# SOLID DISPERSIONS: A PROMISING TOOL FOR ENHANCEMENT OF ORAL BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS

**Kaushik Mukherjee*, Avijit Chatterjee**

*Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur-713206, India.*

.***Corresponding author:**

Mr. Kaushik Mukherjee, Assistant Professor, Dr. B. C. Roy College of Pharmacy and Allied Health Sciences, Durgapur-713206, India. E-mail: kaushik.pharmacyju08@gmail.com, Tel: +91 9477158487.

**ABSTRACT**

Systemic absorption of an orally administered drug is primarily dependent on two important parameters. They are dissolution of drug in the biological fluids at the site of administration and then permeation of the drug through biological membranes. The solubility of a drug in biological fluids is one of the key determinants in its oral bioavailability. There has always been certain drug whose solubility has presented a challenge for development of a suitable formulation for oral administration. Thus the rate of absorption of a poorly water soluble drug is often controlled by the dissolution rate in the gastrointestinal fluid and thus, solubility and dissolution rate are the key factors determining oral bioavailability. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of poorly water soluble drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. Solid dispersion approach has been extensively used as a means to enhance the oral bioavailability of a poorly water soluble drug. This article aims to focus on the mechanism, methods with their drawbacks, various carriers used in preparing a solid dispersion.

***Keywords:*** Bioavailability, dissolution, solid dispersions, carriers.

## INTRODUCTION

Systemic absorption of an orally administered drug is solely dependent on two important parameters. They are dissolution of drug in the biological fluids at the site of administration and then permeation of the drug through biological membranes. The solubility of a drug in biological fluids is one of the key determinants in its oral bioavailability and permeability [1]. There has always been certain drug whose solubility has presented a challenge for development of a suitable formulation for oral administration. Thus the rate of oral administration of a poorly water soluble drug is often controlled by the dissolution rate in the gastrointestinal fluid and thus, solubility and dissolution rate are the key factors determining oral bioavailability. Accordingly, BCS divides drugs and drug candidates into 4 classes based on their solubility and permeability characteristics [2]. Highly water soluble and permeable drugs fall under class I, while the poorly water soluble and permeable molecules are classified as BCS class II drugs. Class II drugs are poorly soluble but permeable through the biological membrane, while the class III drugs are just the opposite of the class II, that is they are highly water soluble but poorly permeable. Among these 4 classes, Class II drugs are poorly soluble but permeable through the gut meaning that oral adsorption is limited by drug solubility and dissolution rate. Thus the problem with Class II drugs is that their oral

absorption (as also bioavailability) is dissolution rate limiting, which in turn is dependent on the solubility of the drug in the gastrointestinal fluid. Therefore, for poorly water soluble drugs various formulation approaches are being explored to enhance solubility and thus its absorption and bioavailability. One such formulation approach that has shown to significantly enhance solubility and absorption of drugs is to formulate Solid dispersion. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate, and consequently, the bioavailability of poorly water soluble drugs [3, 4].

**DEFINITION OF SOLID DISPERSIONS**

The term solid dispersion refers to a group of solid products which consists of at least two different constituents, generally a hydrophilic carrier and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug may be dispersed molecularly, as amorphous particles (clusters) or as crystalline particles [5].

**MECHANISMS OF SOLID DISPERSIONS**

There are various mechanisms by which solid dispersions bring about solubility enhancement of hydrophobic drug molecules. They are

1.Reduced particle size: Solid dispersion molecules represent the last stage of reduced particle size. The reductions in particle size increases manifold the effective surface area available for drug wetting. This attributes to increased absorption of the drug [6].

2.Particles with improved wettability: Drug wettability can be a major reason of increased absorption characteristics, as verified by various research groups. It has been observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as bile salts when used, significantly increase the wettability properties of drugs [7].

3.Particles with improved porosity: Solid dispersion particles have been found to have a higher degree of porosity. Increase in porosity depends on the nature of the carrier used. It has been found that polymers with linear structure produce more porous particles than polymers with reticular structure. Increased porosity results in improved dissolution characteristics of the drug molecules [8].

4.Drug in amorphous state: Poorly water soluble crystalline drug, when converted in amorphous state shows improved solubility and absorption characteristics. This fact can be attributed to the lesser energy that is required to break up the crystal lattice during the dissolution process [9].

**Methods of solid dispersion:**

1.Fusion Method: This method is also known as melt method, which is correct only when the starting materials are crystalline. Fusion or Melting method was first introduced by Sekiguchi et al. in 1961[10] where the drug was melted in a carrier and after cooling, the dry mass that was obtained was pulverized and sieved to obtain powder. Sulfathiazole drug molecule was subjected to solid dispersion process with a number of carriers used like ascorbic acid, acetamide, nicotinamide, nicotinic acid, succinimide and urea. Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. Another polymer frequently applied as a matrix in the fusion method is poly (vinyl pyrollidone) PVP [11]. PVP, supplied in the amorphous state, is heated to above its Tg (glass transition temperature). The drug fuses with or dissolves into the rubbery structure, which on subsequent cooling results in particles of improved solubility. The main advantages of this method are its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material. Though frequently applied, this method also has some serious limitations. Firstly, the method can only be applied when drug and

matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture. Another problem may arise during cooling when the drug-matrix miscibility changes. Thirdly, many substances, either drugs or carriers, may decompose during the fusion process at high temperatures.

2.Solvent evaporation method: Solid dispersion prepared by solvent removal process was termed by Bates as "coprecipitates". In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve. The solvent used must meet the specifications laid down under ICH guidelines.One of the major advantages of this method is that thermal decomposition of the drugs can be prevented as low temperature is required for the evaporation of the organic solvents. This method has several disadvantages these are: (i) high cost of preparation, (ii) difficulty in selecting a common solvent for both the drug and carrier and complete solvent removal from the product can be a lengthy process, and (iii) crystal forms are difficult to reproduce. Drugs whose solubility has been enhanced by this method include valdecoxib [12], fexofenadine hydrochloride [13], and glibenclamide [14].

3.Spray Drying: It consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the solvent [15]. It is often used for the physical transformation of a drug substance into the amorphous or partially amorphous phase.

4.Freeze Drying: This method is particularly suitable for drugs which are susceptible to degradation at higher temperatures. Here the drug molecule is subjected to minimal thermal stress during the preparation of solid dispersions. Lokamatha et al., in 2011[16], prepared SDs of nevirapine with the aim of enhancement of dissolution properties by kneading and freeze drying technique using low molecular weight dextran at various concentrations of drug and carrier. They first dispersed the drug and carrier in water, and then stirred the whole solution for 3 h. The solution is then frozen overnight and then lyophilized over a period of 24 h in a freeze drier. Then the dried powder was sieved through #120 and stored in dessicator. They found that SDs prepared by freeze drying method exhibited a higher release rate than prepared by kneading method.

5.Hot melt extrusion: This technology is native to the plastic industry and to a =lesser extent to the food industry. It involves the use of extruders with conveying systems, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder. This method has the advantage of being environment friendly and economical because it does not utilizes any form of solvent systems. Here the drug-carrier system is not subjected to higher temperatures and that the residence time to high temperature ranges is also less. This is a particular advantage over the fusion or the melt method. Atorvastatin is an example of drug molecule which is shown to have higher solubility characteristics when formulated to SDs [17]. Examples of carriers used in this method include vinyl polymers (polyvinylpyrrolidone (PVP), PVP-vinyl acetate (PVP-VA)), polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives [18].

6.Kneading method: This method primarily involves triturating the drug-carrier mixture in a mortar pestle with a small amount of water in order to obtain a pasty mass. During the process, the water content of the paste has to be empirically adjusted to maintain the consistency of the paste. The paste has to be dried at 45°C-50°C for 48 hours, and then pulverized and passed through sieve # 100. Daizepam-HPâCD

inclusion complexes [19] have been prepared for solubility improvement and then subjected to the development of rapidly disintegrating fast release tablet showed excellent results.

There are other methods of preparation of solid dispersions like supercritical fluid method, co-evaporation method, microwave oven method etc which can be successfully employed to preparations of SDs

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## CARRIER SYSTEMS USED IN PREPARATION OF SOLID DISPERISIONS

The various carrier systems used to prepare solid dispersions are shown in Table no 1.

| Class of carriers | Examples of drugs |
|---|---|
| Poly ethylene glycol | Ofloxacin [20], mebendazole [21], piroxicam [22] |
| Poly VinylPyrrolidone | Nifedipine [23], cefuroxime axetil [24], lansoprazole [25] |
| Urea | Chloramphenical [26], flurbiprofen [27] |
| Sugars | Naproxen [28], prednisolone [29] |
| Emulsifiers | Oxazepam [30], Fenofibrate [31] |
| Polyacrylates and polymethacrylates | Atorvastatin [32] |
| Cellulose derivative | Nilvadipine [33], |
| Cyclodextrins | Diazepam [19] |

**Table 1:** List of drug-carrier systems used in preparation of solid disperisions.

## FUTURE PROSPECTS

Poor bioavailability is a major limitation of successful drug delivery via the oral route. Lot of research work is focused on oral bioavailability enhancement of the poorly absorbed drugs. It is necessary to understand the reason behind the poor bioavailability before designing a delivery system. The positive results obtained with the use of various delivery systems or different approaches of bioavailability enhancement have given positive results. However, the commercial development of the product demands much more research for overcoming the challenges such as scale up, cost effectiveness and instability of some of the formulations.

## CONCLUSIONS

The solid dispersion method is one of the effective and widely adopted approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Various techniques, described in this review, are successfully used for the preparation of SDs. A single solid dispersion method cannot be universally accepted for a variety of drug materials. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a suitable solid dispersion method. 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.

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