



Review Article

PHARMACEUTICAL SOLID DISPERSION TECHNOLOGY: A PROMISING TOOL TO ENHANCE ORAL BIOAVAILABILITY

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Abstract: The solubility behavior of drugs remains one of the most challenging aspects in formulation development with the advent of combinatorial chemistry & high throughput screening, The number of poorly water soluble compounds has dramatically increased. Therefore a drug with poor aqueous solubility will typically exhibit permeation rate limited absorption. Although solid solutions have tremendous potential for improving drug solubility, 40years of research have resulted in only a few marketed product using this approach. Thus a greater understanding of dissolution & absorption behavior of drug with low aqueous solubility is required to successfully formulate them into more soluble & hence bioavailable drug product in case of poorly water soluble drug. Dissolution may be the rate limiting step in the process of drug absorption. Drug with poor water solubility have been shown to be unpredictably & slowly absorbed compared with drugs of higher solubility. Therefore a better oral, parenteral or topical formulation can be developed by increasing the water solubility of the drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approach for solubility enhancement. Solid dispersion refers to a group of solid products consisting of at least two different components, generally hydrophilic matrix & a hydrophobic drug. The matrix can be either crystalline or amorphous. This article gives an overview of sold dispersion systems, preparation methods, characterization & applications of solid dispersions.

Keywords: Solid dispersion, amorphous state, bioavailability, solubility, dissolution, solubility enhancement

INTRODUCTION

Now a days, many hydrophobic drugs were came into the market. Major drawbacks of these drugs are its bioavailability problems due to poor aqueous solubility. So, it is necessary to improve its solubility & its permeability thereby improving the dissolution, absorption & bioavailability of the drugs¹. When a drug administered orally, its rate & extent of absorption depends on rate & extent of dissolution of active ingredient from the dosage form. The drug should dissolve in gastric fluids & then it permeates through membrane. Drugs which are hydrophobic & low permeability show dissolution rate limited & permeation rate limited absorption². Various methods are available to enhance dissolution are salt formation, micronisation, addition of solvent or surface active

agents. Recent advancements were carrying out in solid dispersions which is an effective dissolution enhancing method. Solid dispersion involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state by different methods. Preparation of solid dispersion includes fusion or melting method, solvent evaporation method, freeze drying, lyophilisation, hot melt extrusion etc³. According to BCS classification (Table 1), drugs are classified according to their solubility, permeability & dissolution into class I, II, III & IV. Class II drugs are better drug candidates but their low solubility nature is a limitation to their absorption & bioavailability. So it is necessary to improve their dissolution via solid dispersion⁴.

Table 1: BCS classification system

Sl no:	Class	Solubility	Permeability	Examples of Drugs
1	Class I	High Solubility	High Permeability	Benzapril, Loxoprofen, Sumatriptan
2	Class II	Low Solubility	High Permeability	Loratidine, Aceclofenac, Glimperide
3	Class III	High Solubility	High Permeability	Gabapentine, Topiramide, Atropine
4	Class IV	Low Solubility	High Permeability	Furosemide, Meloxicam

Solid Dispersion system

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. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles as shown in Figure I.



Figure I: Improvement of dissolution by solid dispersion system.

Advantages of solid dispersion

1. PARTICLE SIZE

For hydrophobic drugs, which is in pre existing solid formulation ie,tablet, capsule will have large particle size of about 5~100mm in the git after disintegration. It will exhibit low dissolution. There are some limitations in particle size reduction. Drug with solid dispersion show colloidal particles having fine oily globules in the git after disintegration & the drug show high dissolution⁵.

2. POROSITY

Drugs having high porosity will release faster compared to low porous drug. Solid dispersion have high porosity so it enhance drug release thereby bioavailability. Solid dispersion containing reticular polymer show less porosity & linear polymer has high porosity⁶

3. AMORPHOUS STATE

Crystalline drugs which are poorly soluble in the amorphous state show more solubility & increased drug release. In amorphous state no energy is needed to break the crystalline lattice during dissolution.

4. WETTABILITY

Solubility can be enhanced by increasing the wettability. There by increasing the bioavailability⁷

Limitations of solid dispersion

- It is not using commercially due to its stability problems.
- During processing & storage due to mechanical stress, temperature & humidity more chances of amorphous state undergo crystallization.
- Phase separation may occur because most polymers used will absorb moisture.
- Chances of conversion of metastable crystalline form to

- more stable structure.
- Poor scaleup for manufacture⁸
- Too expensive.
- It is not applicable to thermolabile substances.
- Also cooling & soldifying methods are difficult to carry out.
- In case of hydrophobic drugs solvent used will be more & the drug concentration will be less to get desired therapeutic effect.
- Selection of a carrier is important because only a small number of carriers are currently available for oral use.
- Low solubility of drug in available carrier is a major limitation⁹

Strategies to Overcome the Drawbacks of Solid Dispersions

Development of surface active carriers or self-emulsifying carriers is helpful in enhancing the dissolution. By using these self-emulsifying carriers, particles having large surface area will be formed. It improves dissolution there by its bioavailability. Commonly used self-emulsifying carriers are poloxamers, which are copolymers containing polyoxypropylene chain with a hydrophobic center, and two polyoxyethylene chains which are hydrophilic on both sides. Due to this amphiphilic property, poloxamers are commonly used as surfactant¹⁰. And filling the solid dispersion in a hard gelatin capsule as it melts and it gets solidify on room temperature can overcome the stability problems associated with solid dispersion¹¹. Most common carriers used in the solid dispersion systems are explained in Table 2.

Table 2: Carriers used in Solid Dispersion

Carriers	Examples
Sugars	Dextrose, sucrose, lactose, sorbitol, maltose, mannitol, galactose
Acids	Citric acids, succinic acids
Polymeric Material	Povidone, polyethylene glycol, hydroxyl propyl methyl cellulose, methyl cellulose, hydroxyl ethyl, cellulose, pectin
Insoluble or enteric polymers	Hydroxy propyl methyl cellulose phthalate, Eudrgit RS
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texofor AIP, Deoxycholic acid, Tweens, Spans
Miscellaneous	Urea, Hydroxyalkylxanthins, Urethans

PREPARATION OF SOLID DISPERSION TECHNIQUES

The fusion (melt), solvent evaporation, spray drying, lyophilization (freeze drying), hot-melt extrusion, electrostatic

spinning method, coating on sugar beads using fluidized bed-coating system, supercritical fluid technology, are the methods reported for the preparation of solid dispersions.(Figure II)

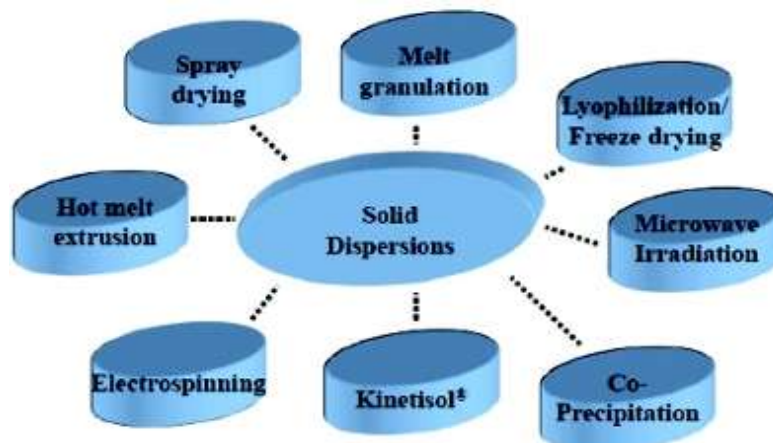


Figure II: Methods of preparation of solid dispersion system.

1. FUSION METHOD

Also called melting method. It is so called because it is used for method which use crystalline as starting material. Fusion or Melting method was first introduced by Sekiguchi et al.in 1961. Drug is made to melt in a carrier & the dry mass obtained after cooling were pulverised & sieved..Carriers used include urea, mannitol, & PVP/VA-64. It is less expensive & sometimes Nitrogen as inert gas, used to prevent oxidation of drug or carrier material. It is applicable only if the drug & carrier are compatible. It is not effective for thermolabile drugs.

2. SOLVENT EVAPORATION METHOD

Organic solvent having drug & carrier in dissolved form & it is evaporated after complete dissolution. The solid mass is ground, sieved & dried¹². Steps involved in the method are,

1. Preparation of a solution containing both carrier & drug.
2. The removal of the solvent resulting in the formation of solid mass.

Formed mass depends on the nature of solvent & rate & temperature of evaporation of the solvent. Decomposition of drug can be avoided because low temperature is required for the evaporation of the solvents. Major drawbacks include time consuming process, expensive & crystal forms are difficult to reproduce¹³.

3. SPRAY DRYING

Drug & polymer is suspended in a solvent & then drying it into a steam of heated air flow to remove the solvent. Evaporation takes place rapidly due to large surface area of droplets. It yields to drugs in amorphous state but sometimes the drug may be partially crystallized during processing.

4. LYOPHILISATION OR FREEZE DRYING

Drug & carrier dissolved or suspended in a solvent & it is frozen & sublimed to obtain solid dispersion. Sublimed pressure under 8-10mm Hg & condensed onto 75 o c.

5. HOT MELT EXTRUSION

Fibres were produced by the liquid when introduced into an electric field. The fibres become harder after cooling, chemical

hardening or evaporation of solvent. These fibres collected on a suitable charged surface¹³

6. SUPERCRITICAL FLUID TECHNOLOGY

A supercritical fluid exists as a single phase above its critical temperature & pressure. Efficient supercritical fluid is carbon dioxide due to low critical temperature & pressure. So, it is effective in thermolabile drugs (12). This technique involves the mixing of drug with an inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle with carbondioxide. When solution is sprayed, precipitation of solid dispersion particles on the vessel. Other fluids include nitrous oxide, water, methanol, ethanol, ethane, propane, n-hexane & ammonia. Technique with carbondioxide has different working principles,

Such as

1. Rapid expansion of supercritical solutions (RESS)
2. Gas antisolvent precipitation (GAS)
3. Supercritical antisolvent precipitation (SAS)
4. Precipitation with compressed fluid antisolvent (PCA)
5. Solution enhanced dispersion by supercritical fluids (SEDS)
6. Precipitation from gas saturated solutions (PGSS), etc

Characterization

1. Spectroscopic methods.

a. UV visible Spectroscopy

Spectra of pure drug and dispersed drug are scanned. Calculation of molar extinction provides evidence of any decomposition.

b. FTIR Spectroscopy

Infra red studies was carried out to rule out interaction between drug and carrier used in formulation of solid dispersion Appearance and disappearance of peak indicate interaction between two compound and degradation of drug.

c. X-ray Diffraction Spectroscopy:

Intensity of X-ray diffraction (or reflected) from sample is measured as function of diffraction angle. It is efficient tool in

studying physical nature of solid dispersion. Used to study quantitatively the concentration of crystalline compound in mixture. Valuable in detecting compound or complex formation since its spectra is markedly different from those of pure drug. Drawback: Inability to differentiate between amorphous precipitations from molecular dispersion, because of disappearance of peak in both the cases.

2. Thermal Methods

Exposing sample to different temperature condition. Studying physicochemical interaction between drug and carrier. Based on principle of change in thermal energy as function of temperature.

a. Differential Scanning Calorimetry (DSC)

Differential Scanning calorimetry is a thermo analytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature. Using this technique it is possible to observe fusion and crystallization events as well as glass transition temperatures T_g. DSC can also be used to study oxidation, as well as other chemical reactions. The data obtained from the DSC is melting point depressions, enthalpy of fusion and degree of crystallinity

b. Differential Thermal Analysis (DTA):

Differential Thermal Analysis: In DTA, the temperature difference that develops between a sample and an inert reference material is measured, at identical heat treatments. Changes in the sample which lead to the absorption or evolution of heat can be detected relative to the inert reference. Phase transitions or chemical reactions can be followed by absorption or evolution of heat.

c. Cooling curve Methods

Physical mixtures were heated. Then homogeneous melt Temperature of each mixture are noted. Plot Temperature – time curve Phase diagram of the samples. Major disadvantages include Time consuming. Requires relatively large amount of sample. Heat sensitive material¹⁵.

D. Thaw Melting Methods

Samples are frozen Heated & it suddenly converted from solid state –liquid state. Disadvantage: Depends upon subjective observation, therefore not highly reproducible Thaw point and melting point can be noted

3. Dissolution Studies

Carried out at physiological temperature by using type II USP dissolution apparatus. Dissolution profile of solid dispersion or compressed tablet made from solid dispersion is determined by comparison between dissolution profile of pure drug, physical mixture and solid dispersion gives idea about dissolution rate. Effect of different carrier and their different proportion on dissolution rate of solid dispersion is main characterization tool²¹.

4. Microscopic Methods:

To determine size and observe morphology of solid dispersion. Scanning Electron Microscopy (SEM): - Sample coated by gold or palladium -using vacuum evaporator -

Examined at accelerating voltage with suitable magnification - eg. Naproxen-chitosan²².

Applications of Solid Dispersions

1. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures²³.
2. Enhancement of dissolution rates and oral absorption of Grisofulvin dispersed in PEG4000 and 6000.
3. PEG was found to be effective in increasing the dissolution of Gliclazide in solid dispersions when compared to pure drug.
4. Improvement of drug release from ointment creams and gels.
5. Enhancement of dissolution rate of purely water soluble drug Furosemide using PEG¹⁷.
6. Improve the dissolution rate and quick anti-inflammatory activity of Rofecoxib can be obtained from its solid dispersions-based oral tablets¹⁸.
7. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
8. To formulate a fast release primary dose in a sustained released dosage form.
9. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
10. To reduce pre systemic inactivation of drugs like morphine and progesterone²⁴.
11. It can be used to improve the onset of action of drugs like Nonsteroidal Anti Inflammatory drugs, where rapid action is necessary to relieve pain²⁵.
12. Injection formulation can be substituted by providing bioavailable oral dosage form for patient comfort and compliance²⁶
13. Glyburid (hypoglycemic drug) tablets were formulated allowing fast reproducible and complete drug dissolution by using solid dispersions in PEG.

CONCLUSION

Solubility is the major criteria for a drug formulation and its therapeutic efficacy. One of the major techniques to enhance the solubility of drug is Solid dispersion technique. It is a promising technique for the enhancement of bioavailability of poorly aqueous soluble drugs. It aims at improving the dissolution & absorption of drugs by various methods like fusion, solvent evaporation, freeze drying etc. Selection of suitable carrier & preparation method are valid for the better enhancement of bioavailability. Development of Self emulsifying carriers and filling of solid dispersion in a hard gelatin capsule as melts improved the advantages of solid dispersion system. A major focus on the future will become the identification of new surface active carriers and self emulsifying carriers for solid dispersion. Apart from all the drawbacks it has promising future in the enhancement of bioavailability of poorly soluble drugs.

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