A Review on Solubility Enhancement of Water Insoluble Drugs by Various Techniques

Madhavi N[1*], Varsha M[2], Shivani[3], Praneeth[4]

[1*,2,3,4] Department of Pharmaceutics,
CMR College of Pharmacy,
Medchal, Kandlakoya, Hyderabad.

***Abstract*: Aim of the current study is to improve the solubility and oral bioavailability of poorly water-soluble drugs. Solid dispersions, one of the technique to improve the solubility and oral bioavailability of poorly soluble drugs. Solid dispersions are mainly prepared for BCS class -II drugs as these drugs have low solubility and high permeability. Solid dispersion can be prepared by various methods which includes Kneading method, Melting method, Solvent method, Electrospinning etc., The present article mainly focuses on various available methods to improve the drug solubility. The water-soluble carriers are used in preparation of solid dispersions which increases the dissolution rate of poorly soluble drug. The carrier selection should be freely soluble in water, pharmacologically inert and possess high dissolution rate. Examples of carriers are cyclodextrins, poly vinyl pyrrolidone, phospholipids and poly ethylene glycol etc.**

***Keywords*: Solubility, Dissolution, Bioavailability, kneading method**

Introduction:

Solid Dispersions can be defined as the dispersion of one or more active ingredients (i.e., hydrophobic) in an inert carrier (i.e., hydrophilic) at a solid state. Some of the drugs which are having low or poor water solubility, they often show poor oral bioavailability because of low levels of absorption. [1] Therefore, development of solid dispersion technologies is especially promising for enhancing the oral absorption and bioavailability of poorly soluble drug. Solid dispersions are mainly prepared for BCS (Biopharmaceutical Classification system) class-II drugs which are having low aqueous solubility and high membrane permeability. [2,3] When the solid dispersions are exposed to aqueous media, the inert carrier gets dissolved and drug is released, thus surface area is increased and it leads to high dissolution rate. Finally, it enhances the bioavailability of poorly soluble drugs. Sulphathiazole was the first drug in which the rate and extent of absorption was increased using the solid dispersion by Sekiguchi and Obi which includes usage of urea as inert carrier.[1]

Selection of the carrier should be such that, it should be freely soluble in water and possess high rate of dissolution, it must be non-toxic in nature and should be pharmacologically inert. Various methods are available, by which solid dispersions can be prepared such as solvent methods, melting method, electrospinning method.[4] Based on the molecular arrangements, the solid dispersions can be classified into following types: [5]

- Eutectic mixtures
- Solid dispersions
- Amorphous solid solutions
- Glass solution and Glass suspensions

Based on recent advancement, solid dispersions can be classified into following types: [4]

First Generation solid dispersion, second generation solid dispersion and third generation solid dispersion.

Commercially available solid dispersion products with reputated drugs are:

Griseofulvin, Nifedipine, Carbamazepine, Albendazole, Prednisolone, Ofloxacin etc.,

Few marketed solid dispersion products are:

- Troglitazone solid dispersion marketed by Parke Davis.
- Sporanox, a solod dispersion of Itraconazole drug. [6,7,8]

Solid inclusion complexes:

To improve the solubility and dissolution rate of the BCS-II drug (e. g. Clozapine), solid inclusion complexes (e. g. Clozapine/Hydroxypropyl-β-Cyclodextrin) were first prepared by evaporation method.

Preparation of solid inclusion complexes:

Molar ratio (1:1) products of Drug/Polymer (CLZ/HP-β-CD) inclusion complexes were prepared by evaporation method. [9] The equal proportion of drug (CLZ) and polymer (HP-β-CD) are dissolved in ethanol and sonicated for 30min. A clear solution was obtained which was evaporated until it becomes dry. After evaporation, remaining solid residue was further dried with a vacuum dryer at 40°C for 24hrs and then it is milled and passed through a sieve (no.80) and stored in a desiccator at room temperature. [10]

Various carriers used in the preparation of solid dispersions:

A wide variety of polymers are available which have tremendous potential in the area of solid dispersions to improve drug bioavailability.

1. Polyethylene glycol (PEG):
These are compounds are obtained from a reaction of ethylene glycol with ethylene oxide. PEG's, molecular weight is above 3,00,000 are commonly termed as polyethylene oxides. For the manufacture of solid dispersions and solutions, PEG's with molecular weights (MW) of 1500-20,000 are usually employed. As the MW rises, the viscosity of the system has been increased, MW up to 600, PEG's are in fluid state, 800-1500 they showed Vaseline-like consistency and from 2000 to 6000 they are in waxy state and those with MW of 20,000 and above form hard, brittle crystals at room temperature. A meticulous advantage of PEG's for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEG's of interest with an average molecular weight of 4600 (range 4400-4800) is 57-61°C and with an average molecular weight of 6000 (range 5000-7000) 60-63°C.

2. Polyvinylpyrrolidone (PVP):
PVP molecular weight ranges from 2500 to 3000000. It is having the solubility in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP gets decomposed at high temperature therefore it is not suitable for preparation of solid dispersions prepared by melt method because melting takes place at a very high temperature. PVP can be classified according to the K value, which is calculated using Fikentscher's equation. The temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (Tg) is high; for example, PVP K25 has a Tg of 1558°C. For this reason, PVPs have only restricted application for the preparation of solid dispersions by the hot melt method. Due to their excellent solubility in an ample variety of organic solvents, they are mostly suitable for the preparation of solid dispersions by solvent method.[11]

Cellulose derivatives are

3. Hydroxypropyl methylcellulose (HMPC):
HPMC's are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% is derivatized with hydroxypropyl groups. The molecular weight of the HPMC's ranges from about 10000 to 1,50,0000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane.

4. Hydroxypropyl cellulose (HPC):
Hydroxypropyl cellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37,000 (Type SSL) to 1,15,0000 (Type H). [11]

5. Carboxymethylethylcellulose (CMEC):
CMEC also belongs to cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixture of dichloromethane and ethanol. [12]

6. Hydroxypropyl methylcellulose phthalate (HPMCP):
HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). They are having a type-dependent solubility in organic solvents. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a evaporate of HPMCP. [13]

7. Polyacrylates and polymethacrylates:
Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mainly used as coatings to change the release of the drug from the dosage form.

8. Phospholipids:
The complexity of glycerides advances by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule. Monoaryl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions. [14]

9. Sugar, polyols and their polymers:
Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates. Even with these drawbacks, several attempts have been reported to prepare solid dispersions using sugars and their derivatives. Mannitol, which has a melting point of 165-168°C and decomposes only above 2500°C, can be employed in some cases to prepare dispersions by the hot melt method. [15]

10. Organic acids and their derivatives: Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin method.

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

Advantages of Cyclodextrins:

a. Increasing the stability of the drug
b. Release profile during gastrointestinal
c. Transit through modification of drug
d. Release site and time profile
e. Decreasing local tissue irritation.

f. Masking unpleasant taste

Solid Dispersions

Advantages of Solid Dispersion:

• Solid dispersion results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. Hence bioavailability is increased.[8-9]

• The carrier used in the solid dispersion plays a major role in improving the wettability of the particles. Improved wettability results in increased solubility thus improving the bioavailability.[10]

• In solid dispersion drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus, presenting the drug in amorphous form and increases the solubility of the particles.[11]

Disadvantages of Solid Dispersion:[14]

• Major disadvantage is their instability. They show changes in crystallinity and a decrease in dissolution rate with ageing.

• Temperature and moisture have more deteriorating effect on solid dispersions than on physical mixtures.

• Difficulty in handling because of tackiness.

Methods of Preparation of Solid Dispersions: [15-22]

1. Kneading Technique
2. Melting method
3. Solvent method
4. Melting solvent method (melt evaporation)
5. Melt extrusion methods
6. Lyophilization techniques
7. Melt agglomeration Process
8. Electrospinning method
9. Spray Drying method
10. Super Critical Fluid (SCF) technology
11. Co-Precipitation method

1. Kneading technique

In this method, carrier is permeated with water and transformed to paste. After that drug is added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

2. Melting method

In melting or fusion method, a physical mixture of the drug and a water-soluble carrier is prepared, by heating it directly until it melts. The final solid mass that is obtained is crushed, pulverized and sieved. However, substances either the drug or the carrier may decompose due to high temperature during the melting process. A method to overcome this problem could be heating the mixture in a sealed container or under vacuum or in the presence of inert gases like nitrogen.

3. Solvent method

This method is also known as solvent evaporation method in which physical mixture of the drug and the carrier is dissolved in common solvent and is evaporated until a clear solvent free film is obtained. The main advantage is that the thermal decomposition of the drug or the carrier can be prevented because the organic solvent requires a low temp for evaporation. The disadvantage in this method is difficulty in removing the solvent and higher cost of preparation.

4. Melting solvent method

This method involves dissolving the drug in an appropriate liquid solvent and then incorporating the solution formed directly into the melt of polyethylene glycol which is evaporated until a clear solvent free film is obtained. This technique is a combination of fusion and solvent evaporation method

5. Melt extrusion method

Using twin screw extruder, the drug/carrier mix is simultaneously melted homogenized and extruded and shaped in different forms such as tablets, granules, pallets, powder etc. The method is applicable for thermolabile drugs as the mixture of the drug and carrier is subjected to elevated temperature for about 1min.

6. Lyophilization Technique

It is a phenomenon of transfer of heat and mass from and to the product. It is an alternative technique to solvent evaporation in which molecular mixture technique is used where the drug and carrier is dissolved in common solvent, frozen and sublimed

7. Melt Agglomeration technique

In this technique binder is use as carrier. There are two methods of preparation of solid dispersing, first is by spraying the drug on melted binder plus excipients and other one is melting of binder drug and excipient above the melting temperature of binder used. For using high binder content rotary process might be preferable for controlling temperature. This technique is advantageous in homogenous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.

8. Electrospinning method

In this technique electric force is used to withdraw a nano size fibre thread from the polymer sol/polymer melt. This a combination of solid dispersion with nanotechnology uses in polymer industry. Stream of Polymer solution /melt is subjected to electric force (5 to 30kv) which cause body of the liquid becomes charged, and electrostatic repulsion counteracts the surface tension. This made a strong cohesive force between the particle or droplets of polymer and a stream of fibre is formed. Then thinning and stretching of

fibre to nano diameter is done by using whipping process called electrostatic repulsion led to formation of uniform fibre in nano diameter. This process all depend on rate of feeding surface tension and electric force used.

9. Spray-drying method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.

10. Supercritical fluid technology

SCF is a substance above its critical temperature and pressure. Critical point represents the highest temperature and pressure at which the substance exists as vapour and liquid in equilibrium. In this technique SCF is used to form solid dispersion of insoluble material/polymer with drug cause increase in dissolution property. It is superior over conventional technique (spray drying, hot melt etc.), in this technique SCF carbon dioxide is mainly used which cause very rapid precipitation of solid mixture giving no time for separation of drug and polymer in preparation of solid dispersion. It forms very stable small particle with higher surface area for good flow and low organic solvent residual. In recent Solid dispersion of carbamazepine with PEG-4000 are made using SCF carbon dioxide in precipitation vessel. Resulting in formation of carbamazepine with increase rate and extent of dissolution with low solvent residual.

11. Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

Pharmaceutical Applications of Solid Dispersion:[22]

The pharmaceutical applications of Solid dispersions technique are:

- To enhance the absorption of drug.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
- To dispense liquid or gaseous compounds.
- To formulate a fast release priming dose in a sustained release dosage form.
- To formulate sustained release preparation of soluble drugs by dispersing the drug in poorly soluble or insoluble carrier.

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