

## IMPROVEMENT OF DRUG SOLUBILITY USING SOLID DISPERSION

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## ABSTRACT

The solubility behaviour of drug is one of the most challenging aspects in formulation development. Thus a greater understanding of dissolution and absorption behaviour of drug with low aqueous solubility is required to successfully formulate them into more soluble and hence bioavailable drug product. Therefore different approaches are being explored to enhance the solubility of poorly water soluble drugs, one of such approach is using different solid dispersion techniques. This article reports different types of solid dispersion, various solubility enhancement strategies in solid dispersion, advantages of solid dispersion over other techniques and applications of solid dispersion. The approaches described are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology.

**Keywords:** Drug Solubility, Lyophilisation, Agglomeration process.

## INTRODUCTION

The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed. The mechanisms involved in solubility and dissolution rate enhancement include transformation of unstable modifications into more stable ones or

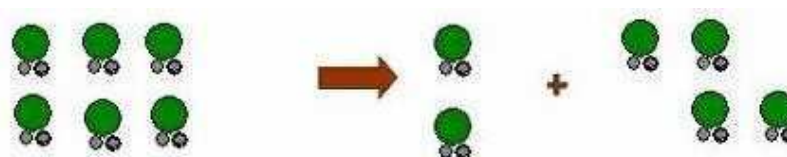
even into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material. However, if a solid dispersion represents a thermodynamically unstable system, it is prone to convert into a more stable state. Especially for substances according to the Biopharmaceutics Classification System, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug <sup>1,2</sup>. Table.1

Table 1: List of poor water soluble drugs, Category and solubility profile [2]

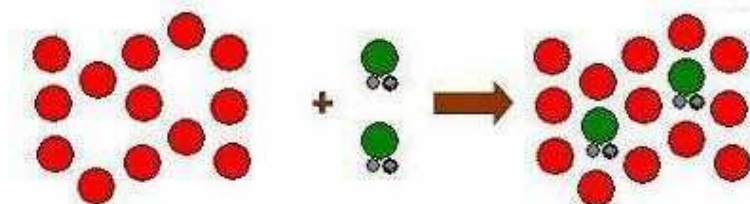
| S. No. | Drugs        | Category                     | Solubility profile  |
|--------|--------------|------------------------------|---|
| 1.     | Ibuprofen    | Anti-inflammatory, analgesic | Ibuprofen is only very slightly soluble in water. Less than 1mg of ibuprofen dissolves in 1ml of water (<1 mg/ml).  |
| 2.     | Furosemide   | Diuretics                    | However it is much more soluble in alcohol/ water mixtures.   |
| 3.     | Gliclazide   | Anti diabetic                | Soluble in acetone, sparingly soluble .   |
| 4.     | Glipizide    | Anti diabetic                | Ethanol (95%), slightly soluble in ether Sparingly soluble in dichloromethane, Slightly soluble in ethanol 95%. Soluble in ether, sparingly soluble ethanol (95%), slightly soluble in acetone. |
| 5.     | Aceclofenac  | Anti-inflammatory, analgesic | Practically insoluble in water; freely soluble in acetone, soluble in ethanol 95%.  |
| 6.     | Indomethacin | Anti-inflammatory, analgesic | Soluble in chloroform sparingly soluble in ethanol 95%.   |
| 7.     | Ketoprofen   | Anti-inflammatory, analgesic | Freely soluble in ethanol 95 %, chloroform and ether.   |
| 8.     | Diclofenac   | Anti-Inflammatory            | Freely soluble in methanol, Soluble in ethanol(95%), sparingly soluble in water and glacial acetic acid.  |
| 9.     | Felodipine   | Calcium Channel blocker      | Sparingly soluble in dichloromethane, slightly soluble in ethanol 95%.  |
| 10.    | Loperamide   | Antidiarrheals               | Soluble in acetone, sparingly soluble in ethanol(95%), sparingly soluble in ether.  |
| 11.    | Morphine     | NSAIDS                       | Soluble in water, Freely soluble in hot Water, more soluble in ethanol.   |
| 12.    | Naproxone    | Anti-inflammatory            | Soluble in water, Freely soluble in hot Water, more soluble in ethanol.   |
| 13.    | Nimodipine   | Calcium channel blocker      | Poor water soluble drug.  |
| 14.    | Ofloxacin    | Antibiotic                   | Soluble in ethanol and chloroform, insoluble in ether.  |



Step 1: Holes opens in the solvent



Step 2: Molecules of the solid break away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

Fig. 1: Process of solubilization<sup>43</sup>

### Process of solubilization

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion<sup>3</sup>. Fig.1

### Factors affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system<sup>4</sup>.

### Particle Size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by<sup>5</sup>

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

Where,

S is the solubility of infinitely large particles

S<sub>0</sub> is the solubility of fine particles

V is molar volume

R is the radius of the fine particle

T absolute temp in degree kelvin

R universal gas constant

### Temperature

Generally, an increase in the temperature of the solution increases the solubility of a solid solute.

### Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility<sup>6</sup>.

### Nature of the solute and solvent

While only 1 gram of lead chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures<sup>7</sup>.

### Molecular size

The larger the molecule or the higher its molecular weight the less soluble the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent<sup>3</sup>. Table. 2

Table 2: Definition Parts of solvent required for one part of solute<sup>3</sup>

|                       |               |
|-----------------------|---------------|
| Very soluble          | < 1           |
| Freely soluble        | 1 – 10        |
| Soluble               | 10 – 30       |
| Sparingly soluble     | 30 – 100      |
| Slightly soluble      | 100 – 1000    |
| Very slightly soluble | 1000 - 10,000 |
| Insoluble             | > 10,000      |

### Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces.

### Polymorphs

The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities<sup>2</sup>.

### Definition of solid dispersion

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 or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement.

**Types of Solid Dispersion**

- I. Simple eutectic mixtures
- II. Solid solutions
- III. Glass solution and suspension
- IV. Amorphous precipitations in a crystalline carrier

**I. Simple eutectic mixtures**

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus the X-ray diffraction pattern of a eutectic constitutes an additive composite of two components <sup>4</sup>. Fig. 2. Ex. Chloramphenicol-urea; Paracetamol-urea; Griseofulvin & Tolbutamide-PEG 2000.

- T A- M.P. of solid A
- T B - M.P. of solid B
- T E - Eutectic Point

**II. Solid solutions**

In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous. In continuous solid solutions, the two components are miscible in the solid state in all proportions. Fig. 3 and 4.

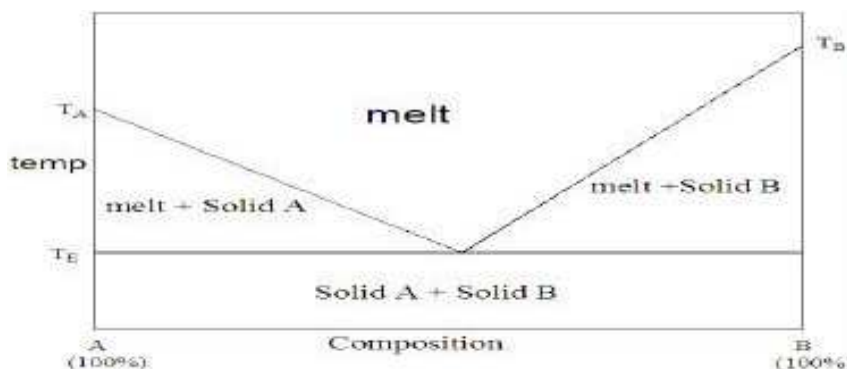


Fig. 2: Simple eutectic mixtures <sup>43</sup>

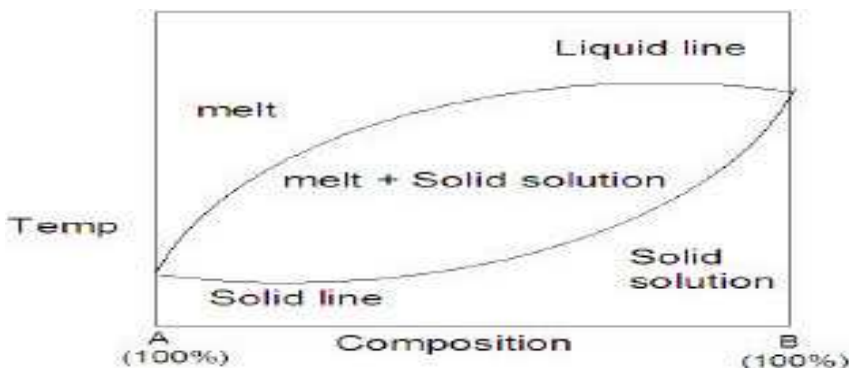


Fig. 3: Continuous Solid Solution - Two solids miscible in solid state in all proportions<sup>43</sup>

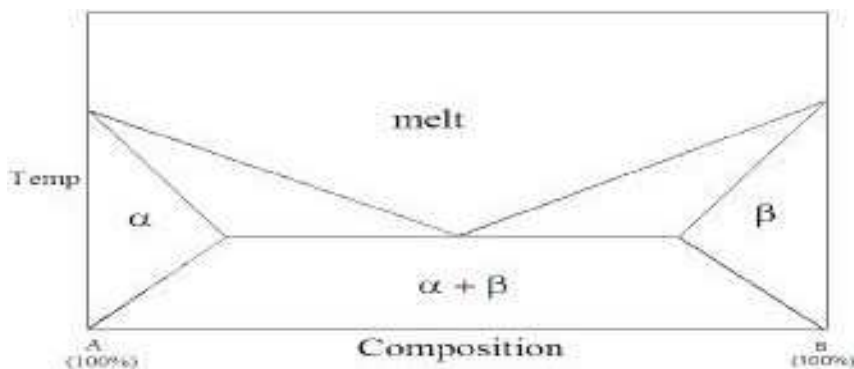


Fig. 4: Discontinuous Solid Solutions - Exist at extremes of composition<sup>43</sup>

### III. Glass solutions and suspensions

A glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. 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. Glasses do not have 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. Fig. 5

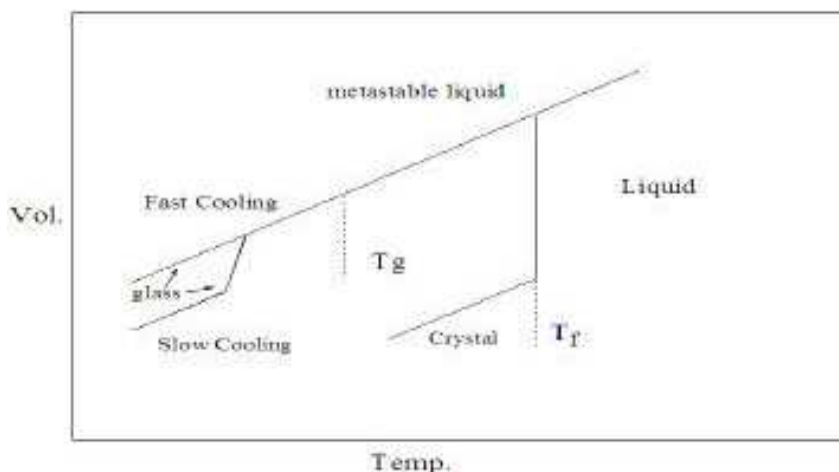


Fig. 5: Glass solutions and suspensions<sup>43</sup>

Tg - glass transition temp; Tf - M.P. of material

### IV. Amorphous precipitations in a crystalline carrier

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. Sulfathiazole was precipitated in the amorphous form in crystalline urea<sup>7</sup>.

#### Selection of carriers

The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. Surface-active agents are substances that at low concentrations adsorb onto the surfaces or interfaces of a system and alter the surface or interfacial free energy and the surface and the interfacial tension. Surface-active agents have a characteristic structure, possessing both polar (hydrophilic) and non-polar (hydrophobic) regions in the same molecule. The surface active carriers are said to be amphipathic in nature. They should generally have the following characteristics:

- Readily soluble in water and in gastrointestinal fluids.
- Physiologically inert.
- Melting point not much higher than that of the drug.
- Thermal stability at melting temperature.
- Relatively low vapour pressure, and
- Should have high molecular weight to fulfill the requirement of the host.
- They should be nontoxic.

Table 3: Materials used as Carriers for Solid Dispersions<sup>3</sup>

| Materials                     | Examples   |
|-------------------------------|--|
| Sugars                        | Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol |
| Acids                         | Citric acid, Succinic acid                               |
| Polymeric materials           | Povidone(PVP), Poly-ethylene glycols(PEG)                |
| Insoluble or enteric polymers | Hydroxypropyl-methyl cellulose phthalate, EudragitL100   |
| Surfactants                   | Polyoxyethylene stearate, Renex, Poloxamer 188, Spans    |
| Miscellaneous                 | Pentaerythritol, Pentaerythrityl tetracetate, Urea       |

Polyethylene glycol 20000 (PEG 20,000), P.E.G 6000, P.E.G 4000, urea, Polyvinyl pyrrolidone, desoxycholic acid, citric acid, pentaerythritol, sugar etc. are some of the carrier which have been generally used (Table 3). An improvement in wetting of the drug is caused by the hydrophilic carrier<sup>42</sup>.

#### Advantages of solid dispersions over other strategies

Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a prodrug. Solid dispersion appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Formulation approaches include solubilization and particle size reduction, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products since they give rise to solid oral dosage forms instead of liquid as solubilization products usually. Milling or micronization for particle size reduction are commonly performed as approaches to improve solubility, on the basis of increase in surface area<sup>8</sup>.

The higher dissolution rates of solid dispersion can be ascribed to a number of factors which includes:

1. The formation of higher energy metastable states of components as a function of the carrier system being used and the proportion of carriers present.
2. The reduction of particle size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption.
3. Formation of amorphous forms of drug and carriers.
4. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug, hence the higher dissolution rates. The presence of carrier polymers also inhibits crystal growth of the drug which facilitates faster dissolution.

5. Co solvent effect on the the drug by the water soluble carriers.
6. Intermolecular hydrogen bonds between drug and carrier.
7. Local solubilization effect of carrier at the dissolution layer <sup>9</sup>.

The different ways of increasing the absorption or bioavailability are:

1. Micronization
2. Use of soluble salt
3. Use of minuscular form of drug adsorb on the insoluble adsorbants
4. Use of surfactants
5. Use of polymorphs
6. Use of hydrates or solvates and
7. Molecular complexation

Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drugs crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different from that of a parent compound <sup>10</sup>. The fusion method can only be applied when drug and matrix are compatible when they mix well at heating temperature. The development of solid dispersions as a practical viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitation of other approaches such as salt formation, solubilization, cosolvency and particle size reduction <sup>41</sup>.

#### Different methods of preparation of solid dispersion

Various strategies investigated by several investigators include fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology.

#### Fusion method

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath. A modification of the process involves spray congealing from a modified spray drier onto cold metal surface. Decomposition should be avoided and is affected by fusion time and rate of cooling <sup>11,12</sup>. Another modification of the above method, wherein SD(s) of troglitazone- polyvinyl pyrrolidone (PVP) k 30 have been prepared by closed melting point method. This method involves controlled mixing of water content to physical mixtures of troglitazone PVP k30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce SD with 0% apparent crystallinity <sup>13</sup>.

#### Solvent evaporation method

The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Large volumes of solvents are generally required which can give rise to toxicological problems <sup>14,15</sup>. Many investigators studied SD of meloxicam, naproxen <sup>16,17</sup>, rofecoxib <sup>18</sup>, felodipine <sup>19</sup> using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poor water drugs.

#### Lyophilization technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. Lyophilization 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. Betageri et al.<sup>20</sup> and Topalogh et al.

<sup>21</sup> have successfully investigated the potential applications of lyophilization in manufacturing of SD(s).

#### Melt agglomeration process

This technique has been used to prepare SD where the binder acts as a carrier. Binder (carrier), drug and excipients are heated to 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 <sup>22</sup>.

#### Extruding method

The extruding method was originally designed as an extraction / casting method for polymer alloys in plastic industry, is now used to process cereals and functionalize food materials, such as tissue products from animal proteins <sup>23</sup>. Hot melt extrusion approach represent the advantageous mean of preparation of SD(s) by using the twin screw hot melt extruder where only thermo stable components are relevant <sup>24</sup>. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die <sup>25</sup>. The effect of screw revolution speed and water content on the preparation of SD(s) should be investigated, since these parameters have profound impact on the quality of SD(s). Nakamichi et al <sup>26</sup>, studied that presence of kneading paddle element of screw results in super saturation on dissolution testing while slow revolution rate of screw and addition of the suitable amount of water increased rate of dissolution although no super saturation occurred.

#### Spray drying

The manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. 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, resulting solid particles. 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 <sup>27,28</sup>. Rankell et al. prepared SD(s) of loperamide with PEG 6000 by this technique wherein solutions containing different concentrations of PEG 6000 and constant amount of loperamide were spray dried. Chouhan et al <sup>29</sup> studied the suitability of this technique for preparation of SD(s) of glibenclamide polyglycolized glycerides.

#### The use of surfactant

The utility of the surfactant systems in solubilization is well known. Surfactant reduces hydrophobicity of drug by reducing interfacial or surface tension because of these unique property surfactants have attracted the attention of investigators for preparation of solid dispersions <sup>30,31</sup>. Recently a new class of surfactant known as Gelucires are introduced which identify by melting points and HLB values. Gelucire is widely used in the formulation of semi solid dispersions. Gelucire is a saturated polyglycolized glyceride consisting of mono-, di- and triglycerides and of mono- and di- fatty acid esters of polyethylene glycol (PEG) derived from natural vegetable fatty acids and having amphiphilic character. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Gelucire 44/14 and gelucire 50/13 are two examples of this synthetic group where 44 and 50 represent melting point, while 14 and 313 represent HLB values of gelucire respectively <sup>32,33</sup>. Hemant et al <sup>34</sup> and Sheen et al <sup>35</sup> studied that polysorbate 80, a commonly used surfactant, results in improvement of dissolution and bioavailability of poorly water soluble drug attributed to solubilization effect of surface active agent. Polysorbate 80 also ensures complete release of drug in metastable finely dispersed state having large surface area.

### Super critical fluid (scf) technology

Since the first experiences of Hannay et al in 1879, a number of techniques have been developed and patented in the field of SCF-assisted particle design. These methods use SCFs either as solvent: rapid expansion from supercritical solution (RESS) or anti-solvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance<sup>36</sup>. Solution enhanced dispersion by supercritical fluids (SEDS), aerosol solvent extraction system (ASES), supercritical anti-solvent (SAS), gas antisolvent (GAS) and precipitation with a compressed fluid anti-solvent (PCA) are process of micronization. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently<sup>37</sup>.

### Applications of solid dispersion

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used:

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds

### Future Prospects

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical, and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drugs in melted carriers and the filling of the hot solutions into hard gelatin capsules. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and, as a result, the bioavailability of solid dispersions is not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may be the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention must also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying

carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP3-based drug metabolism and *p*-glycoprotein-mediated drug efflux, will require careful consideration<sup>38</sup>. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Although a review of literature on this aspect of solid dispersion is outside the scope of the present article, it may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsulefilling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use,<sup>39</sup> it is expected that the research in these two areas will progress simultaneously and be complementary to each other. Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market,<sup>40</sup> so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability. Possible drug-carrier interactions must also be investigated. Although, as mentioned earlier, the direct filling of solid dispersion into hard gelatin capsules is a relatively simple process, there are very limited reports on the scale up of the technology. Further studies on scale up and validation of the process will be essential. Many problems and challenges still remain with solid dispersion systems. Nevertheless, as a result of recent breakthroughs, it will continue to be one of the exciting frontiers of drug development.

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