Review Article

"SOLID DISPERSION " A METHOD FOR SOLUBILITY ENHANCEMENT: A REVIEW

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ABSTRACT

Solid dispersion, technology is the science of dispersing one or more active ingredient in a carrier or matrix at solid state for improving dissolution of poorly water-soluble drugs for enhancement of their bioavailability. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach market due to their poor water solubility. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. Solid dispersions have considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs.

Keywords: Solid dispersion, solubility, Bioavailability.

INTRODUCTION

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, co-solubilisation and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs there are practical limitations of these techniques. The salt formation technique is not feasible for neutral compounds and also the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilisation of drugs in organic solvents or in aqueous media by the use of surfactants and co-solvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to size reduction achieved by commonly used methods as controlled crystallization, grinding, pearl milling etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability due to charge development.[1]

In 1961, Sekiguchi and Obi developed a practical method whereby most of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as "Solid Dispersion" On the other hand, if a solid dispersion or a solid solution is used, a portion of the drug dissolves immediately to saturate the gastrointestinal fluid and the excess drug precipitates out as fine colloidal particles or oily globules of submicron size. Hence, due to promising increase in the bioavailability of poorly water-soluble drugs, solid dispersion has become one of the most active areas of research in the pharmaceutical field.[2]

ADVANTAGES OF SOLID DISPERSIONS [3]

Generally, solid dispersion is mainly used

- To reduced particle size.
- To improve wettability.
- To improve porosity of drug.
- To decrease the crystalline structure of drug in to amorphous form.
- To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets.
- To obtain a homogenous distribution of small amount of drugs at solid state.
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.

- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or Insoluble carriers.

MECHANISM OF DISSOLUTION RATE ENHANCEMENT

The increase in drug dissolution rate from solid dispersion system can be attributed to a number of factors like particle size, crystalline or polymorphic forms and wettability of drug etc. It is very difficult to show experimentally that any one particular factor is more important than another. The main reasons postulated for the observed improvements in dissolution from these systems are as follows:

a) Reduction of Particle Size

In case of glass solution, solid solution and amorphous dispersions, particle size is reduced. This may result in enhanced dissolution rate due to increase in the surface area. Similarly, it has been suggested that the presentation of particles to dissolution medium as physically separate entities may reduce aggregation. [4]

b) Solubilisation Effect

The carrier material as it dissolves may have a solubilisation effect on the drug. Enhancement in solubility and dissolution rate of poorly soluble drugs is related to the ability of carrier matrix to improve local drug solubility as well as wettability.

c) Wettability and Dispersibility

The carrier material may also have an enhancing effect on the wettability and Dispersibility of the drug due to the surfactant action reducing the interfacial tension between hydrophobic drug particle and aqueous solvent phase, increasing the effective surface area exposed to the dissolution medium. This also retards agglomeration or aggregation of the particles, which can slow down the dissolution.

d) Conversion of Polymorphic Nature of Solute

Energy required to transfer a molecule from crystal lattice of a purely crystalline solid is greater than that required for non-crystalline (amorphous) solid. Hence amorphous state of a substance shows higher dissolution rates. But the amorphous solids also demonstrate lack of physical stability due to natural tendency to form crystals. Thus formation of metastable dispersions with reduced lattice energy would result in faster dissolution rate and comparatively acceptable stability. [5]

SELECTION OF CARRIER[6]

One of the most important steps in the formulation and development of solid dispersion for various applications is selection of carrier. The properties of carrier have a major influence on dissolution characteristics of the drug. A material should possess following characteristics to be suitable carrier for increasing dissolution

i. Freely water-soluble with intrinsic rapid dissolution properties
ii. Non-toxic nature and pharmacologically inertness
iii. Thermal stability preferably with low melting point especially for melt method
iv. Solubility in a variety of solvents and should pass through a vitreous state upon solvent evaporation for the solvent method
v. Ability to increase the aqueous solubility of the drug
vi. Chemical compatibility and not forming a strongly bonded complex with drug.

Types of Solid Dispersions

A) Simple Eutectic Mixture

Eutectic mixture of a sparingly water-soluble drug and a highly water-soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline components. These systems are usually prepared by melt fusion method. When the eutectic mixture is exposed to water, the soluble carrier dissolves leaving the drug in a microcrystalline state which gets solubilized rapidly. The increase in surface area is mainly responsible for increased rate of dissolution.[7]

B) Solid Solutions

Solid solutions consist of a solid solute dissolved in a solid solvent. These systems are generally prepared by solvent evaporation or co-precipitation method, whereby guest solute and carrier are dissolved in a common volatile solvent such as alcohol. The solvent is allowed to evaporate, preferably by flash evaporation. As a result, a mixed crystal containing amorphous drug in crystalline carrier is formed because the two components crystallize together in a homogenous single phase system. Such dispersions are also known as “Co-precipitates” or “Co-evaporates”.

Solid solution can generally be classified according to the extent of miscibility between

the two components or the crystalline structure of the solid solution

i. Continuous solid solutions
ii. Discontinuous solid solution
iii. Substitutional solid solution
iv. Interstitial solid solution

i) Continuous Solid Solutions

In this system, the two components are miscible or soluble at solid state in all proportions.

ii) Discontinuous Solid Solution

In this system , in contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature. However, as the temperature is lowered, the solid solution regions become narrower. The free energy of stable and limited solid solutions is also lower than that of pure solvent.

iii) Substitutional Solid Solution

In this type of solid solution, the solute molecule substitutes for the solvent molecules in the crystal lattice of the solid solvent. It can form a continuous or discontinuous solid solution. The size and steric factors of the solute
molecules play a decisive role in the formation of solid solution

iv) Interstitial Solid Solution

The solute (guest) molecule occupies the interstitial space of the solvent (host) lattice . It usually forms only a discontinuous (limited) solid solution. The size of the solute is critical in order to fit into the interstices. It was found that the apparent diameter of the solute molecules should be less than that of the solvent in order to obtain an extensive interstitial solid solution of metals. [8,9]

C) Glass Solution

A glass solution is a homogenous system in which a glassy or a vitreous carrier solubilizes drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (Tg). On heating, it softens progressively without a sharp melting point.

D) Compound or Complex Formation

This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of drug from complex or compound depends on the solubility, association constant and intrinsic absorption rate of complex. Rate of dissolution and gastrointestinal absorption can be increased by the formation of a soluble complex with low association constant.[10]

E) Amorphous Precipitation

Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug. It is postulated that a drug with high super cooling property has more tendency to
solidify as an amorphous form in the presence of a carrier. Hence, amorphous precipitation is rarely observed.[11]

METHODS OF PREPARATION OF SOLID DISPERSIONS

A) Fusion Process

The fusion process is technically less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. Drug and carrier mixture of eutectic composition is molten at temperature above its eutectic temperature. Then molten mass is solidified on an ice bath and pulverized to a powder. [12]

B) Solvent Evaporation Process

Solvent evaporation method In this method, both drug and carrier are dissolved in organic solvent. After entire dissolution, the solvent is evaporated. The solid mass is ground, sieved and dried. [13,14]

C) Fusion Solvent Method

This method consists of dissolving the drug in a suitable solvent and incorporating the solution directly in the melt of carrier. If the carrier is capable of holding a certain proportion of liquid yet maintains its solid properties and if the liquid is innocuous, then the need for solvent removal is eliminated. This method is particularly useful for
drugs that have high melting points or they are thermo-labile. [15]

D) Supercritical Fluid Process

Supercritical CO2 is a good solvent for water-insoluble as well as water-soluble compounds under suitable conditions of temperature and pressure. Therefore, it has potential as an

alternative for conventional organic solvents used in solvent based processes for forming solid dispersions due to its favourable properties of being nontoxic and inexpensive. The process consists of the following steps:

i. Charging the bioactive material and suitable polymer into the autoclave.
ii. Addition of supercritical CO2 under precise conditions of temperature and pressure, that causes polymer to swell
iii. Mechanical stirring in the autoclave
iv. Rapid depressurization of the autoclave vessel through a computer controlled orifice to obtain desired particle size. The temperature condition used in this process is fairly mild (35-75°C), which allows handling of heat sensitive biomolecules, such as enzymes and proteins.[16,17]

E) Lyophilization Technique

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 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.[18, 19]

F) Kneading Technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary. [20]

G) Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use.[21]

H) 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.[22]

EVALUATION OF SOLID DISPERSION[23-25]

1. Percentage Yield

The prepared solid dispersion of all batches accurately weighed. The weight of the prepared solid dispersion calculated by the total amount of all excipients and drug used in the preparation of the solid dispersion, which gives the percentage yield of solid dispersion. It is calculated by using the following equation

Percentage yield =

$$\frac{\text{Actual yield of the product}}{\text{Total weight of excipients and drug}} \times 100$$

2. Solubility study

Solid dispersion formulation containing equivalent amounts of drugs placed in 25 ml stoppered conical flask containing 10 ml of distilled water. The sealed flask will be agitated on rotary shaker for 24 hrs. Sample will be filtered and analyzed on a UV spectrophotometer.

3. Estimation of drug content

The formulation equivalent to 50 mg of solid dispersion weighed and diluted suitably with suitable solvent. The absorbance measured at lambda maximum and the amount of drug in each formulation calculated.

4. Differential Scanning Calorimetry

Differential scanning Calorimetry performed by Differential scanning calorimeter to obtain suitable thermograms. The accurately weighed sample placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment performed under nitrogen flow, at a scanning rate 300C/min. in range of 50-3500C.

5. Infra-red spectrum

Infra-red studies carried out to rule out interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra-red spectrophotometer.

6. Thermal studies

It is carried out to ascertain the effect of heating on stability of the drug. It is based on thaw point melt method by heating drug in capillary melting point tube and allowing it to solidify. The melting point of rapidly solidifying mass noted.

7. Dissolution Studies

The drug release study for solid dispersion is performed using USP dissolution in 900ml of suitable buffer as dissolution media at 50rpm at 37± 0.5°C. 5 ml of the sample is withdrawn at 5min time intervals for 60min and sink conditions will be maintained. Withdrawn samples were analysed spectrometrically at λ_{max} by using UV visible spectrophotometer.

Same procedure followed for the marketed tablet containing solid dispersion.

CONCLUSION

The increasing number of poorly water soluble compounds entering pharmaceutical industries in the recent years has prompts the use of several different formulation approaches to enhance oral bioavailability of such compounds. Solid dispersion has set itself as a proven technology for the purpose with unique set of advantages and limitations. The review provides various methods of preparation of solid dispersions, and discusses as to why, when, and how to develop them. Proper selection of formulation method and carriers greatly append in solubility enhancement of poorly water soluble drugs. Improved understanding of physical stability of solid dispersions is the main driver for increasing future relevance of solid dispersions. With further expansion in polymer science and a greater perceptive of biopharmaceutical properties prevailing dosage form selection, solid dispersions technique will be widely applied to develop oral dosage form of poorly water-soluble drugs.

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