

Solid Dispersion: Solubility Enhancement Technique for poorly water soluble Drugs

P S Argade*¹, D D Magar ², R B Saudagar

¹Department of Quality Assurance Techniques, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nashik, 422213. Maharashtra, India.

²Department of Pharmaceutical Chemistry, KCT'S R.G. Sapkal College of Pharmacy, Anjaneri, Nashik, 422 213. Maharashtra, India.

J. Adv. Pharm. Edu. & Res.

ABSTRACT

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulationscientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. 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. This article reviews historical background of solid dispersion technology, limitations, classification, and various preparation techniques with its advantages and disadvantages. This review also discusses the recent advances in the field of solid dispersion technology. Based on the existing results and authors' reflection, this review give rise to reasoning and suggested choices of carrier or matrix and solid dispersionProcedure.

Keywords: Poorlysoluble drug; solid dispersion; solubility enhancement.

INTRODUCTION [1, 2]

The simplest and easiest way of administering drug is through oral route. The oral dosage forms have many advantages over other types of dosage forms like greater stability, accurate dosage, smaller bulk and easy production is possible. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. Nearly 40% of identified potential new drug by pharmaceutical industry are poorly water soluble. Poor water soluble compounds show decreased release rate & poor bioavailability. So Large dose is required to produce desirable effect but that may leads to toxicity of the drug. So best option for increasing release rate is improvement of the solubility through formulation approaches.

Techniques for Solubility Enhancement [3,10]

I. Chemical Modifications:

1. Salt Formation

Address for correspondence

Dr. P S Argade
KCT'S R.G. Sapkal College of Pharmacy, Anjaneri,
Nashik, 422213 Maharashtra, India
Email: argade.pravin07@gmail.com

Access this article online
www.japer.in

2. Co-crystallization

3. Co-solvency

4. Hydrotropic

5. Solubilizing agent

6. Nanotechnology

II. Physical Modifications:

1. Particle size reduction

2. Modification of the crystal habit

3. Complexation

4. Solubilization by surfactants

5. Drug dispersion in carriers

- Solid solution
- Eutectic mixtures
- Solid dispersion

III. Other:

1) Supercritical fluid method

2) Spray freezing into liquid and Lyophilization

3) Evaporative precipitation into aqueous solution

4) Solvent evaporation method

5) Hot melt extrusion

6) Electrostatic spinning method

7) Direct capsule filling

8) Polymeric Alteration

9) High- Pressure Homogenization

10) Lyophilization technique

11) Inclusion Complexes:

- Kneading Technique
- Co-precipitation
- Neutralization
- Co-grinding
- Spray-Drying Method
- Microwave Irradiation Method

SOLID DISPERSION^[3,11]

There are various techniques for solubility enhancement. Solid dispersion is one of the best approaches for solubility enhancement. The term 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; basically amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers.

First Generation Solid Dispersions^[3,5]

Solid dispersions were first described by Sekiguchi and Obi in 1961 in which they used concept of eutectic mixtures. They mentioned that the formulation of eutectic mixtures improve the rate of drug release and thus increase bioavailability of poorly soluble drug. Thus first generation solid dispersions were prepared using crystalline carriers. Eutectic mixtures are binary systems comprising of poorly water soluble drug and highly water soluble carrier and at eutectic point drug crystallizing out simultaneously only in the specific composition. When eutectic mixture is dissolved in aqueous medium, the carrier part will dissolve quickly and drug will be released in the form of fine crystals. The main disadvantage of first generation Solid dispersion is crystalline nature which leads to less solubility as compare to amorphous form, however, they possess good thermodynamic stability. First generation solid dispersion were generally prepared using crystalline carriers like urea, mannitol.

Second Generation Solid Dispersions

In second generation instead of crystalline carriers, amorphous carriers were used to disperse drugs which are generally polymers. Polymeric carriers can be of fully synthetic origin like povidone, polyethylene glycols and polymethacrylates whereas natural product based polymers comprises of cellulose derivatives like hydroxypropylmethylcellulose, ethyl cellulose or starch derivatives, like cyclodextrins. Amorphous solid dispersions are further classified as solid solutions, solid suspension or mixture of both as per molecular interaction of drug and carrier.

Amorphous carriers: Polyethyleneglycol, Povidone, Polyvinylacetate, Polymethacrylate, cellulose derivatives

Third Generation Solid Dispersions

In the third generation solid dispersion surfactants carrier or mixture of polymer are used as carrier. If carrier has surface active or self-emulsifying properties, the dissolution profile of poorly soluble drug can be improved and hence result in increased bioavailability.

Typically used surfactants as solid dispersion carriers are polaxamer 407, gelucire 44/14, compritol 888 AT027, inulin.

ADVANTAGES^[12]

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages of solid dispersions are as follows:

- **Particles with reduced particle size :**
Solid dispersion, represent the last state on particle size reduction and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug.
- **Particles with improved wettability:**

The solubility enhancement of the drug is related to the drug wettability which can increase bioavailability.

- **Particles with higher porosity :**

Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with solid dispersion that prepared with reticular polymers. More, the porous nature of the particle more increase in dissolution rate.

- **Drugs in amorphous state :**

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

DISADVANTAGES^[20]

The major disadvantages of Solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable

Form can take place which leads to the reduction of drug solubility [18,19]. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness [20].

LIMITATIONS OF SOLID DISPERSIONS

Although a great research interest in solid dispersion in the past four decades, the commercial Utilization is very limited. Problems of solid dispersion involve

- (i) The physical and chemical stability of drugs and vehicles,
- (ii) Method of preparation,
- (iii) Reproducibility of its physicochemical properties,

(iv) Formulation of solid dispersion into dosage forms, and

(v) Scale-up of manufacturing processes [21].

TYPES OF SOLID DISPERSION^[12,13]

- **Binary Solid Dispersion:** It consists of drug and a polymeric carrier.
- **Ternary Solid Dispersion:** It consists of drug, a polymeric carrier and a surfactant.
- **Surface Solid Dispersion:** Surface solid dispersion is formulated with polymers such as polyvinyl pyrrolidone, polyethylene glycol and polyvinyl pyrrolidone-vinyl acetate copolymer by fusion technique to improve its solubility.

It is appropriate to classify various systems of solid dispersion on the basis of their major fast release mechanisms. Solid dispersions into the following six representative types

Based on their molecular arrangement,

Type1- Simple eutectic mixture

Type2-Amorphous precipitations in crystalline matrix.

Type3-Solid solutions

Type4-Glass suspension

Type6-Glass solution

Simple Eutectic Mixtures

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid-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. Ex., Chloremphenicol - urea; Paracetamol - urea; Griseofulvin and Tolbutamide with PEG 2000.

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 or second, according to the way in which the solvate molecules are distributed in the solvendum as, substitutional, interstitial or amorphous.

In Continuous solid solutions, the two components are miscible in the solid state in all proportions. This means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. In Discontinuous solid solutions, the solubility of each of the components in the other component is limited. In Substitutional crystalline solid dispersions, solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules. In Interstitial crystalline solid dispersions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In Amorphous crystalline solid dispersions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

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 point; 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.

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.

Compound or Complex formation

Drug and matrix strongly interact and form complexes in aqueous medium e.g. Cyclodextrins. Low association constant is necessary for dissolution enhancement. The formation of soluble complex possibly takes place when low or intermediate fraction of carrier is employed in the preparation of solid dispersion. Using a high fraction of carrier, drug dissolution may be promoted owing to the formation of a solid solution.

MECHANISM OF SOLID DISPERSION^[14,15]

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

1 Carrier-controlled Release

Corrigan (1986) provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer.

2 Drug-controlled Release

Sjokvist and Nystrom (1991) measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to

reconcile these contradictions Sjokvist-Saers and Craig (1992 used a homologous series of drugs (para-aminobenzoates) in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility and dissolution rate. These noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behaviour as drug-controlled dissolution as opposed to carrier-controlled dissolution. Here the dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated the particles and the possibility of improved wetting and decreased agglomeration.

Common Methods Used for Preparation of Solid Dispersion [8, 17]

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1. Melting method
2. Solvent methods
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomerations Process
7. The use of surfactant
8. Electro spinning
9. Super Critical Fluid (Scf) technologies

1. Melting method

The melting or fusion method is 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. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. However many substances, drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

2. Solvent 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. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

- 1) The higher cost of preparation.
- 2) The difficulty in completely removing liquid solvent.
- 3) The possible 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.

3. Melting solvent method (melt evaporation)^[17]

- It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol.

- Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical stand point, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg

4. Melt extrusion method

- The drug/carrier mix is typically processed with a twin screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed.

- Solid dispersion by this method is composed of active ingredient and carrier, and prepared by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consists of two mixing zones and three transport zones distributed over the entire barrel length, the feeding rate is fixed at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185°C from feeder to die.

- The extrudes are collected after cooling at ambient temperature on a conveyor belt. Samples are milled for 1 min with a laboratory cutting mill and sieved to exclude particles >355µm.

5. Lyophilization Technique^[17,18]

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of as 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.

Vial freeze drying

Dissolve the drug in solvent at a fixed concentration. Dissolve the carrier in water. Mix both the solutions in a ratio of 40/60 v/v. subsequently immerse the mixture in liquid nitrogen until it gets fully frozen. Various concentrations of drug in the resulting solid dispersions are 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,

- 1) Firstly set the pressure at 0.22 mbar & the shelf temperature at (-35°C) for 1 day.
- 2) 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 desiccator 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 feed 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 avoid 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.

6. Melt Agglomeration Process

- This technique has been used to prepare solid dispersion wherein the binder acts as a carrier. In addition, solid dispersion 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. 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 the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous 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.

7. Melt Agglomeration Process

- The utility of the surfactant systems in solubilization 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 investigators for preparation of solid dispersions.

8. Electro spinning

- Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop 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 Nanofibers and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

9. Super Critical Fluid (Scf) Technology

- The supercritical fluid antisolvent techniques, carbon dioxide are used as and 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 remain 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 reducing 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).

10). Spray Drying

Dissolve the various amounts of carriers in water. Then disperse the 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 & spray dry it at an inlet temperature of about 120°C & an outlet temperature of about 65-70°C. 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.

11). 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 Nano suspensions 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, only brittle drug candidates might be broken up into nanoparticles by this technique.

12). Polymeric alteration

Different crystalline forms of a drug that may have different 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 variety of real-world storage conditions

13). Inclusion complexes ^[17]

1. Kneading technique

Mix drug and polymer with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it is dried at 45°C in an oven. Pass the mass through the sieve no. 30 and store in the desiccator.

2. Co-precipitation

Add required amount of drug to the solution of β -cyclodextrins. Keep the system under magnetic agitation with controlled process parameters and protect from the light. Separate the formed precipitate by vacuum filtration and then dry at room temperature in order to avoid the loss of the structure water from the inclusion complex.

3. Neutralization

Add drug in alkaline solution like sodium hydroxide, ammonium hydroxide. Then add a solution of β -Cyclodextrin to dissolve the drug. The clear solution is obtained after few seconds under agitation. Then neutralize it using HCl solution until the equivalence point is reached. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. Finally filter and dry the precipitate.

4. Co-grinding

Weigh the calculated amounts of drug and carriers and mix together with one ml of water. Pass the damp mass obtained, through a 44-mesh sieve; disperse the resultant granules in Petri dishes and dried at 60°C under vacuum, until a constant weight is obtained. Store the granules in desiccators until used for further studies.

5. Spray-drying method

Dissolve drug in suitable solvent and the required stoichiometric amount of carrier material like β -Cyclodextrin in water. Mix the solutions by sonication or other suitable method to produce a clear solution. Dry it using spray dryer.

6. Microwave irradiation method

Drug and Cyclodextrin mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.

CHARACTERIZATION OF THE SOLID DISPERSION SYSTEM [3, 9, 17]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion.

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

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

Stability

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

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media.

PRACTICAL LIMITATIONS IN TECHNIQUE

Problem Related [16]

1. Problem concerned with dosage form development

Poor Flow and Compressibility:-

It is usually found that, the solid dispersion show complexity in sieving and pulverization. Solid dispersion also shows poor compressibility and stability. [13,14] To beat this problem the in- situ drug granulation method is used. In this method, the excipient (CaHPO₄ and sodium starch glycolate) was pre-heated and then rotated in water jacketed blender at 70°C. The drug carrier mixture that is melted at 100°C was then added to moving powder, after mixing the granules were passed through a 20-mesh sieve and allowed to harden at 25°C for 12 hrs, and then the granules are mixed with higher concentration of magnesium stearate (1%) and compressed into tablets. Also it is found that, in developing a tablet formulation for the solid dispersion, they were not Amenable to wet granulation because water could disrupt its physical structure.

Sticking of Granules of Solid Dispersion to Die and Punches:-

In general it is seen that, during compression the solid dispersion stick to dies and punches, to overcome the problem, the small pieces of grease proof paper were placed between metal surface and granules. Due to this direct contact between metal surface and granules is avoided. One of the new methods is, filling of drug-PEG melts in a hard gelatine capsule but care should be taken, while filling the temperature of drug-PEG melt should not exceed 70°C.

2. Problem concerned with scale up and manufacturing

Risk of Condensation of Moisture over Solid Dispersion during Cooling:-

During evaporation there is risk of condensation of moisture over solid dispersion. To overcome this, a continuous cooling operation is done like cooling on the surface moving belt or rotating belt.

Reproducibility of Physicochemical Properties:-

The manufacturing conditions for solid dispersion might greatly influence the physicochemical properties of solid dispersions formed. a range of

investigators observed that heating rate, maximum temperature used, holding time at a high temperature, cooling method and rate, method of pulverization, and particle size may greatly influence the properties of solid dispersions prepared by the melt method. The powder X-ray diffraction patterns of the solid

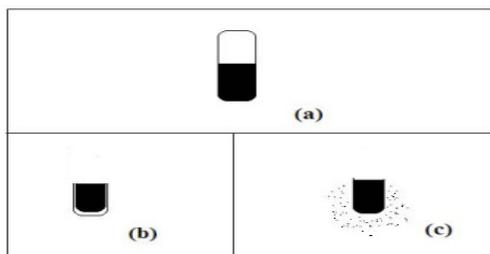
3. Problem concerned with Stability

Commonly, the solid dispersion prepared by the hot melt method, a certain fraction of drug may remain molecularly dispersed in carrier. if the extent of such drug is high it may give rise to phase separation i.e. the crystalline and amorphous phase are get separated .for that reason some polymer like PVP, HPMC, HPMCA are used now days .the polymer acts as a stabilizer in the preparation of solid dispersion by retarding crystallization of drug at low humidity .the preventing mechanism of crystallization is reducing the nucleation rate. This polymer affect nucleation kinetics by increasing their kinetic barrier to nucleation. The rate of performing as efficient barrier is directly proportional to the concentration of the polymer and is independent on the physicochemical properties of such polymer.

SOME NEWER TECHNIQUE [22]

Use of Surface Active Agent

The method of filling of the melt of drug-PEG in hard gelatin capsule is one of the efficient method in the development of the dosage form, but during the dissolution of the drug, the drug rich layer may produce on the dissolving bed which can trim down the dissolution rate of the drug from hard gelatin capsule due to poor water solubility of that. To attain a complete dissolution, a most efficient method is to make use of surface active carrier. They produce a vehicle which vehicle acts as a dispersing or emulsifying agent for the liberated drug, thus put off the formation of water insoluble surface layer and hence the subsequently increase the dissolution rate of drug. Example of such surface active agents are- Gelucire 44/14, Vitamin-E TPGS NF



(a) Capsule shell containing Solid dispersion

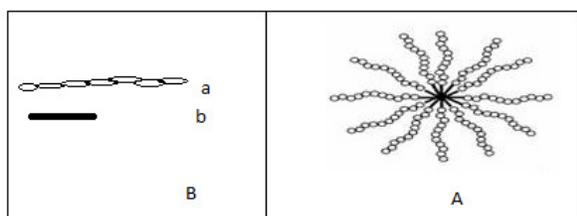
(b) After disintegration Surface rich layer is formed due to absence of surface active carriers and retard dissolution rate

(c) Surface active carriers help to disperse drug from Capsule shell hence improves dissolution rate

Benefit of a surface-active carrier over a non-surface active one in the dissolution of drug from a capsule formulation.

Use of Block Co-Polymer as Dispersed Agent

Some of the surface active agents show toxicity. So it becomes essential to find out new solubility agents. A block co-polymer of polyoxyethylene and polyoxypropylene are the good answer to this problem. In higher concentration they produce monomolecular micelles which then associate to form aggregates of different sizes in such a way that hydrophobic chains are blocked by hydrophilic chains.



A. Aggregates of monomolecular micelles after association in such a way that Hydrophobic Chains are blocked by hydrophilic chains

B. Chain block co-polymer: a- Hydrophilic chain, b- Hydrophobic chain

These aggregates have the property to solubilize the drug. Thus the dissolution rate of the drug gets increased. Also, block co-polymers have properties to boost the stability of the drug which is solubilized in the monomolecular micelles. Thus the block co-polymer

also plays an important task in preventing the problem in the stability of solid dispersion. Examples: Poly(propylene oxide)-poly(ethylene oxide) - poly(propylene oxide), Poly(beta-benzyl-L-aspartate), B-poly(ethylene oxide) etc.

Applications of Solid Dispersions:-

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
2. To stabilize unstable drugs against hydrolysis, oxidation, recombination, isomerization, photooxidation and other decomposition procedures.
3. To reduce side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. Improvement of drug release from ointment creams and gels.
6. To avoid undesirable incompatibilities.
7. To obtain a homogeneous distribution of a small amount of drug in solid state.
8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9. To formulate a fast release primary dose in a sustained release dosage form.
10. To formulate a sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
11. To reduce pre-systemic inactivation of drugs like morphine and progesterone.

CONCLUSION

The poor solubility of new chemical entities decreases the oral bioavailability of these drugs as dissolution is the rate-limiting step. Hence, enhancing solubility and bioavailability is the major challenge faced by formulation scientists. So for enhancing solubility many techniques have been used, solid dispersion being one of them. Solid dispersion has been used since the past decade for the enhancement of solubility. However, the commercial development of this technique requires overcoming the problems such as scale up, cost effectiveness and instability of some

of the drugs. Further research is required for the better implementation of solid dispersion technology on industrial scale as this is an excellent technique for the solubility enhancement of poorly soluble drugs.

REFERENCE

1. Wadke DA, Serajuddin A, Jacobson H, "Preformulation testing". In: Lieberman HA, Lachman L, Schwartz JB, eds. *Pharmaceutical Dosage Forms: Tablets*. New York, NY: Marcel Dekker; 1989.
2. Brahmankar DM, Jaiswal SB. *Biopharmaceutics and Pharmacokinetics*, Vallabh Prakashan, 1st Edn. 1995:347-352.
3. Patel PB, Prajapati ST, Patel NR, Patel NN, Patel CN. *Solid Dispersion: A Method of Improving Bioavailability and Taste Masking*. *Inventi Rapid: Pharm Tech* Vol. 2012; Issue 4.
4. Varshney HM, Chatterjee, A. Solubility enhancement of poorly hydrophilic drugs by using different newer techniques: A Review. *International Journal of Therapeutic Applications*, 2012; 6:8-138.
5. Wairkar SM, Gaud RS. Solid Dispersions: Solubility enhancement technique for poorly soluble drugs. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, Jul- Sep 2013; 4 (3):847-854.
6. Pawar AR, Choudhari PD. Novel techniques for solubility, dissolution rate and bioavailability enhancement of class II and IV drugs. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 2012; 2 (13):9-14.
7. Arane PM, Ghanwat DA, Boyane V, Kothawade SN, Doshi P. Preparation and in Vitro Characterization of Eprosartan Mesylate Solid Dispersions using Skimmed Milk Powder as Carrier. *International Journal of Advances in Pharmaceutical Research*, Dec. 2011; 2(12):658-665.
8. Nagender Reddy CH, Anil Reddy T, Srinivasan S. Review on: Better solubility enhancement of poorly water soluble drugs. *International Journal of Inventions in Pharmaceutical Sciences*, 2013; 1 (4):267-273.
9. Sangada Kirankumar Nanjibh, Jigar Vyas, Upadhyay UM, Sanjay Bamaniya. *Inventi Rapid: Pharm Tech* 2011; 2
10. Ranade VV, Canon JB. *Drug Delivery Systems*. Third Edn., Published by Taylor & Francis group: 231-234.
11. Patidar K, Sharma S, Soni M, Kshirsagar MD, Saini V. Preparation and Characterization of Hydrotrophic Solid Dispersions of Indomethacin. *Inventi Rapid: Pharm Tech*. Vol. 1, Issue 3
12. Remington- *The Science & Practice of Pharmacy*, Published by Lippincott Williams & Wilkins, 21st Edn., 229-230
13. Ingle US, Gaikwad PD, Bankar VH, et al. A Review on solid dispersion: A dissolution enhancement technique. *International Journal of Research in Ayurveda & Pharmacy*, 2011; 2 (3):751-757.
14. Duncan QM Craig. The Mechanism of Drug release from Solid Dispersions and Water soluble polymers. *International Journal of Pharmaceutics*, 2002; 231:131-144.
15. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics and Biopharmaceutics*, 2000; 50:47-60.
16. Md. Armin Minhaz, Md. Mofizur Rahman, Md. Qamrul Ahsan, Md. Habibur Rahman, Md. Raihan Chowdhury. Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. *Int. J. of Pharm. & Life Sci.*, 2012; 3(3):1510-1518.
17. Eun-Jung Kim, et al. Preparation of solid dispersion of felodipine using a solvent wetting method. *European Journal of Pharmaceutics and Biopharmaceutics*, 2006; 64:200-205.
18. X. Wang, Michel A, and Van den Mooter G, "Solid state characteristics of ternary solid
19. Dispersions composed of PVP VA64, Myrj 52 and itraconazole," *Int. J. Pharm.*, 2005; 303(1):54-61.
20. Seth NS, "Formulation and evaluation of solid dispersion of olanzepine," *Int. J. Pharm. Sci. Res.*, 2011; 2(2):691-697.
21. Chavan S, Patel K, Shelar D, Vavia P. Preparation of Oxcarbazine Solid Dispersion by Hot Melt Extrusion for Enhanced Dissolution: Downstream Processing to tablets. *Am. J. PharmTech Res*, 2013; 3 (1).
22. Rohini P, Kiran Kadali SDVS, Bhagvan Raju M, Pavankumar K. Studies on dissolution enhancement of Itraconazole using water-soluble carriers. *Inventi Rapid: Pharm Tech*, 1(1).
23. Dixit M, Kini AG, Kulkarni PK. A novel technique to enhancing the solubility and dissolution of flutamide

- using freeze drying. Turk J. Pharm. Sci.; 2012; 9 (2):139-150.
24. Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersion: A Review. Pak. J. Pharm, April 2009; Vol.22(2):234-246,.
25. Sambath L, Kottai Muthu A, Ashis Kumar M, et al. Formulation and evaluations of Naproxen sustained release tablets using Naproxen solid dispersion. Inventi Rapid: Pharm Tech 2013
26. Arunachalam A, Karthikeyan M, Konam, Pottabathula H, Sethuraman S, Ashutoshkumar S. Solid Dispersions: A Review Current Pharma Research, 2010;1(1).

How to cite this article: P S Argade^{*1}, D D Magar ², R B Saudagar; Solid Dispersion: Solubility Enhancement Technique for poorly water soluble Drugs; J. Adv. Pharm. Edu. & Res. 2013; 3(4): 427-439.

Source of Support: Nil, **Conflict of Interest:** Nil