Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs

Teófilo Vasconcelos[1,2], Bruno Sarmento[1] and Paulo Costa[1]

[1] Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Porto, Rua Aníbal Cunha 164, 4050-047 Porto, Portugal
[2] Laboratory of Pharmaceutical Development, Laboratórios BIAL, À Avenida da Siderurgia Nacional, 4745-457, S. Mamede do Coronado, Portugal

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, for example, melting and solvent evaporation. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. In this review, it is intended to discuss the recent advances related on the area of solid dispersions.

Introduction

Oral drug delivery is the simplest and easiest way of administering drugs [1,2]. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration [3,4]. In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration [4,5], which can detract from the drug's inherent efficacy [6–8]. Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window [9,10]. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability [9,11]. Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs [6,12,13].

Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [9,12,14–16]. Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.

Corresponding author: Vasconcelos, T. (teofilo.vasconcelos@bial.com)

Solid dispersions

First generation solid dispersions

The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water soluble drugs [17]. In the same decade, several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole [18] and chloramphenicol [17] using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability. Later, Levy [19] and Kaning [20] developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures [14]. The observed Improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of drug [21]. These solid dispersions, which could be designed as first generation solid dispersions

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.09.005

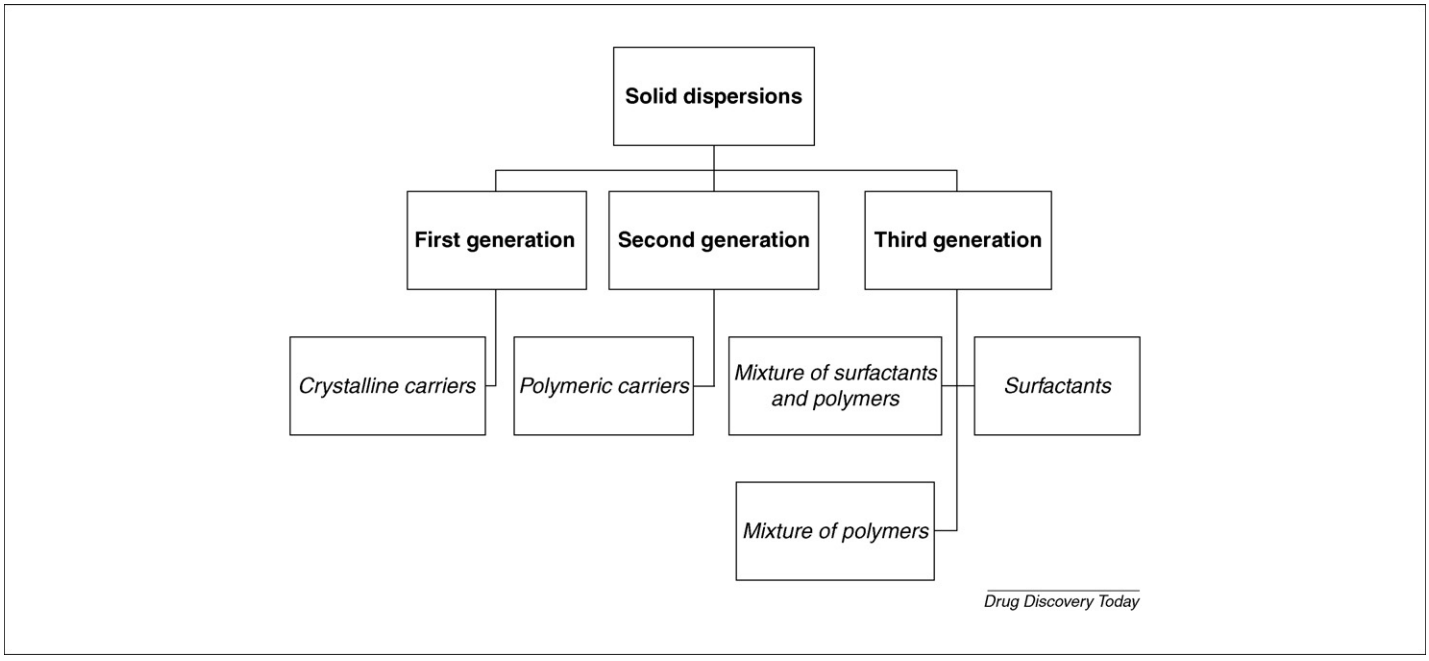

FIGURE 1

The classification of solid dispersions.

(Figure 1), were prepared using crystalline carriers. Crystalline carriers include urea [17,18,21] and sugars [20], which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

Second generation solid dispersions

In the late sixties [22,23] it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable [6,22,24]. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers [25].

Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP) [5,22,26–31], polyethyleneglycols (PEG) [16,24,32–34] and polymethacrylates [35,36]. Natural product-based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC) [13,37,38], ethylcellulose [11,13,39] or hydroxypropylcellulose [12,40] or starch derivates, like cyclodextrins [41,42].

Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both [5,27].

In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them [5]. In these systems, the drug and carrier interaction energy is extremely high, resulting in a really true solution [14]. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved [5,43]. This type of amorphous solid dispersion is homogeneous on a molecular level. Therefore, only one phase is present [5].

Amorphous solid suspensions occur when the drug has a limited carrier solubility or an extremely high melting point [44]. Drugs with a high melting point are candidates for producing an amorphous solid suspension. Molecularly, the obtained dispersion does not have a homogeneous structure, but is composed of two phases. Small drug particles, when dispersed in polymeric carriers, are able to provide an amorphous final product [5,21].

When a drug is both dissolved and suspended in the carrier, a heterogeneous structure is obtained with mixed properties of amorphous solid solutions and amorphous solid suspensions [5].

In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier [24,25,40]. These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers [45,46]. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile [13,14].

Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization.

The use of surfactants such as inulin [5], inutec SP1 [43], compritol 888 ATO [47], gelucire 44/14 [45,48,49] and poloxamer 407 [15] as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of this solid dispersion was 10-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically stable for at least 16 months [50]. HPMC was also associated with poloxamer and polyoxyethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion [37]. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles [7].

Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches [15,31,51].

Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its *in vivo* conversion into acidic or basic forms [52,53]. Moreover, these type of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE [4].

Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do [52,53]. Milling or micronization for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area [7,54]. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 μm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine [7,53,55] and, consequently, to improve the bioavailability [52,53,56]. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle [53,55].

Solid dispersions disadvantages

Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization [28,43,48,57]. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization [57,58]. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate [43,59]. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during *in vivo* performance [28].

Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing. Strategies to overcome the manufacturing process drawbacks will be discussed later.

The advantageous properties of solid dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability [60].

Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers [14]. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [14,61].

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions [53]. It was observed that even carriers without any surface activity, such as urea [17] improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [7,14,62]. Recently, the inclusion of surfactants [43,63] in the third generation solid dispersions reinforced the importance of this property.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity [64]. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate [60]. The increased porosity of solid dispersion particles also hastens the drug release profile [60,64].

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [28,30]. The enhancement of

drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [65]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form [14,43,53].

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them [6].

Strategies to avoid drug recrystallization

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization.

Molecular mobility is a key factor governing the stability of amorphous phases [66], because even at very high viscosity, below the glass transition temperature (T_g), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevant time scales [67,68]. Furthermore, it was postulated that crystallization above T_g would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the appropriate conformation, and by the mobility, because this was related to the number of collisions per unit time [66,69].

Several experiments have been conducted to understand the stabilization of solid dispersions. Recent studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transition beta-relaxation as well as alpha-relaxation [70], which may lead to nucleation and crystal growth [68]. Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as stated by Bhugra *et al.* [71]. Solid dispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable [66].

Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing the T_g of the miscible mixture, thereby reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs [65,67]. For a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug [57,72]. For complete miscibility, interactions between the two components are required. It is recognized that the majority of drugs contain hydrogen-bonding sites [68], consequently, several studies have shown the formation of ion–dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the disruption of the hydrogen bonding pattern characteristic to the drug crystalline structure [65]. These lead to a higher miscibility and physical stability of the solid dispersions [6,72,73]. Specific drug polymer interactions were observed by Teberekidis *et al.* [74], showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions.

Other studies have shown stabilization in systems where hydrogen-bonding interactions are not possible, because of the chemistry of the system [75]. Vippagunta *et al.* [6] concluded that fenofibrate does not exhibit specific interactions with PEG, independent of the number of hydrogen bonds donating groups presented [6]. The same conclusion was achieved by Weuts *et al.* [76] in the preparation of solid dispersions of loperamide with PVP K30 and PVP VA64, in which, hydrogen bonds were no absolute condition to avoid crystallization.

Konno *et al.* [38] determined the ability of three different polymers, PVP, HPMC and hydroxypropylmethylcellulose acetate succinate to stabilize amorphous felodipine, against crystallization. The three polymers inhibited crystallization of amorphous felodipine by reducing the nucleation rate [38]. It was speculated that these polymers affect nucleation kinetics by increasing their kinetic barrier to nucleation, proportional to the polymer concentration and independent of the polymer physiochemical properties [38].

The strategies to stabilize the solid dispersions against recrystallization strongly depend on the drug properties and a combination of different approaches appears to be the best strategy to overcome this drawback. Third generation solid dispersions intend to connect several strategies to overcome the drug recrystallization, which has been the major barrier to the solid dispersions marketing success.

Manufacturing processes

Melting and solvent evaporation methods are the two major processes of preparing solid dispersions [25,28,37,43] (Figure 2).

Melting method

Sekiguchi *et al.* [18] were the first to use a melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drug's incorporation [27]. A common adaptation to the melting phase consists of suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, reducing, therefore, the process temperature [6,45,47].

To cool and solidify the melted mixture, several processes such as ice bath agitation [17,28], stainless steel thin layer spreading followed by a cold draught [23], solidification on petri dishes at room temperature inside a dessicator [47,77], spreading on plates placed over dry ice [78], immersion in liquid nitrogen [33] or stored in a dessicator [6,79] were used. After cooling, the mixture must be pulverized regarding its handling [77,79].

However, the use of high temperatures, and the fact that several drugs can be degraded by the melting process, can be a limitation of this method [52]. The incomplete miscibility between drug and carrier that may occur, because of the high viscosity of a polymeric carrier in the molten state, is another limitation of this process [65]. To avoid the melting method limitations, several modifications, like hot-stage extrusion [7,43,80], Meltrex^{TM} [81] or melt agglomeration [82,83] were introduced to the original method.

Hot-stage extrusion consists of the extrusion, at high rotational speed, of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is

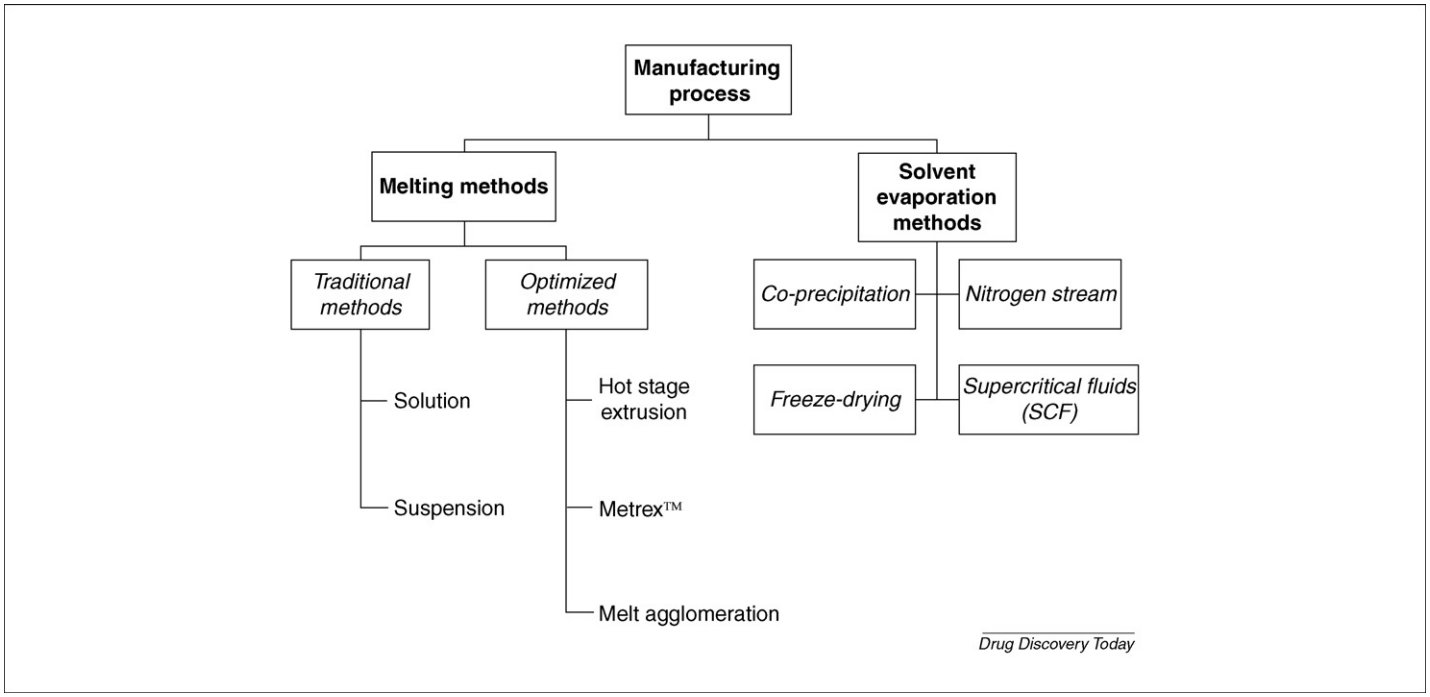

FIGURE 2

Manufacturing processes used to produce solid dispersions.

then collected after cooling at room temperature and milled [7,43,80]. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer [39,84], which broadens the application of hot-stage extrusion to thermally labile compounds [39]. Solid dispersions of *para*-amino salicylic acid/ethylcellulose [39], itraconazole/PVP [80] and itraconazole/ethylcellulose [84] were successfully prepared by this technique. Moreover, it was observed that solid dispersions of itraconazole/inutec SP1 prepared by hot-stage extrusion presented itraconazole in a fully glassy state, whereas it was only partially glassy in solid dispersions prepared by spray drying [43].

Meltrex™ is a patented solid dispersion manufacturing process, also on the basis of the melting process. The crucial elements in the Meltrex™ technology is the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range [81]. This process permits a reduced residence time of the drug in the extruder, allowing a continuous mass flow and avoiding thermal stress to the drug and excipients. Additionally, it is possible that the application of this technique to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture [81].

Melt agglomeration allows the preparation of solid dispersions in conventional high shear mixers. It is made by adding the molten carrier containing the drug to the heated excipients [82,83], by adding the molten carrier to a heated mixture of drug and excipients [85], or by heating a mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier [83]. It is also possible to produce stable solid dispersions by melt agglomeration in a rotary processor [25].

Solvent evaporation method

The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated [29,30,41]. In this method, the thermal decomposition of drugs or carriers can be prevented, since organic solvent evaporation occurs at low temperature [37].

A basic process of preparing solid dispersions of this type consists of dissolving the drug and the polymeric carrier in a common solvent, such as ethanol [31,53,55], chloroform [15,86], or a mixture of ethanol and dichloromethane [40]. Normally, the resulting films are pulverized and milled [12,26,30,31]. The use of the carriers partially suspended, instead of dissolved, was also reported in the preparation of a solid dispersion of indometacin, in which the drug and ethylcellulose were dissolved in ethanol and HPMC was suspended [13].

Differences in solvent evaporation processes are related to the solvent evaporation procedure, which usually include vacuum drying [26,31,59], heating of the mixture on a hot plate [11], slow evaporation of the solvent at low temperature [30,31], the use of a rotary evaporator [35], a stream of nitrogen [16], spray-drying [28,41,43,76], freeze-drying [5,27] and the use of supercritical fluids (SCF) [37].

Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving [43,48,87] or suspending [43,48] the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent [43,48,76]. Van Drooge *et al.* [5] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

The basic freeze-drying process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid

nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized [5,27].

The use of SCF, substances existing as a single fluid phase above their critical temperature and critical pressure, was shown to be efficient in obtaining solid dispersions [37,55,88]. It ensured a very fine dispersion of the hydrophobic drug in the hydrophilic carrier [41]. Carbon dioxide (CO_2) is the most commonly used SCF because is chemically inert, non-toxic and non-flammable [15]. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel [37]. The use of processes using SCF reduces particle size, residual solvent content, without any degradation, and often results in high yield [15,37,88].

Another common process is the co-precipitation method, in which a non-solvent is added dropwise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form microparticles. At the end, the resulted microparticle suspension is filtered and dried [36].

Spin-coated films is a new process to prepare solid dispersions by the solvent evaporation method, which consists of dissolving drug and carrier in a common solvent that is dropped onto a clean substrate highly spinned [38]. Solvent is evaporated during spinning. This process is indicated to moisture sensitive drugs since it is performed under dry conditions [38].

The use of organic solvents, the high preparation cost and the difficulties in completely removing the solvent are some of the disadvantages associated with solvent evaporation methods [7,37]. Moreover, it is also possible that slight alterations in the conditions used for solvent evaporation may lead to large changes in product performance [65].

Conclusion

Most of the promising NCEs are poorly water soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drugs' poor water solubility. Third generation solid dispersions can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. Moreover, new, optimized manufacturing techniques that are easily scalable are also coming out of academic and industrial research.

References

1 Youn, Y.S. *et al.* (2006) Improved intestinal delivery of salmon calcitonin by Lys18-amine specific PEGylation: Stability, permeability, pharmacokinetic behavior and *in vivo* hypocalcemic efficacy. *J. Contr. Release* 114, 334–342

2 Sugawara, M. *et al.* (2005) The use of an *in vitro* dissolution and absorption system to evaluate oral absorption of two weak bases in pH-independent controlled-release formulations. *Eur. J. Pharm. Sci.* 26, 1–8

3 Ikegami, K. *et al.* (2006) Bioavailability and *in vivo* release behavior of controlled-release multiple-unit theophylline dosage forms in beagle dogs, cynomolgus monkeys, and göttingen minipigs. *J. Pharm. Sci.* 95, 1888–1895

4 Charman, S.A. and Charman, W.N. (2003) Oral modified-release delivery systems. In *Modified-Release Drug Delivery Technology* (Rathbone, M.J. *et al.* eds), pp. 1–10, Marcel Dekker

5 van Drooge, D.J. *et al.* (2006) Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm.* 310, 220–229

6 Vippagunta, S.R. *et al.* (2006) Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. *J. Pharm. Sci.* 96, 294–304

7 Pouton, C.W. (2006) Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. *Eur. J. Pharm. Sci.* 29, 278–287

8 Bogdanova, S. *et al.* (2005) Interactions of poly(vinylpyrrolidone) with ibuprofen and naproxen: experimental and modeling studies. *Pharm. Res.* 22, 806–815

9 Streubel, A. *et al.* (2006) Drug delivery to the upper small intestine window using gastroretentive technologies. *Curr. Opin. Pharmacol.* 6, 501–508

10 Gardner, D. *et al.* (1997) The intelisite capsule: a new easy to use approach for assessing regional drug absortion from gastrointestinal tract. *Pharm. Tech. Eur.* 9, 46–53

11 Desai, J. *et al.* (2006) Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. *Int J Pharm* 308, 115–123

12 Tanaka, N. *et al.* (2006) Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): *In vivo* evaluation. *J. Contr. Release* 112, 51–56

13 Ohara, T. *et al.* (2005) Dissolution mechanism of poorly water-soluble drug from extended release solid dispersion system with ethylcellulose and hydroxypropylmethylcellulose. *Int. J. Pharm.* 302, 95–102

14 Leuner, C. and Dressman, J. (2000) Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 50, 47–60

15 Majerik, V. *et al.* (2007) Bioavailability enhancement of an active substance by supercritical antisolvent precipitation. *J. Supercrit. Fluids* 40, 101–110

16 Prabhu, S. *et al.* (2005) Novel lipid-based formulations enhancing the *in vitro* dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. *Int. J. Pharm.* 301, 209–216

17 Sekiguchi, K. and Obi, N. (1964) Studies on Absorption of Eutectic Mixture. Ii. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. *Chem. Pharm. Bull (Tokyo)* 12, 134–144

18 Sekiguchi, K. and Obi, N. (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.* 9, 866–872

19 Levy, G. (1963) Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. *Am. J. Pharm. Sci. Support Public Health* 135, 78–92

20 Kanig, J.L. (1964) Properties of Fused Mannitol in Compressed Tablets. *J. Pharm. Sci.* 53, 188–192

21 Goldberg, A.H. *et al.* (1966) Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol–urea system. *J. Pharm. Sci.* 55, 581–583

22 Simonelli, A.P. *et al.* (1969) Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. *J. Pharm. Sci.* 58, 538–549

23 Chiou, W.L. and Riegelman, S. (1969) Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.* 58, 1505–1510

24 Urbanetz, N.A. (2006) Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur. J. Pharm. Sci.* 28, 67–76

25 Vilhelmsen, T. *et al.* (2005) Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharm.* 303, 132–142

26 Karavas, E. *et al.* (2006) Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. *Eur. J. Pharm. Biopharm.* 64, 115–126

27 Drooge, D.J.V. *et al.* (2006) Characterization of the Mode of Incorporation of Lipophilic Compounds in Solid Dispersions at the Nanoscale Using Fluorescence Resonance Energy Transfer (FRET). *Macromol. Rapid Commun.* 27, 1149–1155

28 Pokharkar, V.B. *et al.* (2006) Development, characterization and stabilization of amorphous form of a low T_g drug. *Powder Technol.* 167, 20–25

29 Hasegawa, S. *et al.* (2005) Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. *Int. J. Pharm.* 302, 103–112

30 Lloyd, G.R. *et al.* (1999) A calorimetric investigation into the interaction between paracetamol and polyethlene glycol 4000 in physical mixes and solid dispersions. *Eur. J. Pharm. Biopharm.* 48, 59–65

31 Yoshihashi, Y. *et al.* (2006) Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry. *J. Therm. Anal. Calorim.* 85, 689–692

32 Guyot, M. *et al.* (1995) Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. *Int. J. Pharm.* 123, 53–63

33 Yao, W.-W. *et al.* (2005) Thermodynamic properties for the system of silybin and poly(ethylene glycol) 6000. *Thermochim. Acta* 437, 17–20

34 Chiou, W.L. and Riegelman, S. (1970) Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethylene glycol 6000. *J. Pharm. Sci.* 59, 937–942

35 Ceballos, A. *et al.* (2005) Influence of formulation and process variables on *in vitro* release of theophylline from directly-compressed Eudragit matrix tablets. *Il Farmaco* 60, 913–918

36 Huang, J. *et al.* (2006) Nifedipine solid dispersion in microparticles of ammonio methacrylate copolymer and ethylcellulose binary blend for controlled drug delivery: Effect of drug loading on release kinetics. *Int. J. Pharm.* 319, 44–54

37 Won, D.-H. *et al.* (2005) Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. *Int. J. Pharm.* 301, 199–208

38 Konno, H. and Taylor, L.S. (2006) Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. *J. Pharm. Sci.* 95, 2692–2705

39 Verreck, G. *et al.* (2006) Hot stage extrusion of p-amino salicylic acid with EC using CO_2 as a temporary plasticizer. *Int. J. Pharm.* 327, 45–50

40 Tanaka, N. *et al.* (2005) Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine. *J. Contr. Release* 108, 386–395

41 Rodier, E. *et al.* (2005) A three step supercritical process to improve the dissolution rate of Eflucimibe. *Eur. J. Pharm. Sci.* 26, 184–193

42 Garcia-Zubiri, I.X. *et al.* (2006) Thermal stability of solid dispersions of naphthalene derivatives with [beta]-cyclodextrin and [beta]-cyclodextrin polymers. *Thermochim. Acta* 444, 57–64

43 Van den Mooter, G. *et al.* (2006) Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. *Int. J. Pharm.* 316, 1–6

44 Chiou, W.L. and Riegelman, S. (1971) Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 60, 1281–1302

45 Karata, A. *et al.* (2005) Improved solubility and dissolution rate of piroxicam using gelucire 44/14 and labrasol. *Il Farmaco* 60, 777–782

46 Damian, F. *et al.* (2000) Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. *Eur. J. Pharm. Sci.* 10, 311–322

47 Li, F.-Q. *et al.* (2006) *In vitro* controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets. *Int. J. Pharm.* 324, 152–157

48 Chauhan, B. *et al.* (2005) Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur. J. Pharm. Sci.* 26, 219–230

49 Yuksel, N. *et al.* (2003) Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: *in vitro* and *in vivo* evaluation. *Eur. J. Pharm. Biopharm.* 56, 453–459

50 Dannenfelser, R.M. *et al.* (2004) Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. *J. Pharm. Sci.* 93, 1165–1175

51 Cutler, L. *et al.* (2006) Development of a P-glycoprotein knockout model in rodents to define species differences in its functional effect at the blood-brain barrier. *J. Pharm. Sci.* 95, 1944–1953

52 Serajuddin, A.T. (1999) Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* 88, 1058–1066

53 Karavas, E. *et al.* (2006) Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *Eur. J. Pharm. Biopharm.* 63, 103–114

54 Craig, D.Q.M. (2002) The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* 231, 131–144

55 Muhrer, G. *et al.* (2006) Use of compressed gas precipitation to enhance the dissolution behavior of a poorly water-soluble drug: Generation of drug microparticles and drug-polymer solid dispersions. *Int. J. Pharm.* 308, 69–83

56 Rasenack, N. and Muller, B.W. (2004) Micron-size drug particles: common and novel micronization techniques. *Pharm. Dev. Technol.* 9, 1–13

57 Vasanthavada, M. *et al.* (2004) Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. *Pharm. Res.* 21, 1598–1606

58 Johari, G.P. *et al.* (2005) Dielectric studies of molecular motions in amorphous solid and ultraviscous acetaminophen. *J. Pharm. Sci.* 94, 2207–2223

59 Wang, X. *et al.* (2005) Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole. *Int. J. Pharm.* 303, 54–61

60 Ghaderi, R. *et al.* (1999) Preparation of biodegradable microparticles using solution-enhanced dispersion by supercritical fluids (SEDS). *Pharm. Res.* 16, 676–681

61 Bikiaris, D. *et al.* (2005) Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques. *Thermochim. Acta* 439, 58–67

62 Kang, B.K. *et al.* (2004) Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int. J. Pharm.* 274, 65–73

63 Ghebremeskel, A.N. *et al.* (2007) Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer-surfactant combinations using solubility parameters and testing the processability. *Int. J. Pharm.* 328, 119–129

64 Vasconcelos, T. and Costa, P. (2007) Development of a rapid dissolving ibuprofen solid dispersion. In *PSWC – Pharmaceutical Sciences Wolrd Conference*

65 Taylor, L.S. and Zografi, G. (1997) Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* 14, 1691–1698

66 Zhou, D. *et al.* (2007) A calorimetric investigation of thermodynamic and molecular mobility contributions to the physical stability of two pharmaceutical glasses. *J. Pharm. Sci.* 96, 71–83

67 Yoshioka, M. *et al.* (1994) Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J. Pharm. Sci.* 83, 1700–1705

68 Gunawan, L. *et al.* (2006) Structural relaxation of acetaminophen glass. *Pharm. Res.* 23, 967–979

69 Zhou, D. *et al.* (2002) Physical stability of amorphous pharmaceuticals: Importance of configurational thermodynamic quantities and molecular mobility. *J. Pharm. Sci.* 91, 1863–1872

70 Shmeis, R.A. *et al.* (2004) A mechanistic investigation of an amorphous pharmaceutical and its solid dispersions, part I: a comparative analysis by thermally stimulated depolarization current and differential scanning calorimetry. *Pharm. Res.* 21, 2025–2030

71 Bhugra, C. *et al.* (2007) Prediction of the onset of crystallization of amorphous sucrose below the calorimetric glass transition temperature from correlations with mobility. *J. Pharm. Sci.* 96, 1258–1269

72 Vasanthavada, M. *et al.* (2005) Phase behavior of amorphous molecular dispersions II: Role of hydrogen bonding in solid solubility and phase separation kinetics. *Pharm. Res.* 22, 440–448

73 Schachter, D.M. *et al.* (2004) Solid state NMR perspective of drug-polymer solid solutions: a model system based on poly(ethylene oxide). *Int. J. Pharm.* 281, 89–101

74 Teberekidis, V.I. and Sigalas, M.P. (2006) Theoretical study of hydrogen bond interactions of felodipine with polyvinylpyrrolidone and polyethyleneglycol. *THEOCHEM* 803, 29–38

75 Van den Mooter, G. *et al.* (2001) Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* 12, 261–269

76 Weuts, I. *et al.* (2005) Salt formation in solid dispersions consisting of polyacrylic acid as a carrier and three basic model compounds resulting in very high glass transition temperatures and constant dissolution properties upon storage. *Eur. J. Pharm. Sci.* 25, 387–393

77 Owusu-Ababio, G. *et al.* (1998) Comparative dissolution studies for mefenamic acid-polyethylene glycol solid dispersion systems and tablets. *Pharm. Dev. Technol.* 3, 405–412

78 Timko, R.J. and Lordi, N.G. (1979) Thermal characterization of citric acid solid dispersions with benzoic acid and phenobarbital. *J. Pharm. Sci.* 68, 601–605

79 Lin, C.-W. and Cham, T.-M. (1996) Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions. *Int. J. Pharm.* 127, 261–272

80 Verreck, G. *et al.* (2005) The effect of pressurized carbon dioxide as a temporary plasticizer and foaming agent on the hot stage extrusion process and extrudate properties of solid dispersions of itraconazole with PVP-VA 64. *Eur. J. Pharm. Sci.* 26, 349–358

81 Breitenbach, J. and Lewis, J. (2003) Two concepts, one technology: controlled release and solid dispersion with meltrex. In *Modified-Release Drug Delivery Technology* (Rathbone, M.J. *et al.* eds), pp. 125–134, Marcel Dekker

82 Gupta, M.K. *et al.* (2002) Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. *Pharm. Res.* 19, 1663–1672

83 Seo, A. *et al.* (2003) The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. *Int. J. Pharm.* 259, 161–171

84 Verreck, G. *et al.* (2007) The effect of supercritical CO2 as a reversible plasticizer and foaming agent on the hot stage extrusion of itraconazole with EC 20 cps. *J. Supercrit. Fluids* 40, 153–162

85 Passerini, N. *et al.* (2002) Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation. *Eur. J. Pharm. Sci.* 15, 71–78
86 Ahuja, N. *et al.* (2007) Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur. J. Pharm. Biopharm.* 65, 26–38
87 Mizuno, M. *et al.* (2005) Inhibition of a solid phase reaction among excipients that accelerates drug release from a solid dispersion with aging. *Int. J. Pharm.* 305, 37–51
88 Sethia, S. and Squillante, E. (2002) Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method. *J. Pharm. Sci.* 91, 1948–1957