



# A Complete Review on Solid Dispersion

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## Abstract:

Solid dispersion is one of the mostly discussed but still remained as a challenging aspect for improving dissolution rate and hence bioavailability of a poorly water soluble drugs. The focus of this review is to highlight technology and various approaches for the preparation of solid dispersion, various advantages, disadvantages and future prospects with its pharmaceutical applications.

## 1. INTRODUCTION

More than 40% of new candidates entering drug development fail because of non-optimal biopharmaceutical properties. These properties have a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties<sup>1</sup>. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability, especially for class II substances according to the Bio pharmaceuticals Classification System (BCS)<sup>2</sup>. Number of techniques has been utilized for solubility enhancement namely<sup>3</sup>:

### I. Physical Modifications

- A. Particle size reduction
  - a. micronization
- B. Modification of the crystal habit
  - a. Polymorphism
  - b. Nano-suspension
- C. Drug dispersion in carriers
  - a. Solid dispersions
  - b. Complexation
- D. Solubilization by surfactants
  - a. Microemulsions
  - b. Self-microemulsifying drug delivery systems

### II. Chemical Modifications

- a. Prodrug
- b. Salt formation
- c. liquid-solid compacts

### III. Other techniques

- a. Co solvency
- b. Hydrotrophy
- c. Solubilizing agents
- d. Nanotechnology approaches
- e. pH adjustment
- f. Microemulsion

But all these techniques have their limitations. In case of salts, the increased dissolution rate in the gastrointestinal tract may not be achieved because of the reconversion of salts into aggregates of their respective acid or base forms. Further, solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from patient acceptability and commercialization. Particle size reduction is commonly used to increase the dissolution rate and there is a

practical limit to how much size reduction can be achieved by commonly used methods such as crystallization and grinding.

## 2. DEFINITION AND TYPES OF PREPARATION

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

a) Simple eutectic mixture: A eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component.

b) Solid solutions: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems.

c) Glass solution of suspension: A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilized drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d) Compound or complex formation: This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

e) Amorphous precipitation: Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug<sup>4</sup>.

## 3. METHODS OF PREPARATION OF SOLID DISPERSION

1) Melting method: The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate.

2) Solvent evaporation method: In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight.

3) Dropping solution method: The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette out and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.

4) Co-precipitation method: Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. 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. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature.

5) Melt Agglomeration Process: This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, 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<sup>5</sup>.

### Selection of a Carrier

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug:

1. Freely water-soluble with intrinsic rapid dissolution properties.
2. Non-toxic and pharmacologically inert.
3. Heat stable with a low melting point for the melt method.
4. Soluble in a variety of solvents.
5. Able to preferably increase the aqueous solubility of the drug.
6. Chemically compatible with the drug and not form a strongly bonded complex with the drug<sup>6</sup>.

### Polymers Used In Solid Dispersions:

Polymers used in solid dispersions are as follows:

a) Polyethylene glycols (PEG): The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. Lower molecular weight PEGs melt at 37°C in the dissolution medium prior to dissolution, further increasing the rate of dissolution. In some drug-PEG solid dispersion systems, the rate dissolution decreases with molecular weight upto a certain composition of the drug.

b) Polyvinyl pyrrolidone (PVP): PVP has a molecular weight ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because it melts at a very high temperature above 275°C, where it becomes decomposed.

c) Cyclodextrins: Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

d) Phospholipids: Phospholipids are major structural components of cell membranes. Phosphatidylcholine was first isolated from egg yolk and brain. Its chemical name is 1, 2-diacyl- in- glycerol-3 phosphocholine. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively.

e) Urea is the end product of human protein metabolism, has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 and it also reveals good solubility in several common organic solvents.

f) Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals, they are mainly used as coatings to change the release of the drug from the dosage form. Commonly, they are referred by the trade name Eudragit drug. Among the Eudragits, Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH, while Eudragit L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as co-evaporate with Eudragit E, the rate of dissolution was much higher than from the pure drug powder. On the other hand, Eudragit L has been successfully used to increase the dissolution of griseofulvin and spironolactone at a pH value of 6.8.

### g) Cellulose Derivatives

1. Hydroxypropyl methylcellulose (HMPC)- HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% are derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10000 to 1500000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids nilvadipine and benidipine.

2. Hydroxypropylcellulose (HPCs) - They exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37000 to 1150000.

3. Carboxymethylethylcellulose- Many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8.

4. Hydroxypropylmethylcellulose phthalate (HPMCP) - HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). They are having a type-dependent solubility in organic solvents. Their molecular weight ranges from 20,000 to 2 000,000. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in co-evaporate of HPMCP. Using a spray-drying technique to form a solid dispersion in HP 55, the dissolution rate of the anti-fungal drug MFB-1041 could be increased by a factor of 12.5 as compared to the best possible dissolution achievable by micronizing the drug<sup>7</sup>.

Hence, the above carriers are used as polymers in the preparation of solid dispersion. The ideal properties of every

polymer should be known in order to attune with the drug and to achieve the desirable product.

#### Advantages and Disadvantages of Solid Dispersions

Among the advantages of solid dispersions are the rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in pre-systemic metabolism. This latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug, as in the case of 17 beta- estradiol; or inhibition of the enzyme by the carrier. Both can lead to the need for lower doses of the drug. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and thereby bioavailability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption. The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystalline and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir) from the market. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures<sup>8,9, 10</sup>.

#### 4. 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 developments of solid dispersion systems for preclinical, clinical and commercial use have 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 drug 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 physico-chemical properties and, as a result, the bioavailability of solid dispersions are 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 dispersion. 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 carrier, 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 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 CYP-3 based drug metabolism and p-glycoprotein-mediated drug efflux will require careful consideration. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, an exemplified by the recent withdrawal of ritonavir capsules from the market, 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 investigate<sup>11,12</sup>.

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