



## REVIEW ARTICLE

## SOLID DISPERSION- STRATEGY TO ENHANCE SOLUBILITY AND DISSOLUTION OF POORLY WATER SOLUBLE DRUGS

Ankush Kumar<sup>1</sup>, Kapil Kumar<sup>2</sup>

Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India.

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#### \*Address for Correspondence:

**Ankush Kumar**, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India, Tel: +91-7830104498, E-mail: [ankushchauhnanapi@gmail.com](mailto:ankushchauhnanapi@gmail.com)

### Abstract

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Over the years a variety of solubilization techniques have been studied and widely used, as maximum drugs are poorly water soluble in pharmaceutical field. The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs. Solid dispersions have attracted many researchers as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. Solid dispersion can form either a eutectic mixture or solid solution or glass solution or amorphous precipitation in a crystalline carrier or compound or complex formation. The focus of this review article is on the advantages, limitations, various methods of preparation and characterization of the solid dispersion.

**Keywords:** Bioavailability, eutectic mixture, solid dispersion, solubility, solubilization techniques.

### INTRODUCTION

Oral drug delivery is the most popular, simplest and easiest way for drugs administration. When a drug is administered orally, it must dissolve in gastric and/or intestinal fluids in order to permeate the membranes of the GI tract to reach systemic circulation<sup>1</sup>. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Maximum drugs have poor solubility<sup>2</sup>. Hence, pharmaceutical research that focus on improving the oral bioavailability of active agents by enhancing solubility and dissolution rate of poorly water-soluble drugs<sup>3</sup>. The term solid dispersion refers to a group of solid products consisting of a hydrophilic matrix and a hydrophobic drug. The matrix can be amorphous or crystalline in nature. Solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion<sup>4</sup>. When the solid dispersion comes in contact of aqueous media, the carrier dissolves and the drug release as a fine colloidal particle, resulting enhanced surface area.

This results in higher dissolution rate and bioavailability of poorly water soluble drugs<sup>5</sup>. In addition, in solid dispersion a portion of drug dissolves immediately to saturate gastro intestinal tract fluid and excess drug precipitates as fine colloidal particles or only globules of submicron size. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs<sup>6</sup>.

BCS takes into account three major factor; solubility, intestinal permeability and dissolution rate, all of which govern the rate extent of oral drug absorption from solid oral-dosage forms<sup>7</sup>.

#### Advantages

1. Enhance solubility and bioavailability of poorly water soluble drugs<sup>8</sup>.
2. Easy to produce.
3. Rapid dissolution rate, leads to increase in extent and rate of drug absorption.
4. Transformation of liquid or gaseous form of drug in to solid form is possible<sup>9</sup>.
5. Avoiding polymorphic changes and the consequent bioavailability problems
6. Easy to prepare rapid disintegration oral tablets by solid dispersion<sup>10</sup>.
7. Improve porosity of drug.

### Disadvantages

The disadvantages of solid dispersion are enlisted below:

1. Poor scale-up for the purpose of manufacturing<sup>11</sup>.
2. Polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. It may lead to decrease solubility and dissolution rate.
3. Difficulty in pulverization and sifting because of their tacky and soft nature<sup>12</sup>.
4. It causes reproducibility of physicochemical characteristics.
5. Poor stability of dosage form.
6. Laborious and expensive method of preparation.
7. Aggregation, agglomeration and air adsorption during formulation<sup>13</sup>.
8. Decrease in dissolution rate with aging for.

## TYPES OF SOLID DISPERSION

### 1. Eutectic mixtures

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. These systems are usually prepared by melt fusion method. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which gets solubilized rapidly. The increase in surface area is mainly responsible for increased rate of dissolution<sup>14</sup>. Examples of this type include phenacetin-phenobarbital, Chloramphenicol-urea, griseofulvin-succinic acid, and paracetamol-urea.

### 2. Solid solution

These consist of a solid solute dissolved in a solid solvent. The particle size of the drug in the solid solution is reduced to its molecular size. These systems are generally prepared by solvent evaporation or coprecipitation method, in which solute and carrier are dissolved in a common volatile solvent such as alcohol<sup>15</sup>. Solid solution differs from eutectic mixture in a way that the drug is precipitated out in an amorphous form in solid dispersion/solution while it is in crystalline form in eutectics. Solid solution can generally be classified according to the extent of miscibility between the two components or the crystalline structure of the solid solution as-

#### i). Continuous Solid Solutions:

In this system, the two components are miscible or soluble at solid state in all proportions. Although it is theoretically possible but no established solid solution of this kind has been shown to exhibit faster dissolution properties. The presence of a small amount of the soluble carrier in the crystalline lattice of the poorly soluble drugs may also produce a dissolution rate faster than the pure compound with similar particle size<sup>16</sup>.

#### ii). Substitutional solid solution:

In substitutional solid solution, the solute molecule substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution. The size of the solute and the solvent molecule should be as close as possible<sup>17</sup>.

#### iii). Discontinuous solid solution

In contrast to the continuous solid solution, this system has only a limited solubility of a solute in a solid solvent. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature<sup>18</sup>.

#### iv). Interstitial solid solution

The solute (guest) molecule occupies the interstitial space of the solvent (host) lattice. It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the apparent diameter of the solute molecules should be less than that of the solvent in order to obtain an extensive interstitial solid solution of metals<sup>19</sup>.

### 3) Glass solution

It is a homogenous system in which a glassy or a vitreous carrier solubilized drug molecules in its matrix. By an abrupt quenching of the melt, the glassy or vitreous state is usually obtained. It is characterized by transparency and brittleness below the glass transition temperature. On heating, it softens progressively without a sharp melting point<sup>20</sup>.

### 4) Compound or complex formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. Rate of dissolution and gastrointestinal absorption can be increased by the formation of a soluble complex with low association constant<sup>21</sup>.

## PREPARATION OF SOLID DISPERSIONS

### 1. Fusion method

First solid dispersions created for pharmaceutical application were prepared by the fusion method. It is also referred as the melt method only when the starting materials are in crystalline state. Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified on an ice bath and pulverized to a powder<sup>22</sup>.

**2. Freeze-drying method:** This method consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. Furthermore the risk of phase separation is minimized as soon as the solution is vitrified<sup>23</sup>.

**3. Spray-drying:** This method consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation<sup>24</sup>.

**4. Dropping method:** It is a new procedure for producing round particles from melted solid dispersions. This method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation<sup>25</sup>.

**5. Solvent evaporation method:** The solvent evaporation method consists of the solubilization of the

drug and carrier in a volatile solvent that is later evaporated such as ethanol, chloroform, mixture of ethanol and dichloromethane. Vacuum evaporation may be used for solvent removal at low temperature and also at a controlled rate. More rapid removal of the solvent may be accomplished by freeze-drying. The difficulties in selecting a common solvent to both drug and carrier may be overcome by using an azeotropic mixture of solvent in water<sup>26</sup>.

### 6. Supercritical fluid methods

In this method carbon dioxide is used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. In these technique drug and carrier are dissolved in a common solvent leads to particle

formation vessel through a nozzle using carbon-dioxide<sup>27</sup>.

In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins. The use of this method reduces residual solvent content, particle size without any degradation<sup>28</sup>.

**Table 1: Classification of carriers.**

Carriers	Examples
Polymers	polyvinylalcohol, polyvinyl pyrrolidone, polypyrrolidone, polyethylene glycols, hydroxypropyl cellulose
Surfactants	Tweens, spans, polyoxyethylene stearates, poly (caprolactone)-b-poly (ethylene oxide)
Carbohydrates	Lactose, sorbitol, mannitol, glucose, maltose, soluble starch, cyclodextrins, galactose, xylitol, galactomannan
Polyglycolized glycerides acids	Gelucire 44/14, gelucire 50./13, gelucire62/05
Cyclodextrins	Beta-cyclodextrins, hydroxypropyl-beta-cyclodextrins
Dendrimers	Citric acid, succinic acid, phosphoric acid, starburst, polyamidoamine
Superdisintegrants	Sodium starch glycolate, croscarmellose sodium, cross-linked polyvinyl pyrrolidone, cross-linked algin, gellen gum, xanthan gum, calcium silicate etc
Hydrotropes	Sodium acetate, sodium citrate, sodium-o-hydroxyl benzoate, sodium-phydroxyl benzoate

### 7. Co-precipitation method

In this method non-solvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the non-solvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried<sup>29</sup>.

**8. Hot melt extrusion method:** In this method extruder is utilized for intense mixing of components. The components of the extruder are barrel, hopper, a kneading screw, heating jacket, and a die. Physical mixture of both the carrier and drug is introduced into the hopper then passed through screw and finally it is extruded from the die. The product produced by this method can easily be handled because any shape can be adopted<sup>30</sup>.

### Characterization

#### 1. Microscopic Methods

These methods are used to determine size and observe morphology of solid dispersion. In scanning electron microscopy sample coated by gold or palladium -using vacuum evaporator examined at accelerating voltage with suitable magnification<sup>31</sup>.

#### 2. Spectroscopic methods

##### a. FTIR spectroscopy

This is used to check interaction between drug and carrier used in formulation of solid dispersion. Appearance and disappearance of peak indicate interaction between two compound and degradation of drug<sup>32</sup>.

##### b. UV visible Spectroscopy

Spectra of pure drug and dispersed drug are scanned. Calculation of molar extinction provides evidence of any decomposition<sup>33</sup>.

##### c. X-ray diffraction spectroscopy

This is used to study quantitatively the concentration of crystalline compound in mixture. It is efficient tool in studying physical nature of solid dispersion. Intensity of X-ray diffraction (or reflected) from sample is measured as function of diffraction angle. Compound or complex formation can be detected by change in spectra of pure drug<sup>34</sup>.

### 3. Thermal Methods

These methods include exposure of sample to different temperature condition. Studying physicochemical interaction between drug and carrier is based on principle of change in thermal energy as function of temperature<sup>35</sup>.

#### a. Thaw Melting Method

In this method samples are frozen heated and suddenly converted from solid state to liquid state. Thaw point and melting point can be noted. A limitation of this method is that it depends upon subjective observation, therefore not highly reproducible<sup>36</sup>.

#### b. Cooling curve Methods

In this method prepared physical mixtures are heated and homogeneous melt temperature of each mixture is noted. Limitations of this method include time consuming process, it requires relatively large amount of sample and not suitable for heat sensitive material<sup>37</sup>.

#### c. Differential Thermal Analysis (DTA)

In this study the temperature difference that develops between a sample and an inert reference material is

measured, at identical heat treatments. Phase transitions or chemical reactions can be followed by absorption or evolution of heat<sup>38</sup>.

#### d. Differential Scanning Calorimetry (DSC)

This technique it is used to observe fusion and crystallization events, glass transition temperatures, oxidation, as well as other chemical reactions<sup>39</sup>.

#### 4. Dissolution Studies

Carried out at physiological temperature by using type II USP dissolution apparatus. Dissolution profile of solid dispersion or compressed tablet made from solid dispersion is determined by comparison between dissolution profile of pure drug, physical mixture and solid dispersion gives idea about dissolution rate. Effect of different carrier and their different proportion on dissolution rate of solid dispersion is main characterization tool<sup>40</sup>.

#### Applications of solid dispersions

Solid dispersion technique has following applications

1. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers<sup>41</sup>.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To stabilize unstable drugs against hydrolysis, oxidation, recombination, isomerisation, photo oxidation and other decomposition procedures<sup>42</sup>.
4. To reduce side effect of certain drugs.
5. Masking of unpleasant taste and smell of drugs.
6. Improvement of drug release from ointment, creams and gels<sup>43</sup>.
7. To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds<sup>44</sup>.
8. To formulate a fast release primary dose in a sustained released dosage form.
9. To dispense liquid or gaseous compounds in a solid dosage.
10. To formulate a fast release primary dose in a sustained released dosage form<sup>45</sup>.

#### CONCLUSIONS

Solubility plays an important role for a drug formulation and its therapeutic efficacy. Hence, enhancing of solubility and bioavailability is the major challenge for the researchers. Solid dispersion technique is one of the major techniques to enhance the solubility of drug. It is a promising technique for the enhancement of bioavailability of poorly aqueous soluble drugs. It aims at improving the dissolution and absorption of drugs by various methods like fusion, solvent evaporation, freeze drying etc. A major focus on the future will become the identification of new surface active carriers and self emulsifying carriers for solid dispersion. So, the commercial development of this technique is necessary. For it further research is necessary for the better implementation of solid dispersion technology on industrial scale.

#### AUTHOR'S CONTRIBUTION

**Kumar A:** writing, review, and editing. **Kumar K:** writing, review, and editing, investigation, conceptualization. All the authors approved the finished version of the manuscript.

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#### CONFLICT OF INTEREST

None to declare.

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