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Review Article

SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS USING SOLID DISPERSION METHOD A REVIEW

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Abstract
Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Up to 40% of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. Solid dispersions of poorly water-soluble drugs with water-soluble carriers reduce the incidence of these problems and enhanced dissolution. Solid dispersion is one of the most promising 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. As per biopharmaceutical classification system, Class II drugs with low solubility and high permeability are the promising candidates for improvement of bioavailability by solid dispersion. In this review, it is intended to discuss about the recent advances related to the area of solid dispersion.
Keywords: Fast Dissolving Tablet, drug delivery system, fast disintegrating, fast melting, Orodispersible.

INTRODUCTION

Solubility is the property of a solid, liquid and gaseous chemical substance called solute to dissolve in a solid, liquid or gaseous chemical substance called solvent to form a homogenous solution. The solubility of a substance depends upon the temperature and pressure. The extend of solubility of a substance in a specific solvent is measured as the saturation concentration which means the maximum possibly quantity of a substance that can dissolve in a standard volume of a specific solvent under standard condition of temperature and pressure. [1,2]

It is seen that 25-30% of new developed drug and approximately 35-40% of known drugs face a problem of poor solubility. By increasing the rate of solubility of poorly soluble drugs, therapeutic effect and bioavailability of the drugs may be improved. There are various methods for the enhancement of the solubility in which solid dispersion technique is more effective and widely used. In solid dispersion, the drug is dispersed in an inert water-soluble carrier like PEG, PVP, HPMC, mannitol, succinic acid etc. at solid state[3,4,5]. Solid dispersion is defined as the dispersion of one or more active ingredient in a carrier or matrix at solid state. Solid dispersion refers to a group of solid products, consists of at least two different components; one is

hydrophilic matrix and another one is hydrophobic drug. [6]

BCS Classification:

Table: BCS Classification

BCS Class	Solubility	Permeability	Oral Dosage Form Approach
I	High	High	Simple solid oral dosage form
II	Low	High	Techniques to increase surface area like particle size reduction, solid solution, solid dispersion Solutions using solvents and or Surfactants
III	High	Low	Incorporate permeability enhancers, maximize local luminal concentration
IV	Low	Low	Combine 1 and 2

Class I:

High permeability, high solubility

These types of drugs dissolve or absorbed and their therapeutic rate is usually higher than excretion.

Class II:

High permeability, Low solubility

The bioavailability of class II drugs is limited by their solvation on rate. A correlation between the in vivo bioavailability and in- vitro solvation can be found.

Class III:

Low permeability, high solubility

The absorption of class III category drug is limited by the permeation rate, but the drug dissolved very fast. If the formulation does not change the permeability or gastrointestinal duration time, then class l criteria can be applied.

Class IV:

Low permeability, low solubility

The bioavailability of class IV category class is very poor. Usually, they are not well absorbed over the intestinal mucosa due to their poor solubility. The drug has no IVIVC can be expected.[11]

Techniques to Improve Solubility:

Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water-soluble drugs which include as following:

a) Particle size reduction
b) Nano-nization
c) Co-solvency
d) Hydro-trophy
e) pH adjustment
f) Solid dispersion
g) Inclusion complexion
h) Self-emulsifying
i) Liquid solid method
j) Supercritical fluid process
k) Sonocrystalliation

SOLID DISPERSION

The term “solid dispersion” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method or fusion solvent method. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[12]

METHOD OF PREPARATION OF SOLID DISPERSION [13]

a) Melting Method or Fusion Method

The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath. Immediately after fusion, the sample are poured onto a metallic plate which is

kept at ice bath. The final solid mass is crushed, pulverized and sieved. An important prerequisite to the manufacture of solid solution by the hot melt method is the miscibility of the drug and the carrier in the molten form.

b) Solvent Method

Solid dispersion is prepared by dissolving the drug and the carrier in a common solvent followed by evaporation of the solvent. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. Another point to consider is the importance of thoroughly removing of the solvent, since most of the organic solvents used toxicity issues.

c) Lyophilization Technique

Freeze- dying involves transfer of heat and mass to and from the product under preparation. Lyophilization has been thought of a molecular mixing technique where the drug and the carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

d) Melt Agglomeration Process

This technique has been used to prepare SDs where the binder acts as a carrier. In addition, SD(s) is 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. A rotary processor has been shown to be alternative equipment for melt agglomeration.

e) Extruding Method

Hot melt extrusion approach represents the advantageous mean of preparation of SD(s) by using the twin screw hot melt extruder where only thermostable components are relevant. The extruder consists of a hopper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die.

f) Spray Drying

Spray dying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive then freeze- drying. It is an established method that is initiated by atomizing suspension or solution into fine droplets followed by a drying process, resulting solid particles.

g) The Use of Surfactant

Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that give interfacial processes such as flocculation/ dispersion, floating, wetting, and Solubilization, detergency, enhanced oil recovery and corrosion inhibition.

h) Kneading method

In this method, drug and polymer are added in mortar and pestle and triturated by adding ethanol to form slurry. Then, kneaded mixture is air dried at 250°C for 24 hour and passed through sieve, if required.

i) Co-precipitation method

Required amount of drug added to the solution of polymer. Then, the mixture is kept under magnetic agitation under dark place. The formed precipitation is separated by using vacuum filtration and dried at room temperature[14].

j) Co-grinding method

Physical mixture of drug and carrier is mixed for some time in a blender at a particular speed. Then, the mixture is charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized, collected and kept at room temperature in a screw capped glass vial until use[15].

k) Gel entrapment techniques

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. The drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Then, remaining mixture are reduced in size by mortar and sieved.[16]

TYPES OF SOLID DISPERSION[17]

1. Simple eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. Solid eutectic mixtures are usually prepared by rapid cooling of a comet of the two compounds in order to obtain a physical mixture of very fine crystal of the two components. When a mixture consisting of a slightly soluble drug and an inert, highly water-soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug.

2. Solid solutions

Solid solutions of a poorly water-soluble drug dissolved in a carrier with relatively good aqueous solubility are of particular interest as a means of improving oral bioavailability. In the case of solid solution, the drugs particle size is reduced to its absolute minimum viz. the molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier. By judicious selection of a carrier, the dissolution rate of the drug can be increased by up to several orders of magnitude. Solid solutions can be classified according to two methods. Firstly, they can be classified according to their miscibility (continuous versus discontinuous solid solution) or second, according to the way in which the solvent molecules are distributed in the solvent (substitutional, interstitial or amorphous).

3. Continuous and discontinuous solid solution

Continuous solid solutions:

In a continuous solid solution, the components are miscible in all proportions. Theoretically, 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. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

Discontinuous solid solutions:

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations, it has been suggested by Goldberg that the term solid "solution" should only be applied when the mutual solubility of the two components exceed 5%.

4. Substitutional crystalline, Interstitial crystalline & Amorphous solid solution Substitutional crystalline solid solutions:

Classical solid solutions have a 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. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial crystalline solid solution:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter.

Amorphous solid solution:

In an amorphous solid solution, the solute molecules are dispersed molecularly but

irregularly within the amorphous solvent. Using griseofulvin in citric acid, the formation of an amorphous solid solution to improve a drug's dissolution properties is reported. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

REASONS FOR IMPROVEMENT OF SOLUBILITY

The enhancement in dissolution rate as a result of solid dispersion formulation, relative to pure drug varies from as high as 400 folds to less than two- fold. The increase in dissolution rate for solid dispersion can be attributed to a number of factors. It is very difficult to show experimentally that any one particular factor is more important than another[18]. The main reasons postulated for the observed improvements in dissolution of these systems are as follows:

1. Particles with reduced particle size:

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water-soluble drug and highly soluble carriers[18].

2. Particles with improved wettability:

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement[19]. Carriers with surface activity, such as cholic acid and bile salts can significantly increase the wettability property of drug[20].

3. Particles with higher porosity:

Particles in solid dispersions have been found to have a higher degree of porosity.21 The increase in porosity also depends on the carrier properties. For instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate[22].

4. Drugs in amorphous state:

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility[23]. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process[24]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form[25].

ADVANTAGES OF SOLID DISPERSION:

1. Improving drug bioavailability by changing their water solubility has been possible by solid dispersion.
2. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2-5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine.
3. Increase in dissolution rate & extent of absorption and reduction in pre-systemic metabolism.
4. Transformation of liquid form of drug into solid form.
5. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

DISADVANTAGES OF SOLID DISPERSION:

1. Most of the polymers used in solid dispersions can absorb moisture, which

may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.

2. Poor scale-up for the purposes of manufacturing.

APPLICATION OF SOLID DISPERSION:

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique may be used:

3. To obtain a homogeneous distribution of a small amount of drug in solid state.
4. To stabilize the unstable drug.
5. To dispense liquid or gaseous compounds in a solid dosage.
6. To formulate a fast release primary dose in a sustained released dosage form.
7. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
8. To reduce pre-systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds.
9. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
10. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo oxidation and other decomposition procedures.
11. To reduce side effect of certain drugs.
12. Masking of unpleasant taste and smell of drugs.

FUTURE PROSPECTS

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful development of solid dispersion systems for preclinical, clinical and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drug and carriers in solvent and filling into hard gelatin capsules or compressed into tablets. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties, as a result the bioavailability of solid dispersions is not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micro ionization and lyophilization of drugs. One major focus of future research will be the identification of new surface- active and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use.

CONCULSION

Solubility is a most important parameter for the oral bio availability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bio availability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the

possible modes that increase the solubility of poorly soluble drugs.

The various technologies discussed have been successful in the laboratory as well as the scale-up. Some products have been marketed using technologies like the surface-active carriers. Hence these technologies are expected to form a basis for the commercialization of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the near future. Solvent systems consisting of mixtures of solvents can be used to optimize concentration in solution processing parameters influence the type of glass amorphous system formed

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