparation of solid dispersions by the solvent method. Similarly to the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid [74].

3.2.2.2. Influence of the PVP chain length The chain length of the PVP has a very significant influence on the dissolution rate of the dispersed drug from the solid dispersion. The aqueous solubility of the PVPs becomes poorer with increasing chain length and a further disadvantage of the high MW PVPs is their much higher viscosity at a given concentration [72]. Studies with coevaporates of chloramphenicol and PVP revealed that the dissolution of chloramphenicol was slower when PVPs of higher MW were used as the carrier [55]. Similarly, the slower dissolution of indomethacin from PVP K90 compared to PVP K12 was attributed to the higher viscosity generated by PVP K90 in the diffusion boundary layer adjacent to the dissolving surface of the dispersion [24]. Other drugs for which release is known to be slower when incorporated in PVPs of higher MW include sulphathiazole [44] and phenytoin [69]. In the case of probucol, however, a somewhat different relationship was seen: here the rank order of release rate was PVP K30 > K25 > K90 [75]. In

Table 2
K values of PVP and the corresponding molecular weights [72]

K value	Approximate molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400000
90	1000000
120	3000000

general, though, the dependency of the release rate on MW is clearer for the PVPs than in the case of solid dispersions prepared with PEGs.

3.2.2.3. Drug/PVP ratio Similarly to PEG, solid dispersions prepared with high proportions of PVP tend to exhibit a higher drug solubility and release rate than those with high proportions of drug. For albendazole, for example, it has been shown that an increase in the %PVP in the dispersion leads to an increase in the release rate [76]. Doherty and York [77] studied the release behaviour of furosemide/PVP dispersions as a function of the degree of crystallinity of the preparation. When solid dispersions comprising 50% furosemide were prepared, crystalline regions could be detected by X-ray diffraction. In contrast, when the drug/carrier ratio was 2:3, the dispersion was amorphous. Dispersions containing crystalline areas exhibited biphasic release profiles, with the amorphous areas dissolving quickly and the crystalline areas more slowly. Similar behaviour was reported by Kearney et al. [45] for the experimental anti-inflammatory compound CI-987. When the carrier comprised 81% of the dispersion, no crystalline areas could be detected and the release rate of the compound was rapid. Interestingly, when the %carrier was further increased, the release rate became slower. In the case of piroxicam/PVP solid dispersions [78], the release rate increased with the %PVP up till a ratio of drug/carrier of 1:4, after which it fell again (at ratios of 1:5 and 1:6). These results were clarified with X-ray diffraction studies. Only the dispersion containing a 1:4 ratio was amorphous; at all other ratios semi-crystalline areas could be detected. In this case, the 1:4 ratio proved to be optimal for the formulation of piroxicam in PVP K30.

3.2.2.4. Drug/PVP systems Most studies of PVP solid dispersions reported in the literature have used PVPs of MW 2500–50 000 (K12 to K30). As in the case of PEGs, griseofulvin has been one of the most widely studied compounds. The first solid dispersions of griseofulvin in PVP were reported in 1966 by Mayersohn and Gibaldi [42]. Improved dissolution of the test compound from solid dispersions prepared with PVP K17 have been reported variously for sulphathiazole [44], hydrochlorothiazide [79], and piroxicam [80]. For a series of non-steroidal anti-inflammatory drugs (NSAIDs) including mefenamic acid, azapropazone, glafenin and flotafenin, it was shown that coevaporates prepared with PVP K25 improved the release and bioavailability of the drug more than those prepared with PEG 6000 [81]. Furthermore, it was shown in the same studies that the NSAIDs were less likely to cause ulceration in the GI tract when administered as a solid dispersion. In another study, the release rates from solid dispersions of etopiside in PEGs and PVPs were compared [50]. PVP K25 produced faster release than PEG 3400, 6000 or 8000. On the other hand, the release rate from PEG 3400 and 6000 was higher than from PVP K17. Using PVP K30 as the carrier, the release rate of the 5-lipoxygenase inhibitor SB 210661 [51], a weakly basic experimental compound, RS 8359 [82] and benidipine HCl [83] could all be improved. In the case of atenolol, the improvement in release rate using PVP K30 proved to be better than the release rate from other carriers tested [84].

3.2.2.5. Toxicity profile of PVP Polyvinylpyrrolidones found their first pharmaceutical application as plasma expanders in the 1940s. This role became less important with the advent of dextrans. However, PVPs are still widely used in the pharmaceutical sector as excipients. When given orally, they are regarded as not being toxic, partly because they have too high a MW to be absorbed from the GI tract. Reports of side effects are restricted to the formation of granulomas after intramuscular injection [72].

3.2.3. Polyvinylalcohol (PVA), crospovidone (PVP-CL), polvinylpyrrolidone-polyvinylacetate copolymer (PVP-PVA)

All three polymers belong to the polyvinyl group. Whereas polyvinylalcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. When solid dispersions of nifedipine were prepared with carrier mixtures consisting of nicotinamide and PVP, hydroxypropylmethylcellulose (HPMC) or PVA in a drug/nicotinamide/polymer ratio of 1:3:1, those prepared with PVA dissolved 20 times as fast as the drug alone [85]. However, the other carriers, HPMC and PVP, yielded even better results. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.5 [86]. Moneghini et al. [84] reported that in the case of atenolol, too high a PVA/PVP content could lead to a decrease in the release rate of the drug. This observation was attributed to high viscosity in the diffusion boundary layer adjacent to the dissolving surface. Similar results were subsequently reported for PVA/PVP coevaporates of carbamazepine [87]. In this case the optimal drug/carrier ratio was 1:4; when the proportion of carrier was either lower or higher, the increase in the release rate was not as dramatic. The fall-off at higher carrier ratios could be attributed to gel formation in this case. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.8 [88] in comparison with either the drug powder or a physical mixture of furosemide with crospovidone. The mechanism of the increase in the release rate of furosemide proved to be the presentation of the drug in the amorphous form in the dispersion, as shown by X-ray diffraction studies.

3.2.4. *Cellulose derivatives*

3.2.4.1. General characteristics of cellulose derivatives - Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by β-1,4-glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- (MC), hydroxypropyl- (HPC), hydroxypropylmethyl- (HPMC) and many other semi-synthetic celluloses. Since each glucose unit has three hydroxyl groups that can be derivatized, the average substitution grade (SG) cannot exceed three, unless of course the hydroxyl groups on the substituents themselves (e.g. in the case of HPMC) are also derivatized. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP).

3.2.4.2. Hydroxypropylmethylcellulose (HMPC) HPMCs are mixed ethers of cellulose, in which 16.5–30% of the hydroxyl groups are methylated and 4–32% are derivatized with hydroxypropyl groups. For example, Type 2910 has an average methoxy content of 29% and an hydroxypropyl content of 10%. The molecular weight of the HPMCs ranges from about 10 000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane [89].

Studies with albendazole, a poorly soluble weak base with incomplete bioavailability, showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC [90]. It was further demonstrated that HPMC was able to inhibit the recrystallization of the albendazole, and that a further improvement in release characteristics could be achieved when a carrier mixture consisting of HPMC and HPMCP was employed. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine [91] and benidipine [83]. In combination with nicotinamide as the carrier system, HPMCs produced the best increase in the release of nifedipine of the series PVP, PVA and HPMC [85].

3.2.4.3. Hydroxypropylcellulose (HPC) Hydroxypropylmethylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 40°C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H) [92]. Yuasa et al. [93] carried out extensive studies of the influence of the chain length and proportion of HPC in the solid dispersion on the release behaviour of flurbiprofen. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

3.2.4.4. Carboxymethylethylcellulose (CMEC) CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5–6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8 [94]. Likewise, the bioavailability of the test substance MFB-1041 could be substantially improved in beagles [95].

3.2.4.5. Hydroxypropylmethylcellulose phthalate (HPMCP) HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type-dependent. Their MWs range from 20 000 to 2 000 000 [96]. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a coevaporate of HPMCP [94]. In this case it was shown that griseofulvin was present in the dispersion in the amorphous form. Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug [95]. Furthermore, the oral bioavailability in beagles was almost 17 times better following administration of the drug in solid dispersion form. In studies of coevaporates of the poorly water soluble cytostatic drug HO-221, it was shown that, while at pH 1.2 the dispersion in HPMCP did not release the drug, at pH 6.5 it released the drug as well as dispersions in the pH-independent polymers PVP and PVP/PVA [86]. In this set of studies, the bioavailability of the various dispersions of HO-221 was assessed in beagles. The coevaporate in PVP/PVA led to an increase in bioavailability of 30–60%, whereas the coevaporate in HPMCP led to almost complete absorption of the drug. Since the intraduodenal application of the PVP/PVA coevaporate also led to virtually complete absorption, it was concluded that the incomplete absorption from PVP/PVA coevaporate after oral administration was due to precipitation of the drug following rapid dissolution and formation of a supersaturated solution in the gastric juice. These studies demonstrated the potential advantage of using a gastric juice resistant polymer as carriers for poorly soluble drugs.

3.2.5. *Polyacrylates and polymethacrylates*

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mostly used as coatings to modify the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit® [97]. Among the Eudragits, Eudragit® E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pHs, while Eudragit® L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a coevaporate with Eudragit® E, the rate of dissolution was much higher than from the pure drug powder [83]. On the other hand, Eudragit® L has been successfully used to increase the dissolution of griseofulvin and spironolactone at a pH value of 6.8 [94].

3.2.6. Urea

Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 in 1 and it also exhibits good solubility in many common organic solvents. In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea [9]. Similarly, Goldberg et al. [21] reported faster dissolution rates of chloramphenicol when prepared with urea as the carrier. Although urea is not often used as a carrier these days, it has been recently shown that the dissolution rate of the poorly soluble compound ofloxacin can be improved by more than three-fold by incorporating it in a coevaporate with urea [98]. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 [70]. A two-fold increase in the dissolution rate of phenytoin has also been achieved with urea; however, in this case PEG 6000 was far more efficient [69].

3.2.7. Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare coevaporates. Despite these drawbacks, several attempts to prepare solid dispersions using sugars and their derivatives have been reported. Mannitol, which has a melting point of 165–168°C and decomposes only above 250°C, can be employed in some cases to prepare dispersions by the hot melt method. Improved release characteristics have been reported for sorbitol dispersions of several compounds, including nitrofurantoin [63], prednisolone [30], ofloxacin [98] and ursodeoxycholic acid [70]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions (the two sugars are isomers) [63]. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol [30]. Chitosan, a derivative of the polysaccharide chitin which is formed by deacetylation at the N position, has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder [99]. In these studies, the performance of the coevaporates was compared to that of physical dispersions prepared by co-grinding. The coevaporates produced faster release rates than co-ground mixtures.

3.2.8. Emulsifiers

The release behaviour of many drugs can also be improved through the use of emulsifying agents. Two mechanisms are possible here: improvement of wetting characteristics and solubilization of the drug. Owing to their potential toxicity problems, such as damage to mucosal surfaces, they are usually used in combination with another carrier. For example, the release of naproxen from solid dispersions in PEG 4000, 6000 and 20 000 could be further enhanced when either sodium lauryl sulphate (SLS) or Tween® 80 (a polyethylene sorbitan fatty acid ester) was added to the system [56]. Inclusion of alkali dodecylsulphate surfactants in carrier systems can lead to conversion of a solid dispersion to a solid solution. Melts of griseofulvin and PEG 6000 normally contain crystalline areas; in the presence of SLS a solid solution is formed [100].

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [27] demonstrated the ability of bile salts such as cholic acid, deoxycholic acid and lithocholic acid to improve not only the release but also the sedative effects of reserpine when given as a coevaporate. Likewise, the release of hydrocortisone can be enhanced by formulation as a solid dispersion in cholesterol and various cholesterol esters [28]. In recent times, however, there has been little activity in this area.

3.2.9. Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin [16,20]. In more recent years, no further studies with these two acids have been published. Melts of nifedipine with nicotinamide, the amide of nicotinic acid, exhibited about a six-fold increase in the dissolution rate compared to the drug powder but even better results were obtained with PEG 6000 as the carrier [68]. By combining the nicotinamide with a polymeric carrier such as HPMC or PVP, the release of nifedipine could be further greatly improved [85]. The best results, a 20-fold increase, were obtained with a dispersion of nifedipine, nicotinamide and HPMC in a ratio of 1:3:1.

3.2.10. Other carriers

Many other substances have been tested as carriers for solid dispersions. A hydrolysis product of collagen, Gelita®

Collagel, was reported to improve the release rate of oxazepam by a factor of six when prepared as a solid dispersion by spray drying [67]. Even after tabletting, the solid dispersion displayed better release characteristics than the physical mixture or the drug powder alone [101]. Other materials tested include pentaerythritol [16] and phospholipids [46].

3.3. Characterization of solid dispersions

The methods that have been used to characterize solid dispersions are summarized in Table 3. Among these, the most important methods are thermoanalytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to delineate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.

Thermoanalytical methods include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC [15].

The principle behind X-ray diffraction is that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5–10% cannot generally be detected with X-ray diffraction.

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not [22].

Release rate experiments cannot be used on a stand-alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve the dissolution characteristics of the drug in question, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixtures of the drug and carrier can help to indicate the mechanism by which the carrier improves dissolution: via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution.

Table 3
Methods for the characterization of solid dispersions

Dissolution testing
Thermoanalytical methods: differential thermoanalysis and hot stage microscopy
Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
X-Ray diffraction
Spectroscopic methods, e.g. IR spectroscopy
Microscopic methods including polarization microscopy and scanning electron microscopy

4. Summary and future perspectives

Experience with solid dispersions over the last 20–30 years indicates that this is a very fruitful approach to improving the release rate and oral bioavailability of poorly soluble drugs. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the dispersion, and the amount of carrier needed to facilitate the required increase in the release rate. When a high carrier/drug ratio must be used, the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or capsule that can be easily swallowed. The higher the unit dose of the drug, the more likely this problem is to occur. Another aspect that must be considered is the correlation between in vitro and in vivo results. Dispersions with a rapid in vitro release rate may fail to improve the oral bioavailability if the in vitro test conditions do not adequately simulate the gastrointestinal conditions, or if there is some specific interaction between the carrier and a component of the GI fluids or a co-ingested foodstuff. Despite these concerns, several products containing solid dispersions are already on the market and the number is expected to increase dramatically in the next years.

Two trends strongly favour an increasing role for solid dispersions in pharmaceutical development: the increasing number of drug candidates which are poorly soluble, and the substantial improvements in the manufacturing methods for solid dispersions that have been made in the last few years. The application of hot melt extrusion to the production of solid dispersions is a particularly important breakthrough for scale-up of solid dispersion manufacture. Another advantage of solid dispersions over other approaches is that many of the carriers that can be applied are already extensively used in the pharmaceutical industry as excipients, so additional toxicity studies above and beyond what is required for the drug itself should not be required. The possibility of combining several carriers to produce an optimized product further extends the range of possibilities for formulation. Yet another advantage of solid dispersions over other approaches is that the increases in solubility and release rate that can be achieved are often much, much greater (up to orders of magnitude). This could potentially lead to an increase in bioavailability that is so great that the dose administered could be lowered.

Aspects that still need to be addressed in the next years include further improvements in manufacturing on a large scale, and better predictions of whether a particular drug/carrier combination will lead to a true solid solution or to a partly crystalline dispersion as well as whether the dispersion will remain physically stable during further processing and storage. Last but not least, although this article has been devoted to the use of solid dispersions for the improvement of the release rate and oral bioavailability, by judicious choice of the carrier it is also possible to delay or slow down the release pattern of a drug by formulating it as a solid dispersion. The availability of a wide variety of polymers that are themselves poorly soluble or which swell under aqueous conditions suggests that solid dispersions have tremendous potential in the area of controlled release dosage forms.

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