



Asian Journal of Research in Biological and Pharmaceutical Sciences

Journal home page: www.ajrbps.com



SOLID DISPERSION: A TECHNIQUE TO ENHANCE SOLUBILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Oral bioavailability is the major problem when a poorly water-soluble drug is delivered via oral route. Solid dispersion systems have been demonstrated to overcome such problems and to enhance the dissolution rate of poorly water-soluble drugs. In the present review, the important points to be considered during formulation of solid dispersion systems viz., preparation methods of solid dispersion which affect on the dissolution rate of the drug as well as its formulation and evaluation techniques have been described.

KEYWORDS

Solubility, Solubility Enhancement and Solid dispersion.

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INTRODUCTION

Famous approaches such as particle size reduction, solubilisation in organic solvents, salt formation, etc are not always successful to achieve desired level of solubility and dissolution for poorly water-soluble compounds because of practical limitations to the degree of particle size reduction achievable by conventional means which limits the use of particle size reduction approach. Salt formation, needs an ionizable functional group on the pharmacophore, which may not be possible for very weakly acidic or basic drug compound. Still when a salt is prepared, it may be fruitless to attain the required absorption enhancement due to pH mediated precipitation of the drug in the GIT following initial dissolution. Additionally, dissolution rate for poorly water-soluble drug can be enhanced by converting drug into its amorphous form. In some cases amorphous

drug, under certain levels of heat and humidity is thermodynamically unstable. They can crystallize into a more stable, poorly water soluble form. Solid dispersion formulations have application to stabilize amorphous drugs, which is very beneficial. Hence to overcome the above problems, solid dispersion formulation is useful. Factors to be considered for preparation of solid dispersions are helpful to achieve desired extent of solubility and dissolution¹⁻³.

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems related to these drugs was its very low solubility in biological fluids, which consequences into poor bioavailability after oral administration. A drug with deprived aqueous solubility will typically demonstrate dissolution rate limited absorption, and a drug with poor membrane permeability will typically reveal permeation rate limited absorption⁴. The solid dispersion is defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid condition prepared by melting (fusion), solvent, or melting solvent method⁵.

SOLUBILITY

Oral route is most desirable route of administering the dosage form. But bioavailability is the major problem in oral administration of drugs. The term solubility is defined as a highest quantity of solute that can dissolve in a definite quantity of solvent or quantity of solution at a specific temperature^{6,7}. As the solubility increases bioavailability increases. Parts of solvent required for one part of solute in solubility is as shown in Table No.1.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying a drug substance depending on its aqueous solubility and intestinal permeability. The BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, when combined with the in vitro dissolution characteristics of the drug product, It classifies drugs into four classes^{9,10} as shown in Table No.2.

ADVANTAGES AND DISADVANTAGES OF SOLID DISPERSION^{11,12}

Advantages and Disadvantages of Solid dispersion are as shown below in Table No.3.

TYPES OF SOLID DISPERSION

Eutectic Mixture

It consists of two miscible compounds in the liquid state but only to a very small amount in the solid state. Eutectic mixture is prepared by quick solidification of fused melt of two components that shows complete liquid miscibility.

Amorphous precipitation in crystalline matrix

This is similar to simple eutectic mixtures but the difference is that drug is precipitated out in an amorphous form.

Solid solution

Solid solutions are analogous to liquid solutions, consisting of just one phase irrespective of the number of components. The drug's particle size in case of solid solution has been reduced to its absolute minimum size and the dissolution rate is determined by the dissolution rate of the material which is used as carrier. Solid solutions are classified by the two ways either as according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are dispersed in the solvent (substitutional, interstitial or amorphous).

Continuous solid solution

All the components are miscible in all proportions in a continuous solid solution. Theoretically, meaning of this is the bonding strength among the two components is stronger than the bonding strength among the molecules of each of the single components. This type of solid solutions has not been reported in the pharmaceutical world till date.

Discontinuous solid solutions

The solubility of each of the components in the other component is limited in the case of discontinuous solid solutions. The term 'solid solution' should be applied only when the mutual solubility of the two components is more than 5%.

Substitutional solid solutions

Substitutional solid solutions are possible only when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules. Classical solid solutions have crystalline structure,

in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules.

Interstitial solid solutions

The dissolved molecules occupy the interstitial spaces among the solvent molecules in the crystal network is known as the interstitial solid solution. Diameter of solute molecule should be not more than 0.59 times than that of solvent molecular diameter.

Glass solution and suspensions:

Solute dissolves homogeneously in glass carrier and forms glassy system as glass solutions. In case of glass suspensions the mixture of precipitated particles are suspended in glass solvent. In glass solution and suspension lattice energy is much lesser¹³.

FACTORS INFLUENCING PREPARATION OF SOLID DISPERSION

Selection of polymer

Major point of consideration for solid dispersion preparation is selection of carrier, which influences dissolution behaviour of the drug. For example, water-soluble carriers show fast and better release of drug from solid dispersion system as compared to water-insoluble carrier. Choice of polymer depends upon the characteristics of polymer including solubility, hydrophilicity, melting point, release behaviour, moisture uptake, influence of pH, etc.

Choice of drug-polymer ratio

To inhibit the crystallization of drug in solution, an optimized quantity of polymer is required.

Miscibility of ingredients

It is an important factor which determines the preparation of single-phase miscible solid dispersion system.

Production technique

Selection of production technique must be based on perceptible of physical properties of drug, carrier/polymer and finishing solid dispersion. For example, in the case of spray drying, the compound's (drug and polymer) solubility's in suitable solvents, is desirable, to ensure homogeneous single-phase system.

Hygroscopicity

Solid dispersions are to be evaluated for hygroscopicity to determine the ability for water

uptake. Hygroscopicity also affects the stability of formulation.

Biological factors

Effect of food

Food effects should be determined, because presence of food in GIT influences the dissolution of drug.

Effect of species variations

Alternative animal models should be investigated, for example, pigs, which act as better model for in vivo studies.

GIT physiology

For lipophilic drug molecules, the GIT regions of optimal absorption need to be evaluated.

Dissolution testing

Apparatus and media

Dissolution testing apparatus should be such that it mimics the GIT, example, medium that match the delivery route, stirring rate, pH, volume, temperature, etc.

Polymer release behaviour

Polymer wettability and release behaviour need to be evaluated.

Super saturation of dissolution media

This evaluation is important to know that active pharmaceutical ingredient will remain in the solution or crystallize out¹.

METHODS OF PREPARATION OF SOLID DISPERSION

Melting method

The melting also called fusion is the method of preparation of physical mixture of a drug and a water-soluble carrier material and heating it directly until it melted. This melted mixture is then rapidly solidified by using an ice-bath with vigorous stirring. The final solid mass is crushed till powdered and then passed through sieve. Suitably 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 air or water flows on the another side of the plate for cooling. In addition, a super-saturation of a solute material or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under this condition, by the instantaneous solidification process, the solute molecules are arrested in the solvent matrix. A

much finer dispersion of crystallites are obtained by the quenching technique when used for simple eutectic mixtures. However due to high temperature used in fusion process many substances, drugs or carriers, may get decompose. It may also cause evaporation of volatile drug or volatile carrier material during the fusion process at high temperature. Some of the way to overcome these problems might be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas such as nitrogen to avoid degradation of drug or carrier by oxidation.

Solvent method

This method involves the physical mixture of the drug and carrier material is dissolved in a solvent, which is evaporated until a clear, solvent free film is retained. The film is further dried till a constant weight obtained. The principal advantage of this method is thermal decomposition of drugs or carriers can be prohibited because of the relatively low temperatures required for the evaporation of organic solvents.

Disadvantages of solvent method:

1. High cost of preparation.
2. The difficulty in completer removal of liquid solvent.
3. Slight adverse effect of traces of the solvent on the chemical stability
4. The selection of a common volatile solvent.
5. The difficulty of reproducing crystal form.
6. In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties^{14,15}.

Melting solvent method (melt evaporation)

This method involves preparation of solid dispersions by dissolving the drug in an appropriate liquid solvent and then incorporating the solution directly into the melt mass of polyethylene glycol, after that the mixture is evaporated until a clear, solvent free film is left. The film is further dried till constant weight obtained. The 5-10% (w/w) of liquid compound can be integrated into polyethylene glycol 6000 exclusive of significant loss of its solid nature. Sometimes it has been found that the selected solvent or drug which is dissolved may be immiscible with the melted polyethylene glycol. Also the liquid which is used as a solvent

may affect the polymorphic form of the drug, which then forms a solid dispersion by precipitation. This technique has same advantages as that of the fusion and solvent evaporation methods. From a practical point of view, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Melt extrusion method

The mixture of drug-carrier is usually processed with a twin screw extruder. The drug/carrier mixture is simultaneously melted, homogenized and then extruded and formulated as tablets, granules, pellets, sheets, sticks or powder. Then the intermediate products can be further processed to form conventional tablets. The hot melt extrusion method has advantage that for about 1 min the drug/carrier mixture is subjected to high temperature, which enables somewhat thermo labile drugs that are to be processed. Solid dispersion formed by this method consists of active ingredients and carrier material and prepare by hot stage extrusion using a co-rotating twin-screw extruder. In the dispersions the concentration of drug is always 40% (w/w).

Lyophilization Technique

Lyophilization technique consists of transfer of heat and mass to and from the product which is under preparation. This technique is optional for solvent evaporation technique. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are dissolved in a common solvent, frozen and then sublimed to get a lyophilized molecular dispersion.

Vial freeze drying

Dissolve the drug in solvent at a specific concentration. Dissolve the carrier material in water. Both the solutions were mixed in a ratio of 40/60 v/v. Subsequently immerse the mixture in liquid nitrogen until it gets completely frozen. Various concentration of drug in the resulting solid dispersions is obtained by adjusting carrier concentrations, while maintaining drug concentration constant. Then lyophilize the frozen solution by lyophilizer. Lyophilization is performed according to a two-step procedure,

- Firstly set the pressure at 0.22 mbar and the shelf temperature at (-35°C) for 1 day.
- Subsequently release the pressure to 0.05 mbar, while raise the shelf temperature up to 200.

Maintain these conditions for another day. After removing the samples from the freeze dryer, place them in a vacuum desiccators over silica gel at room temperature for at least 1 day.

Spray freeze drying

Dissolve the drug in solvent at a fixed concentration and carrier in water. Mix the solution in a ratio of 40/60 v/v. spray the solutions through nozzle in to liquid nitrogen. Set the liquid feeding rate and atomizing air flow. Position the outlet of nozzle at about 10cm above the liquid nitrogen. Hot water is pumped through the jacket of the nozzle in order to keep away from freezing of the solution inside the nozzle. Transfer the resulting suspension (frozen droplets of the solution in liquid nitrogen) to the lyophilizer. Lyophilization procedure is started as soon as all liquid nitrogen is evaporated.

Melt Agglomeration Process

This technique is one of the important techniques used to prepare solid dispersion wherein the binder acts as a carrier material. In addition, solid dispersion is prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersion by melt agglomeration. It has been found that dissolution rate increases when hot melt on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition to the melt in procedure it also results in uniform distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

The role of the surfactant to enhance solubility is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion,

floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of researcher for preparation of solid dispersions.

Electro spinning

Solid fibers are produced in Electro spinning technique from a polymeric fluid stream solution or melt delivered through a millimetre-scale nozzle. This process consists of application of a strong electrostatic field over a conductive capillary connected to a reservoir containing a polymer solution or melt and a conductive collection screen. Charge species accumulated on the surface of a pendant drop when increases the electrostatic field strength but not exceeding a critical value that destabilize the hemispherical shape into a conical shape (commonly known as Taylor's cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited. If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nano fibers and controlling the release of biomedicine, as it is simplest and cheapest.

Super Critical Fluid (SCF) Technology

The supercritical fluid antisolvent techniques, carbon dioxide are used as antisolvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system, precipitation with a compressed fluid anti solvent, gas anti-solvent, and solution enhanced dispersion by supercritical fluids, and supercritical antisolvent. 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. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. 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 decreasing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

Spray Drying

Dissolve the various amounts of carriers in water. Then disperse 10gm of drug, pre-sieved through a 60-mesh screen in the solution. The resulting dispersion is subjected towards the nozzle at a flow rate previously fixed using a peristaltic pump and spray dry it at an inlet temperature of about 120°C and an outlet temperature of about 65-700C. Fix the spray pressure. Maintain the flow rate of drying air at the aspirator. After spray-drying, collect each resulting powders by cyclone separation and transferred to glass vials.

High- pressure homogenization

The high pressure homogenization involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently nanosuspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from micro particles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. However, by this technique brittle drug candidates might be broken up into nanoparticles.

Polymeric alteration

The materials which exist in different crystalline forms of a drug and that may have dissimilar properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. It is preferable

to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a Variety¹⁶⁻¹⁹.

CHARACTERIZATION OF SOLID DISPERSION^{19,20}

Several drugs with different molecular structures in the matrix can be encountered in solid dispersions. To scrutinize the molecular arrangement in solid dispersions various techniques have been applied. However, other properties can also be scrutinized by following methods.

Drug-carrier miscibility

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- Powder X-ray diffraction

Stability

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution

- Dynamic solubility
- Dissolution in bio-relevant media.

Table No.1: Solubility definitions⁸

S.No	Definition	Parts of solvent required for one part of solute
1	Very soluble	<1
2	Freely soluble	1-10
3	Soluble	10-30
4	Sparingly soluble	30-100
5	Slightly soluble	100-1000
6	Very slightly soluble	1000-10000
7	Insoluble	>10000

Table No.2: BCS Classification⁸

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Table No.3: Advantages and disadvantages

S.No	Advantages	Disadvantages
1	Reduction of drug particle size	Possible low stability – changes occurring during the processing (mechanical stress) or storage (temperature and humidity stress) leading to the crystallization of amorphous forms
	Increase drug wett ability	
	Increase solid dispersion particle porosity – porosity depends on the type of carrier, the use of linear polymers allows for a more porous particles than cross-linked	
	Substance in an amorphous state	
2	More acceptable to patients than solubilisation products Allow to obtain a solid oral dosage form instead of liquid form, where the substance is solubilised	Limitations in the case of industrial scale production – laborious and expensive methods of preparation – limitations of reproducibility of physicochemical characteristics – difficulty in incorporating into formulation of dosage forms – limitations of scale up of solid dispersion systems

CONCLUSION

From this review, it is concluded that to resolve the problem of solubility of poorly water-soluble drugs the solid dispersion technology is one of the advanced approach. So, prior to developing a new solid dispersion system for a given drug, it is necessary to investigate the physicochemical

properties of the drug and carrier that can best fit with each other. Also, the preparation methods and the ratio of carrier to drug also play an important role in the enhancement of solubility/dissolution rate of drug. We have attempted in bringing all the things in sequence in this review that how to cater all these aspects to achieve this goal.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to S.M.B.T. College of Pharmacy, Nandi-Hills, Dhamangaon, Nashik, India for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Vaibhav R. Toche et al. Solid dispersion: a technique to enhance solubility of poorly soluble drugs, *Asian Journal of Research in Biological and Pharmaceutical Sciences*, 6(2), 2018, 85-93.