ISSN 0976 – 3333

Available Online at www.ijpba.info.
International Journal of Pharmaceutical & Biological Archives 2010; 1(4): 309-324

REVIEW ARTICLE

Physicochemical Classification and Formulation Development Of Solid Dispersion Of Poorly Water Soluble Drugs: An Updated Review

Tapan Kumar Giri*, Amit Alexander and Dulal Krishna Tripathi

Rungta College of Pharmaceutical Sciences & Research, Kohka Road, Kurud, Bhilai, India.

Received 28 Aug 2010; Revised 15 Sep 2010; Accepted 2 Oct 2010

ABSTRACT

It is commonly recognized in the pharmaceutical industry that more than 40% newly discovered drug candidates are poorly water soluble. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development and also complicating the delivery of poorly water soluble drugs. To improve such poor solubility issues, solid dispersion techniques are widely applied to increase the apparent solubility or enhance the oral bioavailability of poorly water soluble drugs. Inspite of tremendous potential for improving drug solubility, only few products have been marketed since the development of this technology 40 years ago. This article begins with various types of solid dispersion systems including simple eutectic mixture, solid solutions, glass solutions, and amorphous precipitation in a crystalline carrier. The remaining portion of this article is devoted to the various formulation and development techniques for solid dispersion.

KEYWORDS: solubility enhancement, solid solution, supercritical fluid technology, hot-melt extrusion

INTRODUCTION

The therapeutic response of a drug is normally dependent on an adequate concentration of the drug being achieved and then maintained at the site or sites of action of the drug. A majority of drugs are administered orally and vast majority of orally administered drugs are intended to be absorbed from the gastrointestinal tract. The slowest step in the series of rate processes that controls the overall rate and extend of appearance of intact drug in the systemic circulation is called the rate limiting step. The particular rate limiting step may vary from drug to drug. Thus for a drug which exhibits a very poor aqueous solubility, the rate at which the drug dissolves in the gastrointestinal fluids is often the slowest step and therefore exhibits a rate limiting effect on the drug bioavailability. The enhancement of oral bioavailability of such poorly water soluble drugs remains one of the most challenging aspects of drug development.

The biopharmaceutical classification system divides drugs into four classes depending on invitro solubility and invio permeability data[1]. Among the four classes class II drugs shows poor solubility and high permeability. It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption then their ability to permeate through the membrane.

Therefore, the formulation work for class II compounds should focus on the enhancement of aqueous solubility or dissolution rate. There are various strategies available to improve the aqueous solubility or dissolution rate. These are solid dispersions, particle size reduction, salt formation, complexation with cyclodextrin, the use of cosolvents, hydrotropy, nanocrystal technology and self emulsifying system.

Among the various strategies to improve the aqueous solubility or dissolution of drugs[2] the preparation of solid dispersion system has often proven to be very successful[3]. The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier in the solid state[4, 5].

The dissolution rate of a poorly water soluble drug in a solid dispersion is increased by i) increasing the surface area from which dissolution of the

***Corresponding Author:** Tapan Kumar Giri, **Email:** tapan_ju01@rediffmail.com,**Contact No:** 09229206752

IJPBA, Sep-Oct, 2010, Vol. 1, Issue, 4

drug can take place as a result of a reduction in drug particle size upto the molecular level and the impediment of aggregation, ii) improving wetability hence decreasing the thickness of the diffusion layer by appropriate selection of the carrier system, iii) enhancing the solubility of the drug by the formation of a supersaturated solution[6,7]. Moreover, transformation of the crystalline drug to the amorphous state upon solid dispersion formulation increases the dissolution rate since no lattice structure has to be disrupted for dissolution to take place[6-8]. Amorphous drugs are however thermodynamically unstable and tend to recrystallise in time. Contrary to the popularity and promising results of the solid dispersion strategy, only few marketed products rely on this concept. The reasons for this discrepancy are difficulty in incorporating into formulation of dosage forms, scale-up of manufacturing process and stability of the drug and vehicle. This review is therefore devoted to a discussion of various formulation methods that have been tried recently to overcome the limitations and make the preparation more practically feasible.

PHYSICOCHEMICAL CLASSIFICATION OF SOLID DISPERSIONS

Solid dispersion can be classified as follows:

a) Simple eutectic mixture
b) Solid solution
c) Glass solution
d) Complex formation
e) Amorphous precipitation in a crystalline carrier

a) Simple eutectic mixture

A simple eutectic mixture can be described as an intimately blended physical mixture of two crystalline components, which are completely miscible in the liquid state, but not in the solid state (**Figure 1**).

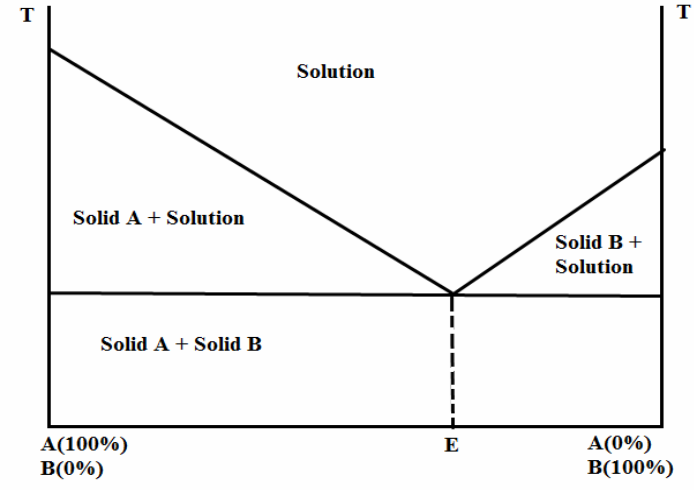

Figure 1: Phase diagram for eutectic system

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously. However, when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a eutectic mixture, composed of a poorly soluble drug and a highly soluble carrier, is exposed to water or gastrointestinal fluids, the soluble carriers dissolve rapidly leaving very fine crystalline state that will rapidly go into solution[4,9]. Due to increased surface area of the insoluble compound, an enhanced dissolution rate and hence an increased oral absorption is obtained as can be derived from the Noyes-Whitney equation.

Differential thermal analysis (DTA) of binary mixtures normally exhibits two endotherms, but a binary mixture of eutectic composition usually exhibits a single endotherm. In the case of a simple eutectic system, the thaw points of binary mixtures of varying compositions are equal to the eutectic temperature of the system.

b) Solid solutions

Solid solution consists of a solid solute dissolved in a solid solvent. The particle size in solid solution is reduced to molecular level. It was reported that a solid solution of a poorly soluble drug in a fast dissolving carrier achieves a faster dissolution rate than a eutectic mixture because the drug particle size is reduced to its absolute minimum as it is molecularly dispersed in the carrier in a solid solution[10-12].

As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. In the case of felodipine-PVP solid dispersions, hydrogen bond interaction between felodipine and PVP has shown to enhance drug dissolution[13]. Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility[14].

Solid solutions can be classified by their miscibility characteristics (continuous or discontinuous) or by the way in which the solute/solvent molecules are distributed in the lattice (interstitial, substitutional or amorphous).

i) Continuous solid solutions

In a continuous solid solution the components are totally miscible with one another in all proportions

in both the liquid and solid state. The lattice energy of the continuous solid solution at all compositions is higher than that of the respective pure components in the solid state, because the hetoromolecular bonding strength is higher than the homomolecular one in order to form a continuous solid solution. **Figure 2** shows the hypothetical phase diagram of a continuous solid solution.

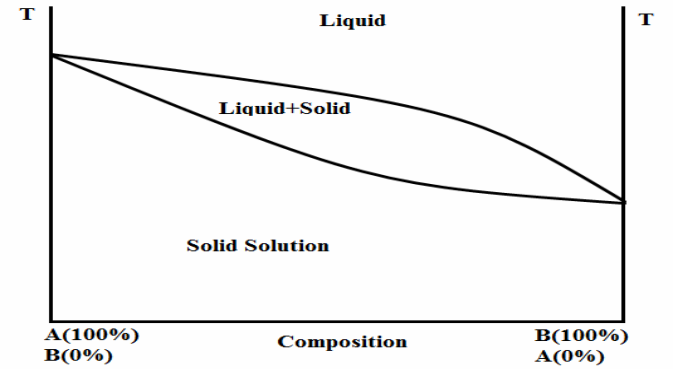

Figure 2: Hypothetical phase diagram of a continuous
solid solution

ii) Discontinuous solid solution

In discontinuous solid solutions, the miscibility or solubility of one component in the other is limited. **Figure 3** shows a typical phase diagram of a discontinuous solid solution. α and β shows the regions of true solid solutions. The region labelled α is a solid solution of B in A that is component A would be regarded as the solvent and B as the solute. Similarly the region labelled β is a solid solution of A in B. Below a certain temperatute, the mutual solubilities of the two components start to decrease. Goldberg et al[12] showed that the term solid solution should only be applied when the mutual solubility of the two components exceeds 5%. Formulation of dosage form with solid solution will depend on both the mutual solubilities of the two components and dose of the drug component. The maximum limit of a tablet or capsule is about 1 gram. Assuming that the solubility of the drug in the carrier is 10%, doses of above 100 mg would not be feasible with this strategy. If the drug solubility in the carrier is significantly higher than 10%, larger doses can be entertained.

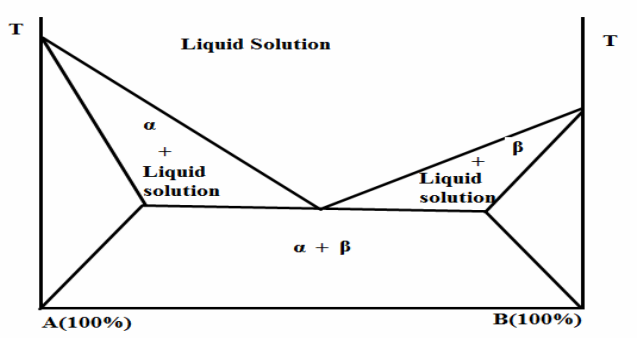

Figure 3: hypothetical phase diagram of a discontinuous solid solution

iii) Substitutional solid solution

In substitutional solid solutions the solid molecules replace the solvent molecule in the crystal lattice of the solid solvent. An extensive solid solution can only be formed when the effective diameter of the solute differs by less than 15%[15] from that of the solvent and when the packing patterns of solvent and solute are comparable. A substitutional solid solution is shown in F**igure 4**.

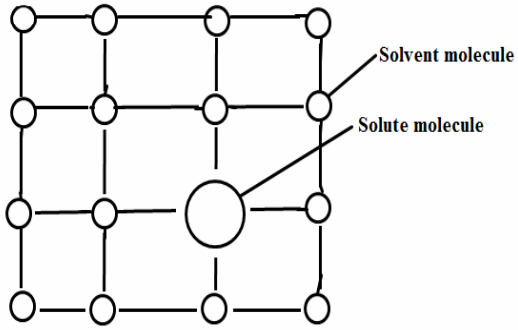

Figure 4: Substitutional solid solution

iv) Interstitial solid solution

In interstitial solid solutions the dissolved molecules occupy the interstitial spaces between the solvent molecules in the solvent crystal lattice. In order to fit into the interstices, the size of the solute molecules is critical. The diameter of solute molecules should be less than 59% of the diameter of the solvent molecules[16]. Furthermore, the volume of the solute molecules should be less than 20% of that of the solvent. **Figure 5** shows the arrangement of molecules in an interstitial solid solution.

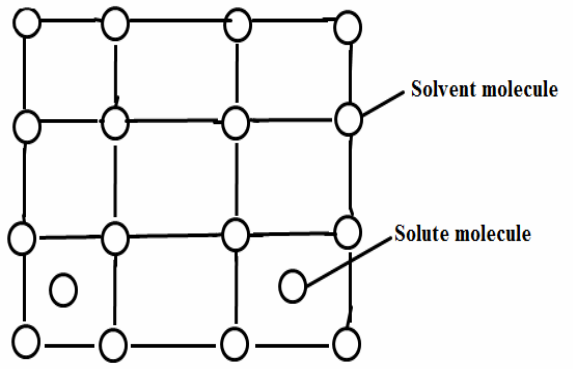

Figure 5: Interstitial solid solution

v) Amorphous solid solutions

The solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Chiou and Rigelman[17] were prepared solid dispersion using griseofulvin in citric acid and showed that they form amorphous solid solution to increase drug dissolution properties. Various carriers that were used included urea, sucrose, dextrose, galactose, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG).

Polymer carriers are particularly to form amorphous solid solutions as the polymer itself is present in the form of an amorphous polymer chain network. In addition, the solute molecules may save to plasticize the polymer, leading to a reduction in its glass transition temperature. An amorphous solid solution is depicted in F**igure 6**.

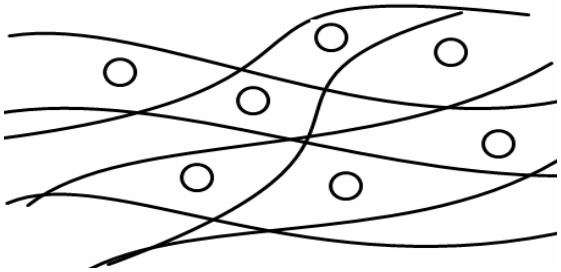

Figure 6: Amorphous solid solution

c) Glass solutions

A glass solution, also known as an amorphous solution, is a homogeneous system in which a glassy or a vitreous form of the carrier solubilises drug molecules. The glassy or vitreous state is characterized by transparency and brittleness below the glass transition temperature (T_g). The temperature at which a glassy polymer becomes rubbery on heating and a rubbery polymer reverts to a glassy one on cooling is called the glass transition temperature, T_g. The glass transition is not a sharp transition but a gradual transition and is the mid value of the temperature region of transition between brittle and soft. Well below the T_g, the glass solutions are hard, stiff glassy materials; at the temperature well above T_g, the materials are rubbery. They are formed by either (rapid) cooling of the melt or (rapid) evaporation of a solution.

Upon cooling or evaporation, the drug is vitrified into its glassy state in the amorphous carrier. Specific volume, specific heat, viscosity, refractive index, compressibility, thermal conductivity and other physico-chemical properties of the glass show changes when cooled or heated through the glass transition temperature. **Figure 7** shows the relationship between temperature (T) and volume (V) or enthalpy (H) for the liquid, glassy and crystalline state of a material.

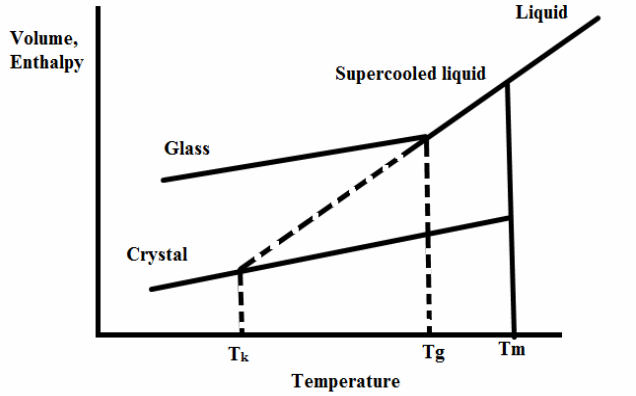

Figure 7: Schematic picture of the variation of enthalpy (or volume) with temperature

As the melted crystalline component is cooled, it may solidify below the melting point(T_m) into a crystalline state, or form a glass. Consider a molecular liquid that is slowly cooled. There is a discontinuity in both H and V at the melting temperature(T_m) representing the first order phase transition to the solid state. The average kinetic energy of molecules no longer exceeds the binding energy between neighbouring molecules and growth of organized solid crystals begins. Formation of an order system takes a certain amount of time. Upon rapid cooling the melt the values of H and V may follow the equilibrium line for the liquid beyond the melting temperature into a "super cooled liquid" region. On cooling further a change in slope is usually seen at a temperature T_g. At T_g the properties of the glassy material deviate from those of the equilibrium super cooled liquid to give nonequilibrium state having higher H and V than the super cooled liquid. As a result of higher internal energy the amorphous state should have enhanced thermodynamic properties relative to the crystalline state (e.g., solubility,

vapour pressure) and greater molecular motion. Below T_g the material is kinetically frozen into a thermodynamically unstable glassy state with respect to both the equilibrium liquid and the crystalline phase. The high internal energy and specific volume of the amorphous state relative to the crystalline state lead to enhance dissolution and bioavailability[18].

The main advantage of glass solutions over solid solutions is that they do not possess a strong lattice as true solid solutions and hence they do not present this barrier to rapid dissolution. An important disadvantage of glass solutions is that the glassy state is metastable compared to the crystalline state, and depending on its physicochemical properties and storage conditions a glass can convert into a crystalline solid[19]. Crystallization from the amorphous state over practical time scales can be prevented by keeping the operating temperature below T_g[20,21] by reducing the water content or by raising the T_g of the system using additives with high T_g values[14].

d) Complex formation

These are dispersions in which a drug forms a complex with an inert water soluble carrier in the solid state. The availability of the drug depends on the solubility and stability constant of the complex and the absorption rate of the drug. The dissolution rate of the drug and oral absorption are believed to be enhanced by formation of a water soluble complex with a high dissociation constant. Cyclodextrins are frequently used complex carriers. Cyclodextrins are cyclic (α-1,4) linked oligosaccharides of α-D-glucopyranose containing a relatively hydrophobic central cavity and hydrophilic outer surface. The parent or natural cyclodextrins consist of 6,7 or 8 glucopyranose units and are referred to as alpha(α-), beta(β-) and gamma (γ-) cyclodextrin respectively. Cyclodextrin forming a cavity of which the interior is rather hydrophobic, whereas the exterior is highly hydrophilic. The resulting complex hides most of the hydrophobic functionality in the interior cavity of the cyclodextrin while the hydrophilic hydroxyl groups on the external surface remain exposed to the environment. The net effect is that a water soluble cyclodextrin-drug complex is formed. Solubility of the various poorly water soluble drugs can be increased by this system[22-25].

e) Amorphous precipitation in a crystalline carrier

Instead of simultaneous crystallization of the drug and the carrier (eutectic system), the drug may also precipitate in an amorphous form in the crystalline carrier. The high energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug[26].

METHODS FOR MANUFACTURING OF SOLID DISPERSIONS

Various manufacturing methods for solid dispersions have been reported in literature. During the manufacturing techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by rapid cooling procedure[3,4]. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Serajuddin[27] reported the major limitation in the development of solid dispersions is the lack of suitable manufacturing techniques that could be scaled up to commercial production.

The various limitations are

a) Laborious and expensive methods of preparation.

b) Reproducibility of physicochemical characteristics.

c) Difficulty in incorporating into formulation of dosage forms.

d) Stability of the drug and vehicle.

Various methods have been tried recently to overcome the limitations and make the preparation more practically feasible while, at the same time, retaining both the physicochemical and bioavailability enhancing properties of solid dispersions.

Solvent Method

The solvent method aims to dissolve the drug and carrier simultaneously in a common solvent, followed by the removal of solvent by evaporation[28-29]. The solvent can be removed by any one of a number of methods. Temperatures used for solvent evaporation usually lie in the range 23-65^{0}C[30,31]. The solvent can also be

removed by freeze-drying[32] or by spray drying[33]. The drug used in solid dispersions is usually hydrophobic and the carrier is hydrophilic. It is often difficult to identify a common solvent to dissolve both components. Frequently used solvents include, ethanol, methanol and methylene chloride. In some cases, large volumes of solvents as well as heating may be necessary to enable complete dissolution of both the components. To minimize the volume of organic solvent necessary, some investigators reported the use of cosolvents[34].

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of solvents. Similarly, 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. However, solvent methods show multiple disadvantages such as; expensive, ecological and environmental problems, difficult to find a common and removable solvent, and residual solvent which can cause health risk and can have an effect on the physicochemical stability of drug, carrier and dispersion.

Tachibechi and Nakumara[35] were the first to dissolve both the drug (β-carotene) and the carrier (PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Mayersohn and Gibaldi[36] prepared solid dispersion by dissolving both griseofulvin and PVP in chloroform, and then evaporating the solvent. The release rate of griseofulvin from the solid dispersion was 5 to 11 times higher than that of micronized drug, depending on the drug/carrier ratio.

Solid dispersion of various poorly water soluble drugs prepared by solvent evaporation method presented in (**Table 1**).

Table 1: Preparation of solid dispersion of poorly soluble drugs by solvent evaporation method.

Drug	Carrier	Solvent	Solvent removal	Reference
Piroxicam	DMPC, PEG 4600.	Chloroform	Under current of N_2 gas for a period of 6 hours.	37
Felodipine	HPMC, Poloxamer 188, Poloxamer 407, HCO-60.	Ethanol	Using a rotary vacuum evaporator set to 45^0C and 45 rpm for 12 hours.	38
ABT-963	Pluronic F-68	Ethanol	Slowly evaporate at ambient condition over one week.	39
Carbamazepine	PVP K30, Gelucire 44/14	Methanol	Under vacuum in a rotavapor at 40^0C and 45 rpm for 24 hours.	40
Phenytoin	PEG 6000, PVP K30	Ethanol	Under reduced pressure at 40^0C.	41
Nimesulide	B-CD	Water: methanol = 1:1	Evaporated at a temperature of 45^0C	42
Pizotifen malate	PVP	Chloroform: methanol=1:1	Evaporated in oven at 40^0C	43
Itraconazole	Lactose, MCC, Primogel, Kolidone CL, AC-Di-Sol	Dichloromethane	Evaporated at 60^0C for 4 hours.	44
Furosemide	PVP	Methanol	Using rotary evaporator under reduced pressure at 70^0C.	45
Diflunisal	PVP	Ethanol or chloroform	Under vacuum in a rotary evaporator at 40^0C.	46
Naproxen	Ethyl cellulose, lactose	Ethyl ether: methanol =1:1	Constantly stirred at 40^0C until complete evaporation.	47
Nilvadipine	L-HPC, Croscarmellose-Na, Carmellose, Carmellose-Ca, Crospovidone	Ethanol	Under reduced pressure at 45^0C	48
Nifedipine	Hypermellose acetate succinate, hypermellose phthalate, povidone K30, methacrylic acid ethyl acrylate copolymer	Ethanol: dichloromethane=1:1	Evaporated at 60-80^0C	49

Melting Method

The melting method aims to heat the physical mixture of drug and carrier to the liquid state followed by cooling, resulting in solidification of the melt. This melting method can be performed by mixing drug and carrier in a beaker on an oil bath followed by cooling the mixture in an ice bath. Sekiguchi and Obi[4] used a melting method to prepare simple eutectic mixtures. Sulfathiazole and urea were melted together at a temperature above the eutectic point and then cooled in an ice bath. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix.

Although frequently applied, the melting method has serious limitations. Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture, [50,51] which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants[52,53]. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separations can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions[54,55]. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to melt matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169^0C was required[56] and in order to get the glassy PVP in the rubbery state a temperature of about 170^0C is required. PEG_S melt at around 70^0C and are therefore often used for the preparation of solid dispersions with the melting method.

Solid dispersion of various poorly water soluble drugs prepared by melting method presented in (**Table 2**).

Table 2: Preparation of solid dispersions by melting method

Drug	Carrier	Melting temperature	Reference
Sodium ferulate	Compritol 888 ATO	75^0C	57
Nifedipine	Pluronic F-68	100^0C	58
Carbamazepine	PEG 6000	200^0C	59
Triamterene	D-mannitol	165^0C	60
Glyburide	PEG 4000, PEG 6000	120^0C	61
Oxazepam	PEG 1500. PEG 4000, PEG 6000	100^0C, 150^0C	62
Itraconazole	PEG 3350, 8000,20000,glycerol,HPMC	120^0C	63
Ibuprofen	PEG 20000	90-95^0C	64

Melting Solvent method

The melting –solvent method is a combination of the two methods mentioned above. It is performed by dissolving the drug in a suitable solvent and mixing of this solution with the molten carrier followed by cooling, resulting in solidification[65,66]. The advantage of this method is that it can reduce maximum temperature and result in less decomposition of thermolabile drugs. However, only a low drug loading is possible for this method.

Hot Melt Extrusion

Hot melt extrusion is a very common way of processing plastics in the polymer industry, but Speiser[67,68] and Huttenrach[69] were the first to adapt the process for pharmaceutical purposes. The process has been useful in the preparation of solid dispersions in a single step. Hot melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained release pellets. A melt extrusion consists of an opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. Typically, a physical mixture of drug substance and other ingredients is fed into the heated barrel of extruder at a controlled rate. As the physical mixture is conveyed through heated screws, it is transformed into its "fluid like state", which allows intimate and homogeneous mixing by the high shear of extruder screws. The die then shapes the melt in the required form such as granules, pellets, films, or powder that can be further processed into conventional tablets or capsules. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drug that are somewhat thermolabile to be processed.

Polymers such as PVP, HPMC, polymethacrylate polymers, poly (ethylene oxides), HPMC acetate succinate, and so forth, were successfully used during hot melt extrusion to form solid dispersions of various drugs (Table 3).

***Corresponding Author:** Tapan Kumar Giri, **Email:** tapan_ju01@rediffmail.com,**Contact No:** 09229206752

Table 3: List of drugs and polymers used during the preparation

Drug	Carrier	Dosage form	Reference
Oxprenolol hydrochloride	Eudragit^{R} RS/RL	Pellets	70
Theophylline	Eudragit^{R} 4135F	Pellets	71
Diltiazem hydrochloride	Eudragit S	Granules	72
Lidocaine	Eudragit E	Transdermal and transmucosal drug delivery systems.	73
Chlorpheniramine hydrochloride	Hydroxypropyl Cellulose	Transdermal and transmucosal drug delivery systems.	74
Chlorpheniramine maleate	Poly(ethylene oxide)	Sustained release tablet	75
Melanotan-1	Poly(lactide-co-glycolide)	Implant	76
Melanotan-1	Poly(lactide-co-glycolide)	Implant	77
17β-Estradiol hemihydrate	PEG 6000, PVP K30	Tablets	78
Metoprolol tartrate	Ethyl cellulose	Sustained release mini-matrices	79

Spray Drying

Spray drying is a process where a solution of drug substance and carrier is evaporated by spraying the solution as fine droplets into a chamber that is maintained under controlled conditions of heat, humidity, and airflow. The spray drying principle involves evaporation of solvent or moisture from a mixture or an atomized feed by mixing the spray and the drying medium. The drying medium is typically air. Drying proceeds until the desired moisture content is reached in the sprayed articles and the product is then separated from the air.

Spray dryers can be used from small to very large scale productions depending on their design. They can reach evaporative capacities of upto 15,000 Ib/hour. The raw materials fluid is sprayed into hot air and transformed into droplets and then dried particles. The particle size of the dry product is very small in comparison with other solvent methods. It also provides the advantage of weight and volume reduction. The dissolution rate of many poorly water soluble drugs has been enhanced using spray drying[80,81]. Organic solvents are normally used during spray drying process as they are easy to evaporate and possess good solvent capacity for many poorly water soluble drugs. The morphology form of solid dispersion, and consequently the drug dissolution and stability, can be impacted by the process parameters and geometry of equipment. For instance, the particle size of spray-dried solid dispersion can be controlled by varying the concentration of solute in spray-drying liquid and the droplet size during spray-drying process[82].

Supercritical Fluid Technology

A supercritical fluid is any substance at a temperature and pressure above its critical point. It can diffuse through solids like a gas, and dissolve materials like a liquid. In addition, close to the critical point, small changes in pressure or temperature result in large changes in density, allowing many properties of a supercritical fluid to be "fine tuned". Supercritical fluids are suitable as a substitute for organic solvents in a range of industrial and laboratory processes. At the critical point, densities of liquid and gas are equal and there is no phase boundary, as shown F**igure 8**.

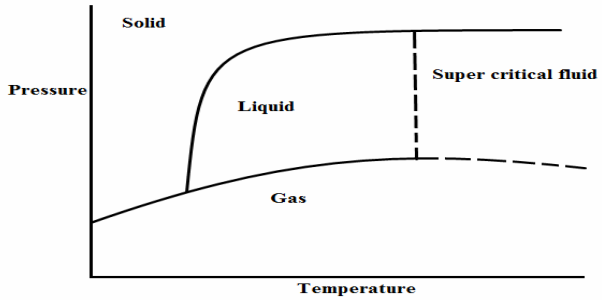

Figure 8: Supercritical region of a hypothetical compound

Above the critical point, that is, in the supercritical region, the liquid possesses the penetrating power typical a gas and the solvent power typical of a liquid. Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature (T_C) and pressure (P_C) [$T_C = 31.1^0$C, $P_C = 73.8$ bar]. Apart from being nontoxic, non-flammable, and inexpensive, the low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals.

Depending on the method by which solution and supercritical fluid are introduced and mixed into

each other, different applications have been described. These includes

a) Precipitation from supercritical solutions-rapid expansion of supercritical solution (RESS).

b) Gas antisolvent (GAS) or supercritical antisolvent (SAS) recrystallization.

c) Solution enhanced dispersion by supercritical fluids (SEDS).

d) Aerosol solvent interaction system (ASES).

e) Precipitation with compressed antisolvent (PCA).

f) Precipitation from gas-saturated solutions (PGSS).

a) Precipitation from supercritical solutions-rapid expansion of supercritical solution (RESS)

When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure, particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. The technique is known as rapid expansion of supercritical solution (RESS). During RESS process, the supercritical fluid is diffused through a bed of solid solute. As the fluid diffuses through the bed, the solid solute dissolves in it. The fluid solution is then depressurized in a separate chamber causing an extremely rapid nucleation and precipitation of high energy solids. However, the application of this technique is very limited, because the solubility in CO_2 of most pharmaceutical compounds is very low[83] and decrease with increasing polarity[84].

b) Gas antisolvent (GAS) or supercritical antisolvent (SAS) recrystallization

In this process, supercritical fluid is filled into a chamber and a batch of solution is introduced later. The supercritical fluid penetrates into the solution and expands it and resulting in precipitation of drug and matrix. When the volume of the solution expands the solvent strength (i.e., the ability to dissolve the drug) decreases. This results in precipitation of matrix and drug.

c) Solution enhanced dispersion by supercritical fluids (SEDS)

One intrinsic limitation of supercritical fluids is their inability to dissolve moderate to high polar compounds. Such compounds can be easily dissolved in suitable organic solvents, and supercritical fluids can be used as antisolvents to precipitate the solids. This procedure has been termed as "Solution enhanced dispersion by supercritical fluids" (SEDS).

d) Aerosol solvent interaction system (ASES)

Here, the solution is sprayed through atomization nozzle into a chamber filled with supercritical fluid. Expansion of solution occurs within the fine droplets of solvent being sprayed, thus creating supersaturation and precipitation of solids as fine particles.

e) Precipitation with compressed antisolvent (PCA)

In precipitation with compressed antisolvent process higher mass transfer rate and efficient crystallization are achieved by spraying compressed antisolvent into solution being sprayed.

f) Precipitation from gas-saturated solutions (PGSS)

In the PGSS process, a melt of the drug and carrier saturated with supercritical CO_2 is rapidly cooled by adiabatic expansion of CO_2 whereupon the solid dispersion precipitates in the form of microparticles. This rapid cooling and expansion of CO_2 produces fine particles with a narrow particle size distribution and, therby, avoids the communition step. In principle, the technique is similar to the RESS process except that on expansion the phase separation is caused by evaporation of the volatile component from the homogeneous liquid phase. Because no organic solvent is used, the tedious process of removal of residual solvent is completely avoided (CO_2 is an inert gas at atmospheric pressure).

Direct Capsule Filling

Francois and Jones[85] was first described the filling of semisolid materials into hard gelatine capsules as melts, which solidify at room temperature. It was not until much later that the potential application of the technique for solid dispersions was fully realized. Chathan[86]prepared PEG-based solid dispersions by filling drug-PEG melt in hard gelatine capsules. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature. 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[87]. Serajuddin et al[88] and Law et al[89] mixed surfactant to drug-carrier melt to avoid formation of a drug-rich surface layer.

Use of surfactant

The interest to use surface active and self-emulsifying carriers for the solid dispersion of poorly soluble drugs increased in recent years[90-91]. Serajuddin et al [92] achieved a complete dissolution of drug from solid dispersions by using surface active or self-emulsifying carriers. Such carriers prevented the formation of the water insoluble surface layers by dispersing or emulsifying the drug in a finely divided state, which resulted in a high surface area of the drug. This would facilitate its dissolution in the gastrointestinal fluids, especially in the presence of bile salts, lecithin, and lipid digestion mixtures.

The commonly used surface active carriers in solid dispersions for bioavailability enhancement of drugs are Gelucire 44/14, vitamin E TPGS NF and Tween 80. Serajuddin and coworkers[88,91,93] demonstrated that Tween 80 could be used in solid dispersions by mixing it with solid PEG. The crystalline structure of solid PEG was minimally affected by polysorbate 80 because the two compounds have a low miscibility in each other. The bioavailability of this kind of solid dispersion showed a 20 fold increase compared to the dry blend of micronized drug with microcrystalline cellulose.

Electrostatic Spinning

In an electrostatic spinning process a drug matrix solution is pumped through an orifice and then subjected to an electrical field. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibres of submicron diameters are formed. As the solvent evaporates, the formed fibres can be collected on a screen to give nanofibers. This electrospun fibre can be incorporated into hard gelatine capsules. This process is restricted to a limited amount of matrices, because only a few high molecular weight materials are fibre forming materials. The fibre diameter can be adjusted by surface tension, electrical field and dielectric constant[81]. After rapid evaporation of the solvent, the fibres can be directly used or milled and further processed[94].

Melt Agglomeration

A rotary processor has been used for the preparation of solid dispersion by melt agglomeration method. Binder acts as a carrier by this technique. Solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray on procedure) by using a high shear mixer. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray on procedure with PEG 3000, poloxemer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerates formation and growth. In addition the melt in procedure also results in homogeneous distribution of drug in agglomerate.

Cryogenic Technique

It is proposed that all fluids which have a critical temperature which lies below or within the normal ambient temperature range be defined as cryogen. The upper limit of the normal ambient temperature range is selected to be 323.18^0K (50^0C). This is the arbitrary but rational. Based on this concept, cryogens then, are those gases which cannot exist as liquids, without refrigeration, regardless of the amount of pressure which is applied. The family of cryogens will begin with Helium II near the lower boundary and include CO_2 at the upper boundary.

Cryogenic processing techniques have been developed to enhance the dissolution rate by creating nanostructured amorphous particles with high degree of porosity. Cryogenic process allow for a reduction in the primary particle size of drug particles without the intense frictional or mechanical forces involved in ball-milling or other processes relying on frictional communition or trituration with a mortar and pestle, which can cause degradation of the drug through thermal stress. Initially the feed solution is dispersed through an injection device (capillary, rotary, pneumatic or ultrasonic nozzle) in a cryogenic medium. After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilisation.

There are various cryogenic techniques for the preparation of solid dispersion particles. These include

a) Spray freezing onto cryogenic fluids
b) Spray freezing into cryogenic fluids
c) Spray freeze drying
d) Ultra rapid freezing

a) Spray freezing onto cryogenic fluids

In this technique, the drug and the carrier were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution. Briggs and Maxvell[95] prepared powder blends by using this technique.

b) Spray freezing into cryogenic fluids

In this technique, a feed solution containing an active pharmaceutical ingredient and pharmaceutical excipient (s) is atomized beneath the surface of a cryogenic liquid, such as liquid nitrogen. The impingement between the feed solution and cryogenic liquid results in intense atomization of the feed into microdroplets, which freeze instantly in the cryogen. Thus, the frozen microparticles are suspended within the cryogenic continuous phase. The suspended frozen phase can be separated from the continuous phase by sieve separation or by allowing the cryogen to evaporate. Once the frozen microparticles are collected, the solvent(s) can be removed by lyophilisation. The dry micronized powder contains the active pharmaceutical ingredient molecularly embedded within a pharmaceutical excipient matrix.

c) Spray freeze drying

The spray freeze drying method typically involves the atomization of a drug containing solution in gaseous nitrogen above a pool of liquid nitrogen. The fine droplets of drug/solvent are frozen, then lyophilized to remove the solvent. The rapid freezing rates in the cryogenic liquids substrate do not allow for molecular arrangement into crystalline domains, so this process produces amorphous drug nanoparticle aggregates with improved dissolution rates. The scalability of this type of technology, however, has limited its widespread industrial use.

d) Ultra rapid freezing

Ultra rapid freezing technology involves the use of a solid cryogenic substrate with a thermal conductivity between 10 and 20 W/m degrees K. A solution of the drug is applied to the solid surface of the substrate, where instantaneous freezing takes place. Brownian motion of the particles in solution is slowed significantly, so reactive species have little to react before being frozen into the solid state. Removal of the frozen particles and lyophilisation of the solvent produces stable amorphous particles. This technique has been investigated for solubility enhancement of repaglinide[96].

Spraying a sugar beads using a fluidized bed coating system

In this method fluidized beds are used to spray solutions onto the granular surface of excipients or sugar spheres to produce granules ready for tableting or drug coated pellets for encapsulation in one step. Here drug and hydrophilic carrier are dissolved in common organic solvent to produce solution which is coated over sugar bead and then solvent is evaporated to form solid solution of drug in carrier absorbed over sugar beads. Kennedy and Niebergall described a hot-melt fluid bed method whereby non-pareils could be coated with PEG_S with molecular weights between 1450 and 4600[97]. Itraconazole solid dispersion with HPMC is coated on sugar sphere by evaporation of organic solvents where HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole[98].

Conclusion

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water soluble drugs. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method. Various techniques described in this review are successfully used for the preparation of solid dispersions in the bench and lab scale and can be used as industrial scale also. These include methods like hot-melt extrusion, spraying on sugar beads, and direct capsule filling. Hence these techniques are expected to form a basis for the commercialization of many poorly water soluble and water-insoluble drugs in their solid dispersion formulations in the near future.

Reference

1. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12: 413-420.
2. Monkhouse DC, Lach JL. Use of adsorbents in enhancement of drug dissolution. I. J Pharm Sci. 1972; 61: 1430-35.
3. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971; 60: 1281-1302.
4. Sekigushi K, Obi N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9: 866-872.
5. Van den Mooter G, Augustijns P, Blaton N, Kinget R. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000

and PVP K30.Int J Pharm. 1998;164: 67-80.
6. Ford JL. 1986. The current status of solid dispersions. Pharm Acta Helv. 1986;61: 69-88.
7. Ozeki T, Yuasa H, Kanaya Y. Application of the solid dispersion method to the controlled release of medicine. IX. Difference in the release of flurbiprofen from solid dispersions with poly(ethylene oxide) and hydroxypropylcellulose and the interaction between medicine and polymers, Int J Pharm. 1997;115: 209-217.
8. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci.1997; 86:1-12.
9. Goldberg AH, Gibaldi M, Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixture II-experimental evaluation of a eutectic mixture; urea-acetaminophen system. J Pharm Sci. 1966; 55:482-487.
10. Levy G. Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. Amer J Pharm. 1963; 135:78-92.
11. Kanig JL, Properties of fused mannitol in compressed tablets. J Pharm Sci. 1964; 53: 188-192.
12. 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: 1145-1148.
13. Karavas E, Ktistis G, Xenakis A, Georgarakis E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. E J Pharm Biopharm. 2006; 63: 499-514.
14. Yoshioka M, Hancock BC, Zogra G. Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. J Pharm Sci. 1995; 84: 983-986.
15. Hume-Rotherly W, Raynor GV. The structure of metals and alloys, Institute of metals, London, 1954.
16. Reed-Hill RE. Physical Metallurgy Principles. D Van Nostrand Co.Inc,1964.
17. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci. 1969;58:1505-1510.
18. Huttenrauch R. Acta Pharm Technol Suppl. 1978; 6: 55-127.
19. Yoshioka M, Hancock BC, Zografi G. Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. J Pharm Sci. 1994; 83: 1700-1705.
20. Jolley JE. Photogr Sci Eng. 1970; 14: 169-177.
21. Okamoto N, Oguni M. Discovery of crystal nucleation proceeding much below the glass transition temperature in a supercooled liquid . Solid State Commun. 1996; 99: 53-56.
22. Brewster ME, Loftsson T. The use of chemically modified cyclodextrines in the development of formulations for chemical delivery systems. Pharmazie. 2002; 57: 94-101.
23. Veiga MD, Diazi PJ, Ahsan F. Interaction of griseofulvin with cyclodextrins in solid binary systems. J Pharm sci. 1998; 87: 891-900.
24. Duchene D, Wouessidjewe D. Pharmaceutical uses of cyclodextrins and derivatives. Drug Dev Ind Pharm. 1990; 16: 2487-2499.
25. 25.Zhang MQ, Rees DC. A review of recent applications of cyclodextrins for drug discovery. Exp Opin Ther Patent. 1999; 9: 1697-1717.
26. Sato T, Okado A, Sekiguchi K, Tsuda Y. Difference in physic-pharmaceutical properties between crystalline and non-crystalline 9,3-diacetylmidecamycin. Chem Pharm Bull. 1981; 29:2675-2682.
27. Serajuddin ATM. Solid dispersion of poorly water soluble drugs: Early promises, subsequent problems, and recent breakthrough. J Pharm Sci. 1999; 88: 1058-1066.
28. Simonelli AP, Mehta SC, Higuchi WI. Dissolution rates of high energy poly(vinylpyrrolidone)(PVP)-sulfathiazole coprecipitates. J Pharm Sci. 1969; 58: 538-549.

29. Thakkar AL, Hirsch CA, Page JG. Solid dispersion approach for overcoming bioavailability problems due to polymorphism of nabilone, a cannabinoid derivative. J Pharm Pharmacol. 1977; 29: 783-784.
30. Kearney AS, Gabriel DL, Mehta SC, Radebaugh GW. Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the anti-inflammatory Ci-987. Int J Pharm. 1994; 104:169-174.
31. El-Zein H, Riad L, Elbary AA. Enhancement of carbamazepine dissolution-in vitro and in-vivo evaluation. Int J Pharm. 1998; 168:209-220.
32. Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilisation techniques. Int J Pharm. 1965;126:155-160.
33. Lo WY, Law SL. Dissolution behaviour of griseofulvin solid dispersions using polyethylene glycol,talc, and their combination as dispersion carriers. Drug Dev Ind Pharm. 1996;22:231-236.
34. Usui F, Maeda K, Kusai A, Ikeda M, Nishimura K, Yamamoto K. Dissolution improvement of RS-8359 by solid dispersions prepared by the solvent method. Int J Pharm. 1998; 170: 247-256.
35. Tachibana T, Nakamura A. A method for preparing an aqueous colloidal dispersion of organic materials by using water-soluble polymers: dispersion of beta-carotene by polyvinylpyrrolidone. Kolloid-Z Polym. 1965; 203: 130-133.
36. Mayersohn M, Gibaldi M. New method of solid-state dispersion for increasing dissolution rates. J Pharm Sci. 1966;55:1323-1324.
37. Prabhu S, Ortega M, Ma C. Novel lipid-based formulations enhancing the in vitro dissolution and permeability characteristics of a poorly water-soluble model drug, piroxicam. Int J Pharm. 2005; 301: 209-216.
38. Won DH, Kim MS, Lee S, Park JS, Hwang SJ. Improved physicochemical characteristics of felodipine solid dispersion particles by supercritical anti-sovent precipitation process. Int J Pharm. 2005; 301: 199-208.
39. 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.
40. Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm. 2004; 272: 1-10.
41. Franco M, Trapani G, Latrofa A, Tullio C, Provenzano MR, Serra M, Muggironi M, Biggio G, Liso G. Dissolution properties and anticonvulsant activity of phenytoin-polyethylene glycol 6000 and polyvinylpyrrolidone K-30 solid dispersions. Int J Pharm. 2001;225: 63-73.
42. Chowdary KPR, Nalluri BN. Nimesulide and β-cyclodextrin inclusion complexes: Physicochemical characterization and dissolution rate studies. Drug Dev Ind Pharm. 2000; 26(11): 1217-1220.
43. Margarit MV, Marin MT, Contreras MD. Solubility of solid dispersions of pizotifen malate and povidone. Drug Dev Ind Pharm. 2001; 27(6): 517-522.
44. Chowdary KPR, Rao SS. Investigation of dissolution enhancement of itraconazole by solid dispersion in superdisintegrants. Drug Dev Ind Pharm. 2000; 26(11): 1207-1211.
45. Lannuccelli V, Coppi G, Leo E, Fontana F, Bernabei T. PVP solid dispersions for the controlled release of furosemide from a floating multiple-unit system. Drug Dev Ind Pharm. 2000; 26(6): 595-603.
46. Martinez-Oharriz MC, Rodriguez-Espinosa C, Martin C, Goni MM, Tros-llarduya MC, Sanchez M. Solid dispersions of diflunisal-PVP: Polymorphic and amorphous states of the Drug. Drug Dev Ind Pharm. 2002; 28(6): 717-725.
47. Iqbal Z, Babar A, Ashraf M. Controlled-release naproxen using micronized Ethyl Cellulose by wet-granulation and solid dispersion method. Drug. Drug Dev Ind Pharm. 2002; 28(2): 129-134.
48. Hirasawa N, Ishise S, Miyata H, Danjo K. Physicochemical characterization and drug release studies of nilvadipine solid dispersions using water-insoluble polymer

as a carrier. Drug Dev Ind Pharm. 2003; 29(3): 339-344.
49. Tanno F, Nishiyama Y, Kokubo H, Obara S. Evaluation of Hypromellose acetate succinate(HPMCAS) as a carrier in solid dispersions. Drug Dev Ind Pharm. 2004; 30(1): 9-17.
50. Greenhalgh DJ, Williams AC, Timmins P, York P.Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci. 1999; 88(11): 1182-1190.
51. Timko RJ, Lordi NG. Thermal analysis studies of glass dispersion systems. Drug Dev Ind Pharm. 1984; 10(3): 425-451.
52. 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(1-2): 87-98.
53. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJ. Solid state characterization of nifedipine solid dispersions. Int J Pharm. 2002; 236(1-2): 111-123.
54. Save T, Venkitachalam P. Studies on solid dispersions of nifedipine. Drug Dev Ind Pharm. 1992; 18(15): 1663-1679.
55. McGinity JW, Maincent P, Steinfink H. Crystallinity and dissolution rate of tolbutamide solid dispersions prepared by the melt method. J Pharm Sci. 1984; 73(10): 1441-1444.
56. Allen LVJ, Yanchick VA, Maness DD. Dissolution rates of corticosteroids utilizing sugar glass dispersions. J Pharm Sci. 1977; 66(4): 494-496.
57. Li FQ, Hu JH, Deng JX, Su H, Xu H, Liu JY. In vitro controlled release of sodium ferulate from compritol 888 ATO-based matrix tablets. Int J Pharm. 2006; 324: 152-157.
58. Mehta KA, Kislalioglu MS, Phuapradit W, Malick AW, Shah NH. Muli-unit controlled release systems of Nifedipine and Nifedipine: Pluronic F-68 solid dispersions: Characterization of release mechanisms. Drug Dev Ind Pharm. 2002;28(3):275-85.
59. Zerrouk N, Chemtob C, Arnaud P, Toscani S, Dugue J. In vitro and in vivo evaluation of carbamazepine-PEG 6000 solid dispersions. Int J Pharm. 2001; 225: 49-62.
60. Arias MJ, Gines JM, Moyano JR, Perez-Martinez JI, Rabasco AM. Influence of the preparation method of solid dispersions on their dissolution rate: study of triamterene-D-mannitol system. Int J Pharm. 1995; 123: 25-31.
61. Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilisation technique. Int J Pharm. 1995; 126: 155-160.
62. Gines JM, Arias MJ, Moyano JR, Sanchez-Soto PJ. Thermal investigation of crystallization of polyethylene glycols in solid dispersions containing oxazepam. Int J Pharm. 1996; 143: 247-253.
63. Kapsi SG, Ayres JW. Processing factors in development of solid solution formulation of itraconazole for enhancement of drug dissolution and bioavailability. Int J Pharm. 2001; 229: 193-203.
64. Newa M, Bhandari KH, Lee DX, Sung JH, Kim JA, Yoo BK, Woo JS, Choi HG, Yong CS. Enhanced dissolution of ibuprofen using solid dispersion with polyethylene glycol 20000. Drug Dev Ind Pharm. 2008; 34: 1013-1021.
65. Vera N, Viga MD, Cadorniga R. Solid dispersions of oxodipine/PEG 6000 characterization and dissolution study. S T P Pharm Sci. 1991; 1:125-129.
66. Fernandez M, Rodriguez IC, Margarit MV, Cerezo A. Characterization of solid dispersions of piroxicam/poly-(ethylene glycol) 4000. Int J Pharm. 1992; 84: 197-202.
67. Speiser P. Galenische Aspecte der Arzneimittelwirkung. Pharm Acta Helv. 1966;41:321-342.
68. Adel EI-Egakey M, Soliva M, Speiser P. Hot extruded dosage forms. Pharm Acta Helv. 1971;46:31-52.
69. Huttenrauch R. Spritzgieβverfahren zur Herstellung peroraler Retardpraperate. Pharmazie. 1974;29:297-302.
70. Follonier N, Doelker E, Cole ET. Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained release capsules containing high loadings of freely soluble drugs. Drug Dev Ind Pharm. 1994; 20(8):1323-1339.
71. Young CR, Koleng JJ, McGinity JW. Production of spherical pellets by a hot-

melt extrusion and spheronization process. Int J Pharm. 2002; 242: 87-92.
72. Follonier N, Doelker E, Cole ET. Various ways of modulating the release of diltizem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. J Control Release. 1995; 36(3): 243-250.
73. Aitken –Nichol C, Zhang F, McGinity JW. Hot-melt extrusion of acrylic films. Pharm Res. 1996; 13(5): 804-808.
74. Repka MA, Gerding TG, Repka SL, McGinity JW. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot melt extrusion. Drug Dev Ind Pharm. 1999a; 25(5): 625-633.
75. Crowley MM, Schroeder B, Fredersdorf A, Obara S, Talarico M, Kucera S. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablet prepared by direct compression and hot melt extrusion. Int J Pharm. 2004b; 271(1-2): 77-84.
76. Crowley MM, Zhang F, Koleng JJ, McGinity JW. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Bio Materials. 2002; 23(21): 4241-4248.
77. Bhardwaj R, Blanchard J. In vitro evaluation of poly(D,L-lactide-co-glycolate) polymer-based implants containing the alpha-melanocyte stimulating hormone analog, melanotan-I. J Control Release. 1997; 45(1): 49-55.
78. Bhardwaj R, Blanchard J. In vitro characterization and in vivo release profile of a poly(D,L-lactide-co-glycolide)-based implant delivery system for the alpha-msh analog, melanotan-I. Int J Pharm. 1998; 170(1): 109-117.
79. Hulsmann S, Backensfeld T, Keitel S, Bodmeier R. Melt extrusion-an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrates. E J Pharm Biopharm. 2000; 49: 237-242.
80. Ambike AA, Mahadik KR, Paradkar A. Spray-dried amorphous solid dispersions of simvastatin, a low T_g drug : In vitro and in vivo evaluations. Pharm Res. 2005; 22: 990-998.
81. Sethia S, Squillante E. Solid dispersions: Revival with greater possibilities and applications in oral drug delivery. Crit Rev Ther Drug Carrier Syst. 2003; 20: 215-247.
82. Elversson J, Millqvist-Fureby A, Alderborn G, Elofsson U. Droplet and particle size relationship and shell thickness of inhalable lactose particles during spray drying. J Pharm Sci. 2003; 92: 900-910.
83. Subramaniam B, Rajewski RA, Snavely K. Pharmaceutical processing with supercritical carbondioxide. J Pharm sci.1997; 86(8): 885-890.
84. Kompella UB, Koushik K. Preparation of drug delivery systems using supercritical fluid technology. Crit Rev Ther Drug Carrier Syst. 2001; 18(2): 173-199.
85. Francols D, Jones BE. The hard capsule with the soft center. European capsule technology symposium, constance, October 11-13. 1978: 55-61.
86. Chatham SM. The use of bases in SSM formulations. S T P Pharm. 1987; 3: 575-582.
87. Serajuddin ATM, Sheen PC, Mufson D, Bernstein 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.
88. Serajuddin ATM, Sheen PC, Augustine MA. 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.
89. Law SL, Lo WY, Lin FM, Chaing CH. Dissolution and absorption of nifedipine in poly(ethylene glycol) solid dispersion containing phosphatidylcholine. Int J Pharm. 1992; 84: 161-166.
90. Dannenfelser RM, He H, Joshi Y. Development of clinical dosage forms for a poorly water soluble drug: application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. J Pharm Sci. 2004; 93: 1165-1175.
91. Morris KR, Knipp GT, Serajuddin ATM. Structural properties of poly(ethylene glycol)-polysorbate 80 mixture, a solid

dispersion vehicle. J Pharm Sci. 1992; 81: 1185-1188.

92. Serajuddin ATM, Sheen PC, Mufson D, Bernstein DF, Augustine MA. Physicochemical basis of increased bioavailability of a poorly water-soluble drug following oral administration as organic solutions. J Pharm Sci. 1988; 77: 325-329.
93. Joshi HN, Tejwani RW, Davidovich M, Sahasrabudhe VP, Jemal M, Bathala MS, Varia SA, Serajuddin ATM. Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80mixture. Int J Pharm. 2004; 269: 251-258.
94. Verreck G, Chun I, Peeters J, Rosenblatt J, Brewter ME. Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning. Pharm Res. 2003; 20: 810-817.
95. Briggs AR, Maxvell TJ. Process for preparing powder blends. Patent US 3721725, 1973.
96. Purvis T, Mattucci ME, Crisp MT, Johnston KP, Williams RO. Rapidly dissolving Repaglinide powders produced by the ultra-rapid freezing process. AAPS Pharm Sci. 2007; 8(3):1-9.
97. Kennedy JP, Niebergall PJ. Development and optimization of a solid dispersion hot bed fluid bed coating method. Pharm Dev Technol. 1996; 1: 51-62.
98. Gills PA. Beads having a core coated with an antifungal and a polymer. US patent 5633015, 1997.