Research Article

Solid Dispersion: A Novel Approach for Bioavailability Enhancement

Nishant Thakur*[1], Manish Goswami[1], Payal Mittal, Pradeep Goyal[1], Aditya Sood[2]
[1]UIPS, Chandigarh University, Gharuan, Mohali, Punjab, India.
[2]Department of Biotechnology, Chandigarh University, India.
***Corresponding author's E-mail:** nishant.thakur33@rediffmail.com

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ABSTRACT

The rate and extent of dissolution of the drug from any solid dosage form determines the rate and extent of absorption of the drug. In case of poorly water soluble drug, dissolution rate is rate limiting step in the process of drug absorption. Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited. Two basic procedures used to prepare solid dispersions are the melting or fusion and solvent evaporation techniques. The mechanisms for increased dissolution rate may include reduction of crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersbility of the drug from the dispersion, dissolution of the drug in the hydrophilic carrier or conversion of drug to an amorphous state. The present review deals in detail about solid dispersion technology and its manufacturing techniques at laboratory level and compiles some of the recent technology transfers. The different types of solid dispersions based on the molecular arrangement have been highlighted.

Keywords: Solid dispersion; eutectic, poor solubility; bioavailability; dissolution.

INTRODUCTION

Among all of the newly discovered chemical entities about 40% drugs are lipophillic in nature and fail to reach market due to their poor water solubility. The BCS classification is used for classifying a drug based on its aqueous solubility and intestinal permeability.[1] It is obvious from the BCS scheme that BCS-2 drugs, due to their low water solubility are not able to permeate through the intestinal wall effectively. Consequently poor solubility results in low bioavailability, increase in the dosage, large inters and intra-subject variation and large variation in blood drug concentrations under fed versus fasted conditions. The enhancement of oral bioavailbility of such poorly water-soluble drugs remains one of the most challenging aspects of drug development[2]. Thus more stress is given on the solubility enhancement of such drugs.[3]

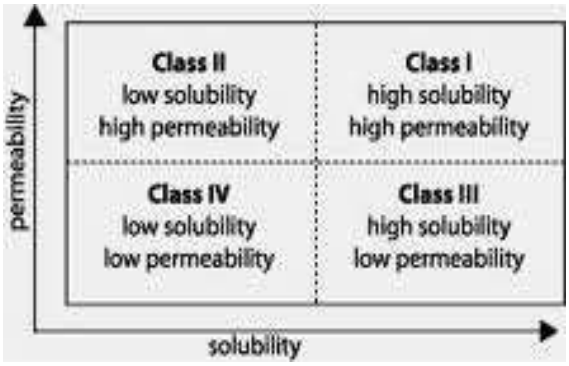

Figure 1: The BCS classification scheme

Several techniques have been developed for the solubility enhancement of poorly soluble drugs by physical and chemical modifications[4]. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states by using various techniques like micronization, use of metastable polymorphs, solvent deposition, selective adsorption on insoluble carriers, solid dispersion, solute solvent complexation, complexation with cyclodextrins[5].

Chemical modifications includes soluble salt formation and prodrug approaches[6].

Solid Dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water soluble carrier in the early 1960s. Solid dispersion represents a useful pharmaceutical technique for increasing the solubility profile of BCS class-2 drugs and they have proven to increase the dissolution, absorption and therapeutic efficacy of drugs in dosage forms[1,7-12].

In solid dispersion system, drug and carrier matrix are mixed. Generally a hydrophilic coat is developed upon the drug. The solid dispersion system has lower energy so that it dissolves easily and effectively as compared to the pure drug. The solid dispersion represents the system with lower crystallanity.

A solid dispersion can be defined as "A dispersion of one or more active ingredients in an active carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method,[13] or some time by kneading".

Physiochemical Classification of Solid Dispersions

Based on the molecular arrangements solid dispersions can be classified into the following categories[14]

- Simple Eutectic Mixtures
- Solid Solutions
- Glass Solutions and Glass Suspensions
- Amorphous Precipitations in Crystalline Carriers
- Compound or complex formations
- Combinations of previous five

Simple Eutectic Mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of fused melt of two components that show complete liquid miscibility but negligible solid-solid solubility in order to obtain a physical mixture of very fine crystals of the two components. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. When a mixture with composition E (figure-2), consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium the carrier will dissolve rapidly, releasing very fine crystals of the drug[15,16]. The large surface area of resulting suspensions should result in an enhanced dissolution rate and thereby improved bioavailability. Examples of this type include phenacetin-phenobarbital[17], chloramphenicol-urea[10], griesofulvin-succinic acid[18].

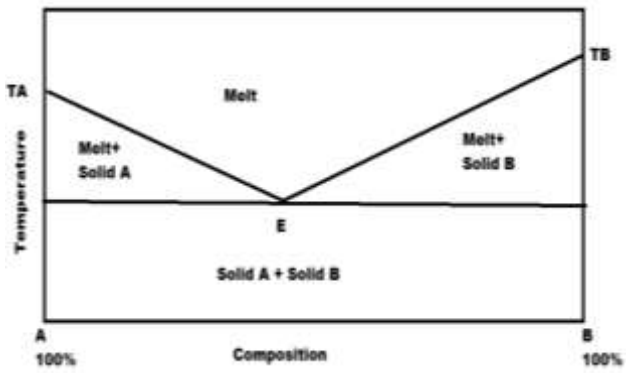

Figure 2: Binary phase diagram of composition E

Solid Solutions

In a solid solution, the two components crystallize together in a homogeneous one phase system. Because of reduction of particle size to its molecular level, solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of number of components.

Solid solutions of a poorly water soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as to improve solubility and bioavailability. In case of solid solutions, drugs particle size has been reduced to its absolute minimum viz the molecular dimensions[19] and the dissolution rate is determined by the dissolution rate of carrier, by judicious selection of carrier. The dissolution rate of the drug can be increased by up to several orders of magnitude.

According to the extent of miscibility of two components, solid solutions can be classified in to two types i.e. continuous and discontinuous and on the basis of molecular size of the two components; the solid solutions are classified as substitutional or interstitial.

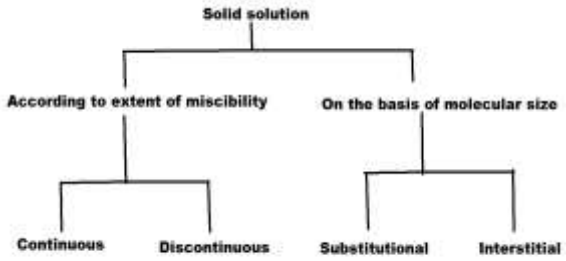

Figure 3: Solid solution classification

Continuous and Discontinuous Solid Solutions

Continuous Solid Solutions

In continuous solid solutions, the two components are miscible in the solid state in all proportions as shown in (figure4). Theoretically, this means that the bonding strength between the molecules of each of the individual components.

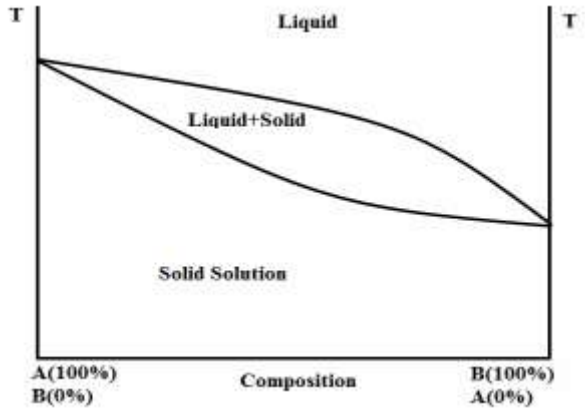

Figure 4: Hypothetical phase diagram of a continuous solid solution

Discontinuous Solid Solutions

In the case of discontinuous solid solutions, the solubility of each component in the other component is limited. Due to several practical implications it has been suggested by[19] that the term solid solution should only be applied when the mutual solubility of the two component exceeds 5%.

A typical phase diagram is shown in(figure5), α and β regions show true solid solutions. Discontinuous solid

solutions exists as extremes of compositions. In general, some solid state solubility can be expected from all component systems. In these regions, one of the solid component is completely dissolved in the other solid component but below a certain temperature, the mutual solubilities of two components start to decrease.

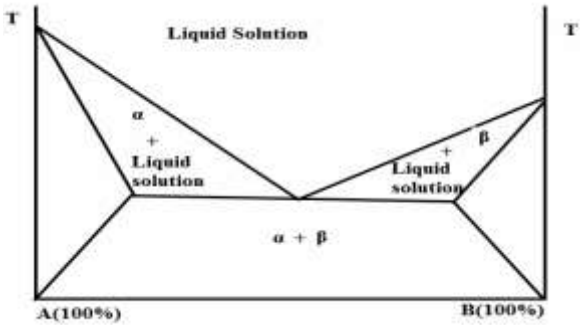

Figure 5: Hypothetical phase diagram of a discontinuous solid solution

Substitutional Crystalline, Interstitial Crystalline Solid Solutions

Classical solid solutions have a crystalline structure, in which solute molecule can either substitute for solvent molecule in the crystal lattice or fit into the interstices between the solvent molecules (Figure 6 b). Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecule.

Interstitial Crystalline Solid Solutions

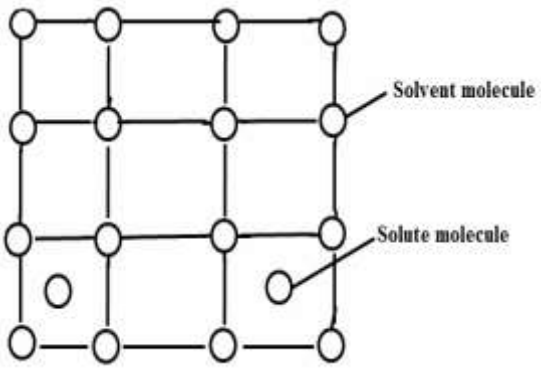

Figure 6a: Interstitial Solid Solution

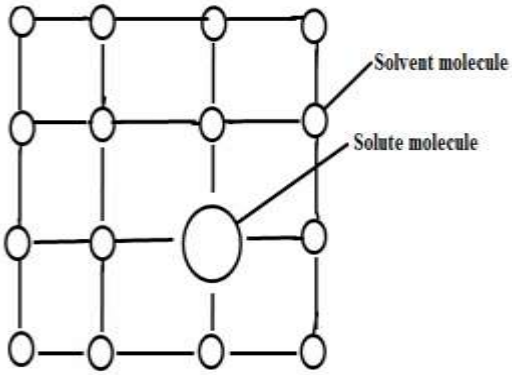

Figure 6b: Substitutionally Solid Solution

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice (Figure 6a). In the case of interstitial crystalline solid solutions, the solute molecules should have a diameter not greater than 0.59 of the solvent molecules diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent. Owing to their large molecular size, polymers favour the formation of interstitial solid solutions.

Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy carrier while a glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature (T_g). Glasses do not have a sharp melting points; instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions. Examples of carriers that form glass solutions and suspensions include citric acid, sugars such as dextrose, sucrose and galactose, PVP, urea and PEG.

Amorphous Precipitations in a Crystalline Carriers

This type of solid dispersion is distinguished from a simple eutectic mixture by the fact that the drug is precipitated out in an amorphous form. In a simple eutectic mixture, the drug is precipitated out in a crystalline form. It is postulated that a drug with a propensity to supercooling has more tendency to solidify as an amorphous form in the presence of a carrier. An example of this is the precipitation of sulfathiazole in the amorphous form in crystalline urea.[15]

Compound or Complex Formation

When two substances form a molecular compound, it usually gives rise to a maximum in the phase diagram. An example of this is the quinine-phenobarbital system[17]. It is difficult to generalize the influence of complex formation on dissolution. A complex between digoxin and hydroquinine exhibited a high dissolution rate[18].

Combinations and Miscellaneous Mechanisms

Quite often a solid dispersion does not entirely belong to any of the previously classes. For example, in a solid dispersion system, the drug can exist in both the amorphous state and the crystalline state in the carrier. Therefore, the observed increase in dissolution and absorption may be due to the combination of several mechanisms.

The Advantageous Properties of Solid Dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particle properties. Parameters such as carrier molecular weight and composition, drug crystallinity and particle porosity and washability, when

successfully controlled, can produce improvements in bioavailability[20].

Particles with Reduced Particle Size

As solid dispersion 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[21]. A high surface area is formed, resulting in an increased dissolution rate and consequently, improved bioavailability[22].

Particles with Improved Wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions[23,24] observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co solvent effects[21,25-26] in the third generation solid dispersions reinforced the importance of this property.

Particles with Higher Porosity

Particles in solid dispersions have been found to have a higher degree of porosity[27]. The increase in porosity also depends upon the carrier properties, i.e solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers resulting in a higher dissolution rate.[20]

Drugs in Amorphous State

Poorly water soluble crystalline drugs, when in amorphous state tend to have higher kinetic solubility[28-30]. The enhancement of drug release can usually be achieved using the drug in its amorphous form. Because no energy is required to break up the crystal lattice during the dissolution process[31]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drug precipitated, it is as a metastable polymorphic form with higher solubility than most stable crystal form[21,23,32]. These characteristics can be exploited to enhance the rate and extent of absorption of poorly water soluble APIs from the GI tract[33]. Such formulations approaches have been described for many APIs including indomethacin, griseofulvin and several barbiturates[33-35].

Methods of Preparation of Solid Dispersions

Solid dispersions can be prepared by various methods. It was also observed in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure[10,15]. 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 phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Fusion Method

The fusion method is sometimes referred to as the hot melt method; which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix[15] which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I or eutectics[36] Poly (ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III or solid solutions[36] since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its *Tg* (glass transition temperature). The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V(Glass suspension) or VI(Glass solution) are obtained. The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.

Limitations:

(i) This method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature.

(ii) Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur.

(iii) Slow cooling yields crystalline dispersions while rapid cooling yields amorphous dispersions[37,38].

Hot Melt Extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar[39], but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms[40]. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid state miscibility and to select matrices suitable

for melt extrusion. High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials[41,39].

Advantages:

(i) Possibility of continuous production, so used for large scale production.

(ii) Easy to handle.

(iii) Facility to shape the extruder mixture.

Limitations:

(i) Thermolabile substances can not be processed.

(ii) Large difference between drug and matrix melting point

Solvent Evaporation Method

The utmost requirement in this method is the complete solubility of both drug and matrix in same solvent. The solvent must be volatile enough that it must evaporate easily and completely. Also the solvent must not be toxic. Using the solvent method, the pharmaceutical engineer faces two challenges. To reduce the drug particle size in the solid dispersion, the drug and matrix have to be dissolved in the solvent as fine as possible[42] preferably drug and matrix material are in the dissolved state in one solution. Various strategies have been applied to dissolve the lipophilic drug and hydrophilic matrix material together in one solution. Low drug concentrations are used to dissolve both drug and matrix material in water[43] but this requires evaporation of tremendous amounts of solvent, making the process expensive and impractical. Solubilizers like cyclodextrins or surfactants like Tween80® increase the aqueous solubility of the drug substantially. However, the amounts of solubilisers or surfactants in the final product are often eminent. This results in solid dispersions that, to a significant extent, consist of solubilisers or surfactants, materials that significantly change the physical properties of the matrix (e.g., decrease of Tg). Moreover, only dosage forms with low drug loads are possible. In addition, they are not always tolerated well in the body or may even be toxic. Chloroform[44] or dichloromethane[45] have been used to dissolve both drug and PVP as matrix simultaneously. These solvents are used also in other preparation methods. However, according to the ICH-Guidelines, these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is avoidable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol[5], or dichloromethane and ethanol[46] have been used for this purpose. However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favouring phase separation (e.g.,crystallization). Thus this problem can be resolved by reducing the pressure and carrying the process at low temperature. This enables the drug to solidify in less time and not allow it to disnature[47].

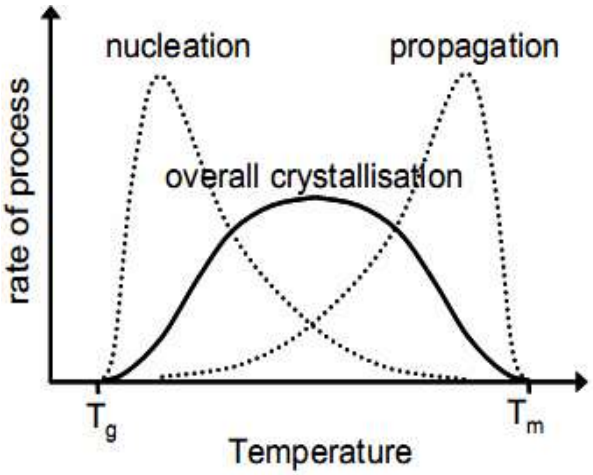

Figure 7: Overall crystallization rate as a function of temperature. Tg is the glass transition temperature and Tm is the melting temperature. Adapted from[48].

Now a days the solvent evaporation technique is used widely. The new commercially available rotary vaccum evaporators are used for the same purpose. It works under lower temperature and reduced pressure so thermo sensitive drugs can be easily used in it. Secondly the solvent used can also be recovered in them. Figure 8 shows a model of a rotary vaccum evaporator.

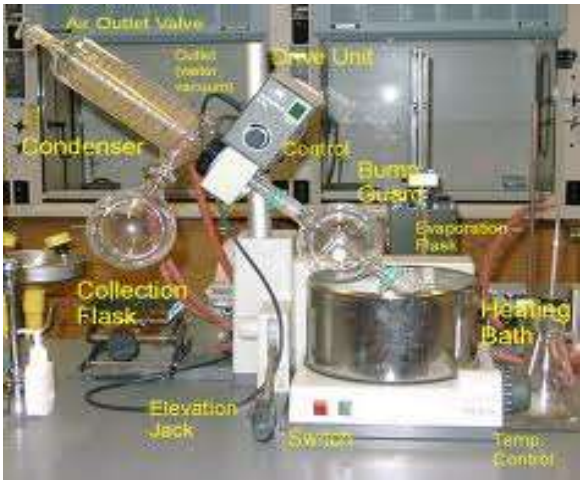

Figure 8: Rotary Evaporator

Limitations:

(i) Hard to select a suitable solvent with low toxicity.

(ii) Cost of solvent always a factor of consideration.

(iii) Various factors like temperature, pressure need to be maintained.

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. 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°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).

Limitations:

(i) High pressure is required convert gas to liquid. It requires sophisticated machinery.

(ii) Gases other than CO_2 like chlorofluorocarbons', halogens are flammable and harmfull to environment.

Kneading Method

In kneading method drug and polymer are taken in pestle and mortar. A solvent is added and mixture being triturated. A thick paste is formed. Then it is dried at 45°C and crushed. Then it is sifted through sieve no. 30.[49,50]. Kneading method gives the facility to work with drug and polymer of different melting point ranges. This method facilitates the formulator to work with heat sensitive materials.

Limitations:

(i) Surface morphology can be changed during trituration.

(ii) Loss of kneaded mass during the process.

(iii) Chances of demixing on excess trituration.

CONCLUSION

Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poor water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various techniques, described in this review, are successfully used for the preparation of solid dispersion in the 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. Although there are some hurdles like scale up and manufacturing cost to overcome, there lies a great promise that solid dispersion technology will fasten the drug release profile of poorly water soluble drugs.

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