International Journal of Drug Delivery 3 (2011) 149-170
http://www.arjournals.org/index.php/ijdd/index

Review

ISSN: 0975-0215

Solid dispersion: A promising technique to enhance solubility of poorly water soluble drug

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Abstract

Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The present review deals in detail about solid dispersion technology and its manufacturing techniques at laboratory and industrial level. This highlight about various hydrophilic polymers used in this technique to enhance solubility of poorly soluble drugs. It also discusses about modern characterization technique to characterize solid dispersion. In this review, it is intended to discuss the recent advances related on the area of solid dispersion technology.

Keywords: Solid dispersion; Carriers; Solubility; Dissolution; Bioavailability.

Introduction

The solubility of a drug is a key determinant of its oral bioavailability and permeability. 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 [1, 2]. Therefore formulation approaches are being explored to enhance bioavailability of poorly water-soluble drugs. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion.

Scientists gave different explanations of Solid dispersion. Chiou and Riegelman [3] defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures". Sekiguchi and Obi [4] suggested that the drug presented in a eutectic mixture in a microcrystalline state, after few years Goldberg et al.[5] reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by melting or solvent method. Therefore, based on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished. They are described in Table 1.

Table 1: Classification of solid dispersions in six subtypes.

Solid Dispersion	Type	Matrix*	Drug**	Remarks	No. of phases	Reference
I	Eutectics	C	C	the first type of solid dispersions prepared	2	3
II	Amorphous precipitations in crystalline matrix	C	A	rarely encountered	2	6, 7
III	Solid solutions					
	Continuous solid solutions	C	M	miscible at all compositions, never prepared	1	5
	Discontinuous solid solutions	C	M	partially miscible,	2	4
	Substitutional solid solutions	C	M	molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinous: 2 phases even though drug is molecularly dispersed	1 or 2	8, 9
	Interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG.	2	3, 10
IV	Glass suspension	A	C	particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	3, 11
V	Glass Suspension	A	A	particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	3, 11
VI	Glass solution	A	M	requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP	1	12

*: A: matrix in the amorphous state
C: matrix in the crystalline state
**: A: drug dispersed as amorphous clusters in the matrix
C: drug dispersed as crystalline particles in the matrix

Mechanism of Dissolution

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, composition, drug crystallinity, particle porosity and wettability, when successfully controlled can produce improvements in bioavailability [13,14].

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. A high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability [15, 16].

Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability [17]. It has been suggested that the presentation of particles to the dissolution medium as physically separate entities may reduce aggregation. In addition, many of the carriers used for solid dispersions may have some wetting properties; hence improved wetting may lead to reduced agglomeration and increased surface area [18].

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity [19].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. The increased porosity of solid dispersion particles also hastens the drug release profile [20].

Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility [21, 22] 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 [23]. 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, 16].

Disadvantages OF Solid Dispersions

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 [24-26]. 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 [27]. 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 [28]. Therefore, exploitation of the full potential of amorphous solids requires their stabilization in solid state, as well as during in vivo performance. Another drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

Pharmaceutical Applications of Solid dispersion:

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed-

1. To enhance the absorption of drug;
2. To obtain a homogeneous distribution of a small amount of drug in solid state;

3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.;
4. To dispense liquid or gaseous compounds;
5. To formulate a fast release priming dose in a sustained release dosage form;
6. To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier;
7. To reduce side effects-(a) the binding ability of drugs for example to the erythrocyte membrane is decreased by making its inclusion complex, (b) the damage to the stomach mucous membranes by certain non-steroidal anti-inflammatory drugs can be reduced by administration as an inclusion compound;
8. To mask unpleasant taste and smell. The very unpleasant taste of anti-depressant famoxetine hindered the development of oral liquid formulations. The bitter taste was greatly suppressed when the solid complex of famoxetine was formulated as aqueous suspension;
9. To convert liquid compounds into formulations. Liquid drugs can be manufactured as solid drug formulations such as powders, capsules or tablets e.g., unsaturated fatty acids, essential oils, nitroglycerin, benzaldehyde, prostaglandin, clofibrate etc.

Method of Preparation

Various preparation methods for solid dispersions have been reported in literature. Some laboratory and industrially feasible methods are summarized here:

Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Sekiguchi et al. [4] 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. 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, therefore reducing, the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature, inside a dessicator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a dessicator were used. After cooling, the mixture must be pulverized regarding its handling [29-31].

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. 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. 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 [32-34]. To avoid the melting method limitations, several modifications, like hot-stage extrusion, Meltrex^{TM} or melt agglomeration were introduced to the original method.

Solvent method

The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties [35, 36].

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.

Using the solvent method, the pharmaceutical engineer faces many challenges. The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic and complete solvent removal from the product can be a lengthy process. Moreover subtle alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of solvents are generally required which can give rise to toxicological problems.

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 preparation of solid dispersions. Many investigators studied solid dispersion of felodipine [37] meloxicam [38], naproxen [39, 40], atenolol [41], and nimesulide [42] using solvent evaporation technique.

Hot melt extrusion

Hot-stage extrusion (HME) 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 then collected after cooling at room temperature and milled [43-45]. A reduction in processing temperature can be achieved by the association of hot-stage extrusion with the use of carbon dioxide as a plasticizer [46, 47], which broadens the application of hot-stage extrusion to thermally labile compounds. Solid dispersions of para-amino salicylic acid/ethylcellulose [48], itraconazole/ PVP [49] and itraconazole/ethylcellulose [50] were successfully prepared by this technique. Moreover, it was observed that solid dispersions of itraconazole/inutec SPI 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 [51]

HME also offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, more possibility of the formation of solid dispersions and improved bioavailability [52].

An amorphous solid dispersion of itraconzole with HPMC was formed from milled melt extrudate and resulted in a significantly increased dissolution rate compared with the physical mixture; the formulation was found chemically and physically stable for periods in excess of 6 months [53, 54]. The tablets formed by compressing milled melt-extruded glassy powder with additional excipients showed high oral bioavailability [55].

Electrostatic spinning method

In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Electrospun samples dissolved dependent on the type of formulation and the drug:polymer ratio. The technique has been successfully used in the pharmaceutical industry for the preparation of solid dispersions [56-58].

Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and nonbiodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct

incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared by using this technique [59, 60].

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of triamterene-PEG 1500 using a Zanasi LZ 64 capsule-filling machine (Zanasi Co, Bologna, Italy) [61, 62]. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug [63]. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (eg, polysorbate 80 with PEG, phosphatidylcholine with PEG [64, 65]. The temperature of the molten solution should not exceed above 70°C because it might compromise the hard-gelatin capsule shell.

Supercritical fluid (SCF) process

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power [66, 67]. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specialising in particle engineering via SCF technologies for particle size reduction and solubility enhancement [68, 69].

Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), solution enhanced-dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES) [70, 71].

It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. SCF technology offers tremendous potential, as it is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

Lyophillization technique

Lyophillization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion [72]. This technique was proposed as an alternative technique to solvent evaporation. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. Betageri et al. [73], Topalogh et al. [74], Badry et al. [75] and Fathy et al. [76] have successfully

investigated the potential applications of lyophilization technique using glyburide, ketoprofen, meloxicam, amylobarbitone in solid dispersion manufacturing.

An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum. Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration.

Drooge et al. [77] suggested spray freeze-drying process to produce 9- tetrahydrocannabino containing inulin based solid dispersions with improved incorporation of tetrahydrocannabino in inulin.

Spray drying

Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications [78-80].

The spray drying technique is a useful method to obtain spherical particle and narrow distribution. The role of porous materials such as calcium silicate, controlled pore glass and porous cellulose is appreciated to formulate solid dosages forms because they confer special characteristics such as decrease of melting point and a decrease in the crystallinity of drug entrapped in pores. In addition, porous material controls polymorphs and stabilizes meta-stable crystals in solid dispersions under sever storage conditions. Moreover, porous silica has been reported to improve solubility and dissolution rates of indomethacin and tolbutamide [81, 82]. The frequent use of the organic solvent in spray drying pose problems such as residues in products, environmental pollution and operational safety as well as corporate problems such as capital investment.

Solid dispersion of loperamide and PEG 6000 were prepared by this technique [83]. The prepared SD(s) exhibited higher dissolution rates than that of pure crystalline loperamide. Chouhan et al. [84] studied the suitability of this technique for preparation of SD(s) of glibenclamide with polyglycolized glycerides. This study revealed the improvement in solubility, dissolution rates and in therapeutics efficacy of glibenclamide in SD(s).

Carriers in solid dispersion

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance dissolution of drugs. The carriers which have been reported in literature are described in detail below.

Polyethylene glycol

Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200 ± 3,00,000. 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) [85]. These relatively low melting points are advantageous for the manufacture of solid dispersions by the melting method. Even the

dissolution rate of a relatively soluble drug like carbamezapine can be improved by formulating it as a solid dispersion in PEG 6000.

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 [86].

Ozkan et al. [87] reported increasing solubility of etodolac with PEG 6000 as a carrier by melting method. Similarly Dehghan and Jafar [88] studied meloxicam solid dispersions prepared by physical mixing, co-grinding and solvent evaporation methods with PEG 6000. The enhanced dissolution rate of meloxicam by solid dispersion technique may be due to increased wettability and hydrophilic nature of carrier.

Further drugs which exhibit elevated release rates when formulated as PEG 6000 solid dispersions include ofloxacin [89], silymerin [90], gliclazide [91], dapsone [92] , mebendazole [93], Cisapride [94], Nitrendipine [95], oxazepam [96], valdecoxib [97], isosorbide dinitrate [98], zolpidem [99], piroxicam [100], fenofibrate [101], glibenclamide [102], ketoprofen [103]. PEGs with higher MW have also been use with success e.g. products containing PEG 8000 [104] and PEG 10,000 [105] showed enhanced dissolution rates compared to the pure drug.

Poly vinyl pyrrolidone

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 [106]. 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 [107]. 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 and viscosity lowers with increasing chain length.

Solid dispersions of praziquantel (PZQ) containing varying concentrations of PVP with different MW (3000, 11,000 and 34,000) were prepared. The solubility of PZQ in the coprecipitate was greater when PVP of a smaller molecular weight was used [108]. An enhancement of 6.15-fold in dissolution rate of ipriflavone (IP) solid dispersion [109] was noted with PVP K-30 as that of IP alone and 40 fold increase with piroxicam [110] when PVP K 17 is used.

Further drugs which exhibit elevated release rates when formulated as PVP solid dispersions include diflunisal [111], nifedipine [112], tanshinone [113], cefuroxime axetil [114], flunarizine [115], daidzein [116], nitrendipine [117], ketoprofen [118], bicalutamide [119], quercetin [120], lansoprazole [121].

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 [4]. Similarly, Goldberg et al. [5] 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 coevaporate

with urea [122]. In the case of Rofecoxib [123] the release rate from urea dispersions was faster than from other carriers studied, including PEG 4000. A increase in the dissolution rate of piroxicam [124] has also been achieved with urea; however, in this case PEG 4000 was far more effficient . Maheshwari [125] reported solubility enhancement by using urea as a hydrotropic agent. Verma investigated increased dissolution of flurbiprofen with urea and xylitol [126].

Sugars

Although sugars and related compounds are highly water soluble but few sugars have 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.

Lactose is useful as a carrier for the production of solid dispersions of drugs having a primary amide group in their structures like carbamazepine or ethenzamide prepared by melting and rapid cooling showed marked increase in dissolution same results were shown in study with naproxen [127, 128].

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 [129]. In solid dispersion with 1:1 ratio oflaxacin to chitosan, showed as the best carrier for drug release [130]. Similar results were found with fenofibrate [131], oxazepam [132] and miconazole [133].

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 [134], prednisolone [135], ofloxacin [136] and uresodeoxycholic acid [137]. In most of these cases, other carriers produced better results. Interestingly, nitrofurantoin showed better release from sorbitol than mannitol dispersions. Indeed, a dispersion of prednisolone in sorbitol released the drug faster than all other carriers tested, including PEG, PVP, urea and mannitol [138].

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 used in combination with another carrier. For example, the enhanced release of mefenemic acid from solid dispersions, using PEG 6000 with tween 20 [139]. An increase in 7 fold in solubility observed when solid dispersions of nitrendipine were prepared by using a melting method with PEG 6000 and polysorbate 80 as carriers [140]. The fenofibrate solid dispersion tablets prepared by solvent-melting method using PEG 4,000 and sodium lauryl sulfate has showed increased release [141]. Shokri and Azami proved the effect of anionic (SLS), cationic (CTAB) and nonionic (Myrj 52) surfactants as carriers on enhanced dissolution rate of oxazepam. Surfactants are suitable carriers for low dose and very low water soluble drugs [142].

Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Because of their amphiphilic structure, the polymers have surfactant properties that make them useful in industrial applications. Among other things, they can be used to increase the water solubility of

hydrophobic and oily substances or otherwise increase the miscibility of two substances with different hydrophobicities. For this reason, these polymers are commonly used in industrial applications, cosmetics and pharmaceuticals.

Kwon and Kim [143] suggested pluronic F 127 polymeric micelles could improve the oral bioavailability of genistein. Badry and Fathy used pluronic F 98 for dissolution enhancement of piroxicam [144]. Similar results like increased solubility and enhanced bioavailability have been showed by nifedipine and ebselen [145,146].

Chen et al. improved the dissolution and bioavailability of ABT-963, a poorly water-soluble compound by preparing solid dispersion using Pluronic F-68 as a carrier by evaporation and hot melt method [147].

The recently used surface-active carrier is Gelucire® 44/14 and other grades of Gelucire®. The carriers are prepared to have a high melting point but not more than 70°°C so as to compatible to be filled in hard gelatin capsule. The grades of Gelucire® is denoted by different number like 44/14 and 13, in that first digit denotes the melting point of carrier and second digit denote HLB value of carrier. Gelucire® 44/14 is a mixture of glyceryl and PEG-1500 ester of long-chain fatty acid and is official in European pharmacopoeia as a lauryl macrogolglycerides [148].
Dordunoo et al. [149] studied the effect of Gelucire® 44/14 for improving the solubility of temazepam in comparison with various poly ethylene glycol and shown large increase in its water solubility. Enhanced dissolution was observed with lornoxicam [150], tiaprofenic acid [151], thiocarboxanilide UC-781 [152] and carbamazepine [153] when gelucire 44/14 is used as surfactant alone and with other carriers.

Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important for the emulsification of fats and oils in the diet. Like other surfactants, they enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate. Stoll et al. [154] 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 [155].

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 in coatings to modify the release of the drug from the dosage form. Commonly they are referred by the trade name Eudragit [156]. 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 pH values, while eudragit L can be used when it is desirable to avoid release in the stomach. Jun and Jeong observed improved dissolution of atorvastatin calcium with eudragit E100 as a carrier [157].

Cellulose derivative

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. A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP) [158].

Suspension formulated employing paracetamol-HPMC solid dispersions gave highest improvement in the dissolution rate and dissolution efficiency of paracetamol [159]. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine [160] and benidipine [161], Carbamezapine [162] and cisapride [163]. Yuasa et al. [164] 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 molecular weight HPCs were used as the carrier.

Characterization of Solid Dispersion

There have been several reports on the analysis of solid dispersions. A variety of techniques, such as XRPD, NMR, Raman and IR have been used to identify the crystal form in a wide selection of dosage forms, including tablets, capsules, ointments, suppositories and microspheres [165]. A small selection of the available literature will be discussed here.

Powder Xray diffraction

As a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field. The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction. However, too much crystallinity causes brittleness. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of crystallinity in the material [166-170].

Differential scanning calorimetry (DSC)

DSC is a well-known technique that measures heat flow into or out of a material as a function of time or temperature. Crystallinity can be determined with DSC by quantifying the heat associated with melting (fusion) of the material. Glass transitions may occur as the temperature of an amorphous solid is increased. This is due to the sample undergoing a change in heat capacity; no formal phase change occurs. As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (Tc). This transition from amorphous solid to crystalline solid results in an exothermic peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (Tm). The melting process results in an endothermic peak in the DSC curve.

The exact nature of the thermal transitions has to be determined with complementary methods such as microscopic observations, thermogravimetry, X-ray diffraction or spectroscopic techniques to distinguish [171-175].

Hot stage microscopy

Hot stage microscopy is one of the oldest and most straightforward methods for studying phase transitions in crystals. Varying the temperature of a substance while viewing it under a microscope, often through crossed polarizers, provides a wealth of information about melting or recrystallization behavior as well as solid-state transformations. This technique also allows the detection of solvates by observing the evolution of a gas or liquid from a crystal. Novel polymorphs can be generated in this experiment either by high temperature transition of one form to another or by crystallization from the melt. Coupling hot stage microscopy with vibrational spectroscopy or DSC can further expand the utility of this method [176, 177].

Macroscopic techniques

Macroscopic techniques measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and dynamic mechanical analysis (DMA) determine the module of the elasticity and

viscisity and thus affected by the degree of crystallinity.

Nuclear magnetic resonance spectroscopy

Solid-state nuclear magnetic resonance (SS-NMR) spectroscopy can be used to investigate polymorphism by probing the environments of atoms in the solid state; non-equivalent nuclei will resonate at different frequencies and these changes in chemical shift can often be connected with changes in conformation or chemical environment of the compound.

SS-NMR is also useful because it is able to determine the number of crystallographically inequivalent sites in a unit cell. Unlike PXRD, SS-NMR spectroscopy is well-suited to studying amorphous forms of pharmaceuticals and solvates that are usually small to detect. Collecting spectra at various temperatures is a powerful tool in understanding polymorphic transformations and molecular motion in the solid [178-180].

Vibrational spectroscopy

Most prominent among the vibrational spectroscopic methods for polymorph identification are infrared and raman spectroscopy. Both techniques offer information on structure and molecular conformation in the solid state by probing vibrations of atoms. These methods are especially important for characterization of polymorphs because hydrogen-bonding patterns often differ among forms and the functional groups affected will display shifts of varying degrees. Other information gained from vibrational spectroscopies, which can be helpful in distinction of polymorphs, includes low energy lattice vibrations caused by differences in crystal packing.

Infrared absorption spectroscopy has enjoyed the most use in polymorph investigations primarily because it is a robust technique available in most laboratories. Several limitations of the technique are worth considering especially for studies involving small quantities of sample or single crystals. These studies are most conveniently conducted by IR microscopy and this is the method of choice for studies on single crystals. However, an IR transparent substrate must be employed and it is difficult to collect spectra of all but the thinnest crystals due to transmittance issues. Substrate and sample transmittance issues can be circumvented by using attenuated total reflection (ATR) or diffuse-reflectance infrared (DRIFT) spectroscopy [181, 182].

Raman spectroscopy is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. In a light scattering experiment, light of a known frequency and polarization is scattered from a sample. A raman spectrometer interfaced to a microscope has an additional advantage of being able to pinpoint small crystalline samples, which do not have to be removed from crystallization vials for analysis, thus eliminating sample preparation. In addition, the spatial resolution of raman microscopy is limited by the wavelength of the visible light probe rather than infrared radiation, making this technique suitable for examining minute sample quantities in complex matrices. [183, 184]

Water vapour sorption

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. The method requires accurate data of the hygroscopicity of both completely crystalline and completely amorphous samples. In some studies amorphous material were plasticized by water sorption and crystallized during the experiment. However crystallization can be accompanied by expel of water depending on the degree of hydration of crystalline material [185].

Conclusion

The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Various techniques, described in this review, are successfully used for the preparation

of solid dispersion in the bench and lab scale and can be used at industrial scale also. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

References

1. Kerns EH. High throughput physicochemical profiling for drug discovery. J Pharm Sci. 2001;90:1838–1858.
2. Bevan C, Lloyd RS. A high throughput screening methods for the determination of aqueous drug solubility using laser nephelometry in microtiter plates. Anal Chem. 2000;72:1781–1787.
3. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-1302.
4. Sekiguchi K, Obi N. Studies on Absorption of Eutectic Mixture. I. A comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9:866-872.
5. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of the literature. J Pharm Sci. 1965;54(8):1145-1148.
6. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002;54(2):107-117.
7. Mullins JD, Macek TJ. Some pharmaceutical properties of novobiocin. J Am. Pharm Assoc Sci Ed. 1960;49:245-248.
8. Rastogi RP, Rama Varma KT. Solid-liquid equilibria in solutions of non-electrolytes. J Chem Soc. 1965;2:2097-2101.
9. Wilcox WR, Friedenberg R, Back N. Zone melting of organic compounds. Chem Rev. 1964;64:187-220.
10. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci. 1969;58:1505-1510.
11. Sarkari M, Brown J, Chen X, Swinnea S, Williams RO. Enhanced drug dissolution using evaporative precipitation into aqueous solution. Int J Pharm. 2002;243:17-31.
12. Simonelli AP, Mehta SC, Higuchi WI. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. J Pharm Sci. 1969;58:538-549.
13. Craig DQM. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm. 2002;231:131–144.
14. Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersions: A Review. Pak J Pharm Sci. 2009;22:234-246.
15. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50:47-60.
16. Kang BK, Lee JS , Chon SK, Jeong SY, Yuk SH. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int J Pharm. 2004;274:65-73.
17. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. Eur J Pharm Biopharm. 2006;63:103-114.
18. Pouton CW. Formulation of poorly water-soluble drugs for oral administration: physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci. 2006;29:278-287.

19. Vasconcelos T, Costa P. Development of a rapid dissolving ibuprofen solid dispersion, Pharmaceutical Sciences World Conference, 2007:DD-W-103.
20. Ghaderi R, Artursson P, Carifors J. Preparation of biodegradable microparticles using solution enhanced dispersion by supercritical fluids (SEDS). Pharm Res. 1999;16:676-681.
21. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low Tg drug. Powder Technol. 2006;167:20-25.
22. Lloyd GR, Craig DQ, Smith A. A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. Eur J Pharm. Biopharm.1999;48:59-65.
23. Taylor LS and Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res. 1997;14:1691-1698.
24. Van den Mooter G, Weuts I, Ridder TD, Blaton N. Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. Int J Pharm. 2006;316:1–6.
25. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamide polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur J Pharm Sci. 2005;26:219–230.
26. Vasanthavada M, Tong WQ, Joshi Y, Kislalioglu, M.S. Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. Pharm Res. 2004;21:1598–1606.
27. Johari GP, Kim S, Shankar, R. Dielectric studies of molecular motions in amorphous solid and ultraviscous acetaminophen. J Pharm Sci. 2005;94:2207–2223.
28. Wang X, Michoel A, Van den Mooter G. Solid state characteristics of ternary solid dispersions composed of PVP VA64, Myrj 52 and itraconazole. Int J Pharm. 2005;303:54–61.
29. Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci. 1999;88:1182-1190.
30. Timko RJ, Lordi NG. Thermal analysis studies of glass dispersion systems. Drug Dev Ind Pharm.1984;10:425-451.
31. Damian F, Blaton N, Kinget R, Van den Mooter G. Physical stability of solid dispersions of the antiviral agent UC-781 with PEG 6000, Gelucire 44/14 and PVP K30. Int J Pharm. 2002;244:87-98.
32. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJW. Solid-state characterization of nifedipine solid dispersions. Int J Pharm. 2002;236:111-123.
33. Vippagunta SR, Wang Z, Hornung S, Krill SL. Factors affecting the formation of eutectic solid dispersions and their dissolution behavior. J Pharm Sci. 2006;96:294-304.
34. McGinity JW, Maincent P, Steinfink H. Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. J Pharm Sci. 1984;73:1441-1444.
35. Hernandez-Trejo N, Hinrichs WLJ, Visser MR, Muller RH, Kayser O, Frijlink E. Enhancement of the in vitro dissolution rate of the lipophilic drug buparvaquone by incorporation into solid dispersions. Pharm Sci Fair Nice. 2005.
36. Butler, MJ. Method of producing a solid dispersion of a poorly water-soluble drug. US Patent No. 5 1999;985:326.
37. Kim EJ, Chun MK, Jang JS, Lee I H, Lee KR, Choi HK. Preparation of a solid dispersion of felodipine using a solvent

wetting method. Eur J Pharm Biopharm. 2006;64:200-205.
38. Chowdary KPR, Hymavathi R. Enhancement of dissolution rate of meloxicam. Indian J Pharm Sci. 2001;150-154.
39. Rao MG, Suneetha R, Reddy P, Ravi TK. Preparation and evaluation of solid dispersions of naproxen. Indian J Pharm Sci. 2005;67:26-29.
40. Mura P, Zerrouk N, Mennini N, Masterly F, Chemtob C. Development and characterization of naproxen solid systems with improved drug dissolution properties. Eur J Pharm Sci. 2003;18:67-75.
41. Moneghini M, Carcano A, Zingone G, Perissutti. Studies in dissolution enhancement of atenolol. Int J Pharm. 1998;175:177-183.
42. Jain RK, Sharma DK, Jain S, Kumar S, Dua JS. Studies on solid dispersions of nimesulide with pregelatinized starch. Biosci. Biotechnol Resc Asia. 2006;3:151-153.
43. Lakshman JP, Cao Y, Kowalski J, Serajuddin AT. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Mol Pharm. 2008;5:994-1002.
44. El-Egakey MA, Soliva M, Speise P. Hot extruded dosage forms, Pharm Acta Helv. 1971;46:31-52.
45. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002;54:107-117.
46. Chokshi R, Hossein Z. Hot–Melt Extrusion Technique: A Review. Iran J Pharm Res. 2004;3:3-16.
47. Perissutti B, Newton JM, Podezeck F, Ru bessa F. Preparation of extruded Carbamazepine and PEG 4000 as a potential rapid release dosage form. Eur J Pharm Biopharm. 2002;53:125-132.
48. Verreck G, Decorte A, Heymans K, Adriaensen J, Liu D, Tomasko D, Arien A, Peeters J, Van den Mooter G, Brewster ME. Hot stage extrusion of p-amino salicylic acid with EC using CO_2 as a temporary plasticizer. Int J Pharm. 2006;327:45-50.
49. Miller DA, McConville JT, Yang W, Williams RO, McGinity JW. Hot-melt extrusion for enhanced delivery of drug particles. J Pharm Sci. 2007;96(2):361-76.
50. Verreck G, Decorte A, Heymans K, Adriaensen J, Liu D, Tomasko D, Arien A, Peeters J, Rombaut P, Van den Mooter G, Brewster ME. The effect of supercritical CO_2 as a reversible plasticizer and foaming agent on the hot stage extrusion of itraconazole with EC 20 cps. Journal of Supercritical Fluids. 2007;40:153-162.
51. Van den Mooter G, Weuts I, De Ridder T, Blaton N. Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersions for poorly soluble drugs. Int J Pharm. 2006;316:1-6.
52. Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, McGinity JW, Martin C. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev Ind Pharm. 2007;33:909-26.
53. Verreck G, Baert L, Peeters J, Brewster M. Improving aqueous solubility and bioavailability for itraconazole by solid dispersion approach. AAPS PharmSci. 2001;3:M2157.
54. Verreck G, Six K, Vanenmoter G, Baert L, Peeters J, Brewster ME. Characterization of solid dispersions of itraconazole and hydroxypropylmethyl cellulose prepared by melt extrusion- Part I. Int J Pharm. 2003; 251:165-174.
55. Baert L, Thone D, Verreck G, Antifungal compositions with improved bioavailability. 1997: World patent 9:744:014.
56. Reneker DH, Chun I. Nanometre diameter fibres of polymer, produced by

electrospinning. Nanotechnology. 1996;7:216-223.
57. Ignatious F, Baldoni JM, inventors. Smith kline Beecham Corp, assignee. Electrospun pharmaceutical compositions. 2001; World patent 0:154:667.
58. Wnek GE, Kenawy ER, Bowlin GL. Rele ase of tetracycline hydrochloride from electrospun poly(ethylene-co-vinyl-acetate), poly(lactic acid) and a blend. J Control Release. 2002;81:57-64.
59. Deitzel JM, Kleinmeyer J, Harris D, Beck Tan NC. The effect of processing variables on the morphology of electrospun nanofibers and textiles. Polym. 2001; 42:261-272.
60. Verreck G, Chun I, Peeters J, Rosenblatt J , Brewster ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. Pharm Res. 2003; 20:810-817.
61. Wiley GJ, Ullah I, Agharkar SN. Develo pment of a semiautomatic system for R&D and clinical use for liquid filled hard gelatin encapsulation. Pharm Technol. 1995;19:72-76.
62. Walker SE, Ganley JA, Bedford K, Eaves T. The filling of molten and thixo formulations into hard gelatin capsules. J Pharm Pharmacol. 1980;32:389-393.
63. Serajuddin ATM, Sheen PC, Mufson D, B ernstein DF, Augustine MA. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water-soluble drug from solid dispersions. J Pharm Sci. 1988;77:414-417.
64. Serajuddin ATM, Sheen PC, Augustine M A. Improved dissolution of a poorly water-soluble drug from solid dispersions in poly (ethylene glycol): polysorbate 80 mixtures. J Pharm Sci. 1990;79:463-464.
65. Law SL, Lo WY, Lin FM, Chaing CH. D issolution and absorption of nifedipine in poly (ethylene glycol) solid dispersion containing phosphatidylcholine. Int J Pharm. 1992;84:161-166.
66. Phillips EM, Stella VJ. Rapid expansion from supercritical solutions: application to pharmaceutical processes. Int J Pharm. 1993;94:1-10.
67. Subramaniam B, Rajewski RA, Snavely K. Pharmaceutical processing with supercritical carbon dioxide. J Pharm Sci. 1997;86:885-890.
68. McHugh MA, Krukonis VJ. Supercritical Fluid Extraction: Principles and Practice. Butterworth-Heinmann, Newton MA; 1994.
69. Sunkara G, Kompella UB. Drug delivery applications of supercritical fluid technology. Drug Del Technol. 2002;2:44-50.
70. Dohrn R, Bertakis E, Behrend O, Voutsas E, Tassios D. Melting point depression by using supercritical CO_2 for a novel melt dipersion micronization process. J Mol Li. 2007;131:53-59.
71. Wong DH, Kim M S, Lee S, Jeong SP, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-solvent precipitation process. Int J Pharm. 2005;301:199-208.
72. Tsinontides SC, Rajniak P, Pham D, Hunke WA, Placek J, Reynolds SD. Freeze drying-principles and practice for successful scale-up to manufacturing. Int J Pharm. 2004;280:1-16.
73. Betageri GV, Makarla KR. Enhancement of dissolution of Glyburide by solid dispersion and lyophilization techniques. Int J Pharm. 1995;126:155-160.
74. Yalcin T, Gulgun Y, Gonullu U. Inclusion of ketoprofen with skimmed milk by freeze-drying. Farmaco. 1999;54:648-652.
75. Bandry MB, Fathy M. Enhancement of the dissolution and permeation rates of meloxicam by formation of its freeze-dried solid dispersions in polyvinylpyrrolidone K-30. Drug Dev Ind Pharm. 2006;32:141-150.

76. Fathy M, Sheha M. In vitro and in vivo evaluation of an amylobarbitone /hydroxypropyl-betacyclodextrin complex prepared by a freeze-drying method. Pharmazie. 2000;55:513- 517.
77. Drooge DJV, Hinrichs WLJ, Dickhoff HJ, Elli MNA, Visser MR, Zijlastra GS. Frijlink HW, Spray freeze drying to produce a stable Δ -9-tetrahydrocannabino containing inulin based solid dispersion powder suitable for inhalation. Eur J Pharm. 2005;26:231-240.
78. Chronakisa IS, Triantafyllou AO. Solid state characteristics and redispersible properties of powders formed by spray-drying and freeze-drying cereal dispersions of varying (1 3, 1 4)-β -glucan content. Journal of cereal science. 2005;40:183-193.
79. Patrice TT, Stephanie B, Hatem F. Preparation of redispersible dry nanocapsules by means of spray drying: Development and characterization. Eur J Pharm Sci. 2007;30:124-135.
80. Lachman L, Lieberman HA, Kanig JL eds. The theory and practice of industrial pharmacy. 3rd ed. Bombay, Varghese Publishing house; 1987;p 61-69.
81. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int J Pharm. 2005;293:155-164.
82. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. Powder technology. 2004;141:187-195.
83. Weuts I, Kempen D, Verreck G, Decorte A, Heymans K, Peeters J, Brewster M, Mooter GV. Study of the physicochemical properties and stability of solid dispersions of loperamide and PEG 6000 prepared by spray drying. Eur J Pharm Biopharm. 2005;59:119-126.
84. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamidepolyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur J Pharm Sci. 2005;26:219-230.
85. Price JC. Polyethylene glycol. In: Wade A, Weller PJ, Ed. Handbook of Pharmaceutical Excipients. Washington DC/London: American Pharmaceutical Association/The Pharmaceutical Press; 1994:355-361.
86. Shah JC, Chen JR, Chow D. Preformulation study of etoposide, increased solubility and dissolution rate by solid-solid dispersions. Int J Pharm. 1995;113:103-111.
87. Ozkan Y, Do anay N, Dikmen N. Enhanced release of solid dispersions of etodolac in polyethylene glycol. II Farmaco. 2000;55:433-438.
88. Hassan M, Dehghan G, Jafar M. Improving dissolution of meloxicam using solid dispersions. Iranian J Pharm Res. 2006;4:231-238.
89. Okonogi S, Puttipipatkhachorn S. Dissolution Improvement of High Drug-loaded Solid Dispersion. AAPS PharmSciTech. 2006;7:52.
90. Feng-Qian L, Jin-Hong H. Improvement of the dissolution rate of silymarin by means of solid dispersions. Chem Pharm Bull. 2004;52:972-973.
91. Sukmadjaja A, Farmasi WS. Enhancement of gliclazide dissolution with PEG 6000 solid dispersion method. Acta Pharmaceutica. 2006;31:111-115.
92. Liang C, Yongqiang L. Preparation of dapsone solid dispersions and determination of its dissolution. Yiyao Daobao. 2006;25(4):333-334.
93. Kalaiselvan R, Prasad GS, Naik PR, Manavalan R. Enhancement of dissolution and bioavailability of mebendazole for the effective and safe management of human echinococcosis. Indian J Pharm Sci. 2003;65:605-613.

94. Rao B, Babu S, Naveen N, Ramana MKV. Studies on release of Cisapride from solid dispersion systems of Cisapride. Int J Pharm Excip. 2001;3:5-8.
95. Zong L, Hui Z, De-Ping W, Jia-Bi Z. Enhancement of nitrendipine dissolution by PEG 6000 and Polysorbate 80. Peop Rep China. 2000;31:21-24.
96. Arias MJ, Moyano JR, Gines JM. Study by DSC and HSM of the oxazepam-PEG 6000 and oxazepam-D-mannitol systems: Application to the preparation of solid dispersions. Thermochimica Acta. 1998;321: 33-41.
97. Biradar SS, Mulla JS, Bhagavati ST, Jamakandi VG, Gadad AP. Enhancement of solubility of valdecoxib by solid dispersion technique. Pharma Review. 2006;4:154-155.
98. Xue-yan D, Qing-fei L, Qiang S; Kai-shun B, Yi-ming W, Guo-an L, Studies on preparation and in vitro evaluation of isosorbide dinitrate solid dispersion. Peop Rep China. 2008;17:682-684.
99. Giuseppe T, Massimo F, Andrea L. Physicochemical characterization and in vivo properties of zolpidem in solid dispersions with polyethylene glycol 4000 and 6000. Int J Pharm. 1999;184:121-130.
100. Ryh-Nan P, Jing-Huey C, Rhei-Long CR. Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. Drug Dev Ind Pharm. 2000;26(9):989-994.
101. Xiuhua R, Gao L. Preparation of fenofibrate solid dispersion tablets. Peop Rep China. 2003;34:238-240.
102. Bartsch SE, Griesser UJ. Physicochemical properties of the binary system glibenclamide and polyethylene glycol 4000. Journal of Thermal Analysis and Calorimetry. 2004;77:555-569.
103. Fikri A, Nurono S, Sukmadjaja A, Farmasi J. Influence of PEG 4000 concentration on dissolution rate of ketoprofen in solid dispersion system of ketoprofen-PEG 4000. Majalah Farmasi Indonesia. 2006;17:57-62.
104. Perng CY, Kearney AS, Patel K, Palepu NR, Zuber G. Investigation of formulation approaches to improve the dissolution of SB-210661, a poorly water soluble 5-lipoxygenase inhibitor. Int J Pharm. 1998;176:31-38.
105. Khan GM, Zhu JB. Preparation, characterization, and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (PEG), talc, and PEG-talc as dispersion carriers. Drug Dev Ind Pharm. 1998;24:455-462.
106. Walking WD. Povidone. In: Wade A, Weller PJ, Ed. Handbook of Pharmaceutical Excipients. Washington DC/London: American Pharmaceutical Association/The Pharmaceutical Press; 1994:392-399.
107. Aso Y, Miyazaki T, Yoshika S, , Kawanishi T. Molecular mobility of flufenamic acid in solid dispersions as determined by 19F-NMR relaxation time. AA Pharm Sci. 2009;11:S2.
108. Paloma DLT, Susana T, Santiago T. Preparation, dissolution and characterization of praziquantel solid dispersions. Chem Pharm Bull. 1999;47:1629-1633.
109. Ya-Ping L, Xian-Ying Z, Jian-Jun Z, Yuan-Ying P. Preparation and dissolution property of ipriflavone solid dispersion. Zhongguo Yaoli Xuebao. 1999;20:957-960.
110. Tantishaiyakul V, Kaenopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. Int J Pharm. 181:143-151.
111. Rodriguez-Espinosa C, Martinez-Oharriz MC, Martin C, Goni MM, Velaz I, Sanchez M. Dissolution kinetics for coprecipitates of diflunisal with PVP K30. Eur J Drug Meta Pharmac. 1998;23:109-112.

112. Dawei C, Xing L, Wenyan F. Studies on preparation and dissolution of solid dispersions of nifedipine-polyvinylpyrrolidone. Zhongguo Yaoxue Zazh., 2000;35;598-600.
113. Mao-quan C, Song L, Hong-chen G, Guo-jie L. Study on solid dispersions of tanshinone. Huadong Ligong Daxue Xuebao. 2001;27:191-194.
114. Xue K, Qineng P, Aiming S. Formation and solubilization of cefuroxime axetil solid dispersion. Zhongguo Yaoxue Zazhi. 2001;36:106-108.
115. Marin M, Teresa Margarit M, Salcedo V, Gloria E. Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone. II Farmaco. 2002;57:723-727.
116. Li G, Shengrong G, Fengsheng Z. Effect of PVP K30 on solubility of daidzein. Zhongguo Yiyao Gongye Zazhi. 2003; 34:273-275.
117. Gang H, Jianfeng Z, Hailiang C. Manufacture of solid dispersion tablets of nitrendipine and its dissolution in vitro. Huaxi Yaoxue Zazhi. 2003;18:28-29.
118. Ruxing W, Dawei C, Haiyang H, Kexin L. Preparation and dissolution of the solid dispersions of ketoprofen-polyvinylpyrrolidone. Shenyang Yaoke Daxue Xuebao. 2006;23:201-204.
119. Fuzheng R, Qiufang J, Yanhui T, Yongjia S, Jialei C, Feng G, Jingbin C. Characteristics of bicalutamide solid dispersions and improvement of the dissolution. Drug Dev Ind Pharm. 2006;32:967-972.
120. Jing Z, Zhao-Gang Y, Xiao-Mei C, Jia-Bei S, Gulisitan A, Xuan Z, Qiang Z. Preparation and physicochemical characterization of solid dispersion of quercetin and polyvinylpyrrolidone, J Chinese Pharm Sci. 2007;16:51-56.
121. Mamatha T, Venkateswara RJ, Mallik B, Shagufta A, Shanthi M. Studies to enhance dissolution of Lansoprazole. Indian Pharmacist. 2008;7:65-70.
122. Okonogi S, Oguchi T, Yonemochi E, Puttipipatkhachorn S, Yamamoto K. Improved dissolution of ofloxacin via solid dispersion. Int J Pharm. 1997;156:175-180.
123. Liu C, Desai K, Goud H, Liu C, Park H. Enhancement of dissolution rate of rofecoxib using solid dispersions with urea. Drug Dev Res. 2004;63:181-189.
124. Ryh-Nan P, Jing-Huey C, Russel Rhei-Long C. Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems. Drug Dev Ind Pharm. 2000;26:989-994.
125. Maheshwari RK, Solid dispersion and syrup formulation of poorly water-soluble drug by hydrotropy. Indian Pharmacist. 2006;5:87-90.
126. Varma MM, Pandit JK. Influence of urea and xylitol on the dissolution rate of flurbiprofen. Indian Pharmacist 2005;4:97-99.
127. Noriyuki H, Hirokazu O, Kazumi D. Lactose as a low molecular weight carrier of solid dispersions for carbamazepine and ethenzamide. Chem Pharm Bull. 1999;47: 417-420.
128. Noriyuki H, Kazumi D, Mitsumasa H, Akinobu O. Physicochemical characterization and drug release studies of naproxen solid dispersions using lactose as a carrier. Chem Pharm Bull. 1998;46:1027-1030.
129. Portero A, Remunanlopez C, Vilajato JL. Effect of chitosan and chitosan glutamate enhancing the dissolution properties of the poorly water soluble drug nifedipine. Int J Pharm. 1998;175:75-84.
130. Okonogi S, Viernstein H. Effect of chitosan on the physicochemical and dissolution properties of ofloxacin solid dispersion. Advances in Chitin Science. 2002;5:161-165.
131. Xiuhua R, Gao L. Preparation of fenofibrate solid dispersion tablets.

Zhongguo Yiyao Gongye Zazhi. 2003;34:238-240.
132. Shokri J, Azarmi, S, Saboury A, Shokri MH. Enhancement of oxazepam dissolution rate using oxazepam-surfactant solid dispersions. Ulum-i Daroei. 2006;4:35-45.
133. Pignatello R, Mangiafico A, Panto V, Puglisi G, Furneri PM, Solid dispersions of chitosan glutamate for the local delivery of miconazole: characterization and in vitro activity. Open Drug Delivery Journal, 2008;2:44-51.
134. Ali AA, Gorashi AS. Absorption and dissolution of nitrofurantoin from different experimental formulations. Int J Pharm. 1984;19:297-306.
135. Jachowicz R. Dissolution rates of partially water-soluble drugs from solid dispersion systems. I. Prednisolone. Int J Pharm.1987;35:1-5.
136. Okonogi S. Oguchi T, Yonemochi E, Puttipipatkhachorn S, Yamamoto K, Improved dissolution of ofloxacin via solid dispersion. Int J Pharm.1997;156:175-180.
137. Okonogi S, Yonemochi E, Oguchi T, Puttipipatkhachorn S, Yamamoto K. Enhanced dissolution of uresodeoxycholic acid from the solid dispersion. Drug Dev Ind Pharm, 1997;23:1115-1121.
138. Ghebremeskel AN, Vemavarapu C, Lodaya M. 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. 2007;328:119–129.
139. Owusu-Ababio G, Ebube NK, Reams R, Habib M. Comparative dissolution studies for mefenamic acid-polyethylene glycol solid dispersion systems and tablets. Pharm Dev Tech. 1998;3:405-412.
140. Li Z, Zhu H, De-Ping W, Jia-Bi Z. Enhancement of nitrendipine dissolution by PEG 6000 and Polysorbate 80. Zhongguo Yaoke Daxue Xuebao. 2000;31:21-24.
141. Ren X, Li G. Preparation of fenofibrate solid dispersion tablets. Zhongguo Yiyao Gongye Zazhi. 2003;34:238-240.
142. Shokri J, Azarmi S, Saboury A, Shokri MH. Enhancement of oxazepam dissolution rate using oxazepam-surfactant solid dispersions. Ulum-i Daroei. 2006;4:35-45.
143. Kwon S H, Kim SY, Ha KW, Kang MJ, Huh JS, Im TJ, Kim Y M, Park YM, Kang KH, Lee S, Chang JY, Lee J, Choi YW. Pharmaceutical evaluation of genistein-loaded Pluronic micelles for oral delivery. Archives Pharml Research. 2007;30:1138-1143.
144. El-Badry M, .Fathy M. Properties of solid dispersion of piroxicam in Pluronic F-98. J Drug Del Sci Tech, 2004;14:199-205.
145. Ho HO, Chen CN, Sheu MT. Influence of Pluronic F-68 on dissolution and bioavailability characteristics of multiple-layer pellets of nifedipine for controlled release delivery. J Cont Rel. 2000;68:433-440.
146. Zhang M, Yu Y, Liu J, Liu Z, Li Z. Preparation and dissolution of ebselen solid dispersion. Huaxi Yaoxue Zazhi. 2005;20:512-513.
147. Chen Y, Zhang GGZ, Neilly J, Marsh K, Mawhinney D, Sanzgiri YD. Enhancing the bioavailability of ABT – 963 using solid dispersion containing Pluronic F – 68. Int J Pharm. 2004;286:69–80.
148. Gattefosse technical brochure, Pharmaceutical excipient for oral semisolids formulations. 1999;12-15.
149. Dordunoo SK, Ford JL, Rubinstein MH. Preformulation studies on solid dispersions containing triamterne or tamezapam in polyethylene glycols or gelucire 44/14 for liquid filling of hard gelatin capsules. Drug Dev Ind Pharm. 1991;17:1685-1713.

150. Ren B, Zhang J, Gao Y, Yu J. Characteristics of enthalpy change and dissolution improvement of lornoxicam from solid dispersions. Zhongguo Yaoke Daxue Xuebao. 2003;34:433-437.
151. Saygili MS, Uzunkaya G, Ozsoy Y, Araman A. Enhanced dissolution rate of tiaprofenic acid using Gelucire 44/14. Scientia Pharmaceutica. 2002;70:295-307.
152. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustijns P, Van den Mooter G. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. Euro J Pharm Sci. 2000;10:311-322.
153. Perissutti B, Rubessa F, Princivalle F. Solid dispersions of carbamazepine with Gelucire 44/14 and 50/13. STP Pharma Sciences. 2000;10:479-484.
154. Stoll RT, Bates TR, Nieforth KA, Swarbrick J. Some physical factors affecting the enhanced blepharototic activity of orally administered reserpine cholanic acid coprecipitates. Pharm Sci. 1969;58:1457-1459.
155. Kim KH, Jarowski CI. Surface tension lowering and dissolution rate of hydrocortisone from solid solutions of selected n-acyle esters of cholesterol. J Pharm Sci. 1977;66:1536-1540.
156. Shukla AJ. Polymethacrylates. In: Wade A, Weller PJ, Ed. Handbook of Pharmaceutical Excipients. Washington DC/London: American Pharmaceutical Association/The Pharmaceutical Press; 1994:362-366.
157. Lee JH, Ku J, Park JS, Park JH, Ahn, S, Mo JH, Kim YT, Rhee JM, Lee HB, Khang G. Improved dissolution and characterization of solid dispersed atorvastatin calcium. Yakche Hakhoechi. 2008;38:111-117.
158. Harwood RJ, Johnson JL. Hydroxypropylmethylcellulose. In: Wade A, Weller PJ, Ed. Handbook of Pharmaceutical Excipients. Washington DC/London: American Pharmaceutical Association/The Pharmaceutical Press; 1994:229-232.
159. Chowdary KPR, Prasad TRS. Physical stability and dissolution rate of paracetamol suspensions formulated employing its solid dispersions. Int J Pharm Excip. 2003;19-22.
160. Okimoto K, Miyake M, Ibuki R, Yasumura M, Ohnishi N, Nakai T. Dissolution mechanism and rate of solid dispersion particles of nilvadipine with hydroxypropylmethylcellulose. Int J Pharm. 1997;159:85-93.
161. Suzuki H, Miyamoto N, Masada T, Hayakawa E. Solid dispersions of benidipine hydrochloride. Preparations using different solvent systems and dissolution properties. Chem Pharm Bull. 1996;44:364-371.
162. Barzegar-Jalali M, Valizadeh H, Dastmalchi S, Shadbad MRS, Barzegar-Jalali A, Adibkia K, Mohammadi G. Enhancing dissolution rate of carbamazepine via cogrinding with crospovidone and hydroxypropylmethylcellulose. Iranian J Pharm Res. 2007;6:159-165.
163. Wei Z. Mao S, Bi D, Li Y. Dissolution improvement of cisapride by solid dispersion with HPMC. J Chinese Pharm Sci. 2004;13:254-258.
164. Yuasa H, Ozeki T. Solid dispersion method for controlled medicine release. Part 2. Controlled release through the drug-polymer interaction and the interpolymer complexation. Pharm Tech Japan. 1999;15:1135-1138.
165. Newman AW, Byrn SR. Solid-state analysis of the active pharmaceutical ingredient in drug products. Drug Discovery Today. 2003;8:898-905
166. Bettinetti GP. X-ray diffractometry in the analysis of drugs and pharmaceutical forms. Boll Chim Farm**.** 1989;128:149-62.

167. Phadnis NV, Cavatur RK, Suryanarayanan R. Identification of drugs in pharmaceutical dosage forms by X-ray powder diffractometry. Biomed Anal. 1997;15:929-43.
168. Luger. Modern X-Ray Analysis on Single Crystals, de Gruyter, 1980.
169. Klug HP, Alexander LE. X-Ray Diffraction Procedures. London, John Wiley and Sons; 1962.
170. Guinier A, Fournet G. Small-Angle Scattering of X-Rays. New York, JohnWiley & Sons; 1955.
171. Hohne G, Hemminger W, Flammersheim HJ. Differential Scanning Calorimetry. Heidelberg, Springer; 2003.
172. Wunderlich B. Thermal Analysis, New York, Academic Pres; 1990.
173. Ford JL, Timmins P. Pharmaceutical Thermal Analysis-Techniques and Applications. Chichester, Ellis Horwood; 1989.
174. Giron D, Thermal analysis of drugs and drug products, In: Swarbrick J, Boylan JC, Ed. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker; 2002:2766-2793.
175. Clas SD, Dalton CR., Hancock B, Calorimetry in pharmaceutical research and development. In: Swarbrick J, Boylan JC, Ed. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker; 2002:289–301.
176. Kuhnert-Brandstatter M. Thermomicroscopy in the Analysis of Pharmaceuticals. New York, Pergamon Press; 1971.
177. McCrone WC Jr. Fusion Methods in Chemical Microscopy. New York, Interscience Publishers; 1957.
178. Byrn SR, Pfeiffer RR, Stephenson G, Grant DJW, Gleason WB. Solid-State Chemistry of Drugs. West Lafayette, SSCI; 1999.
179. Bugay DE. Solid-state nuclear magnetic resonance spectroscopy: theory and pharmaceutical applications. Pharm Res. 1993;10:317–327.
180. Tishmack PA, Bugay DE, Byrn SR. Solid-state nuclear magnetic resonance spectroscopy-pharmaceutical applications. J Pharm Sci. 2003;92:441– 474.
181. Li J, Guo Y, Zografi G. The solid-state stability of amorphous quinapril in the presence of beta-cyclodextrins. J Pharm Sci. 2002;91:229-243.
182. Rogers TL, Hu JH, Brown J, Young T, Johnston KP, Williams RO. A novel particle engineering technology to enhance dissolution of poorly water soluble drugs: spray-freezing into liquid. Eur J Pharm Biopharm. 2002;54:271-280.
183. Breitenbach J, Schrof W, Neumann J. Confocal Raman-spectroscopy: analytical approach to solid dispersions and mapping of drugs. Pharm Res. 1999;16:1109-1113.
184. Fini A, Cavallari CO. Raman and thermal analysis of indomethacin/PVP solid dispersion enteric microparticles. Euro J Pharm Biopharm. 2008;70(1): 409-420.
185. Buckton G, Darcy P. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. Int J Pharm. 1995;123:265-271.