A Review on Solid Dispersion with Advanced Techniques

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Abstract- *Over 40% of active pharmaceutical ingredients (API) in development pipelines are poorly water-soluble drugs which limit formulation approaches, clinical application and marketability because of their low dissolution and bioavailability. Solid dispersion has been considered one of the major advancements in overcoming these issues with several successfully marketed products. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilisation by cosolvents, and particle size reduction.*

Keywords- solid dispersion, bioavailability, carrier, solubility

I. INTRODUCTION

Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophilic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug.

Solid dispersion

Chiou and Reigelman first defined solid dispersion as "dispersion of one or more active ingredients in an inert carrier or matrix (hydrophilic) at solid state prepared by fusion, solvent or melting solvent method" or solid dispersion defined as "a dispersion that include the formation of eutectic mixtures of drug with carriers that soluble in water easily by melting of their physical mixtures"

The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Drugs that undergo dissolution rate limited absorption, their dissolution rate can be enhanced by micronisation or size reduction but this leads to aggregation of particles which leads to poor wett ability. Various other approaches for increasing the bioavailability of poorly water soluble drugs include salt formation, solubilisation using a co-solvent, complexation with cyclodextrin and particle size reduction; all these approaches have various limitations. Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches. Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophillic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug.

The first drug whose rate and extent of absorption was significantly enhanced using solid dispersion was sulfathiazole by sekiguchi and obi (sekiguchi, 1961), in which eutectic mixture of sulfathiazole with urea as the inert carrier was formed. Lyopilization is a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion (lin, 1980).

Noyes Whitney equation:

The rate of dissolution can be expressed by using Noyes Whitney equation, which provides various parameters that can help improve the bioavailability of a poorly soluble drug.

$dc/dt = AD(Cs-C)/ h$

dc/dt- is the rate of dissolution
A- Surface area available for dissolution
D- Diffusion coefficient of the compound
Cs- solubility of the compound in the dissolution medium
C- Concentration of drug in the medium at time t

h- Thickness of diffusion boundary layer adjacent to the surface of dissolving compound

Classification of solid dispersions

Depending on the molecular arrangement, solid dispersions can be of the following types:

Eutectic mixtures: solid eutectic mixtures are usually prepared by rapidly cooling the co-melt of the two components in order to obtain a physical mixture of very fine crystals of the two components. Solid solutions: Depending on the miscibility, the two types of solid solutions are:

Continuous solid solutions: In continuous solid solutions, the components are miscible in all proportions i.e. the bonding strength between the components is stronger than the bonding between the individual component.

Discontinuous solid solutions: In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.11

Solid solutions

Depending on the distribution of the solvates in the solvent, solid solutions can be of two types:

Substitution crystalline solution: These are those solid solutions which have a crystalline structure, the solute molecules substitute for the solvent molecules in the crystal lattice.

Interstitial crystalline solid solution: These are those solid solutions in which the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.

Amorphous solid solutions: In amorphous solid solutions, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

Glass solutions and glass suspension: A glass solution is a homogenous system in which the solute dissolves in the glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. The term glass refers to a pure chemical or a mixture of pure chemicals in the glassy state.

Classification of solid dispersion on the basis of recent advancement

First generation solid dispersion

The solid dispersions which could be prepared by using crystalline carriers are categorized as the first generation solid dispersions.6 Examples of used crystalline carriers are urea and sugars.7 In this type, thermodynamically stable crystalline solid dispersion get formed which releases the drug slowly.6 The dissolution rate is faster in case of amorphous solid dispersions (ASDs) as compared to crystalline sold dispersions.

Second generation solid dispersion

These contain amorphous carriers like PVP, PEG, cellulose derivatives, etc.7 Second generation solid dispersions were found more effective than first generation solid dispersions (SD) because of their thermodynamic stability.9 According to the physical state of drug, ASDs can be classified as amorphous solid suspensions and amorphous solid solutions [glass solutions]. Amorphous solid suspensions consist of two separate phases while amorphous solid solutions contain molecularly homogenous mixture of both the drug and amorphous carriers. Amorphous carriers can be synthetic polymer or natural polymer.

Third generation solid dispersion

The dissolution profile of drug can be improved using third generation solid dispersions which consists of carriers having surface activity or emulsifying properties.9 Use of special type of carrier for formulation of solid dispersions will overcome precipitation and recrystallization problems. Use of surfactant or emulsifiers not only improve the dissolution profile of drug but also improves physical and chemical stability of drug in solid dispersion. Examples of these carriers are inulin, Gelucire, poloxamer, etc.8 The physical and chemical stability of solid dispersion get enhanced by preventing nucleation and agglomeration.

Fourth generation solid dispersion

These type of dispersions can be referred as controlled release solid dispersions (CRSD). It contain poorly water soluble drug with a short biological half-life.8 The carrier used are either water soluble carrier or water insoluble carrier.7 Solubility enhancement and extended release of drug in controlled manner are the two targets in CRSD.8 The water soluble carriers used in CRSD are ethyl cellulose, Eudragit RS, Eudragit RL, HPC, etc.7

Classification According to Physical State and Molecular Arrangement of API and Carrier

Class	API	Carrier
C-C	Crystalline	Crystalline
C-A	Crystalline	Amorphous
A-C	Amorphous	Crystalline
A-A	Amorphous	Amorphous
M-C	Molecularly dispersed	Crystalline
M-A	Molecularly dispersed	Amorphous

SELECTION OF CARRIER

A carrier should posses the following characteristics to be suitable for increasing the rate of dissolution of a drug

- The carrier should be freely soluble in water with a high rate of dissolution
- It should be non-toxic in nature
- It should be pharmacologically inert should possess heat stability with a low melting point
- It should be able to enhance aqueous solubility of the drug
- it should possess chemical compatibility with the drug, and should not form strongly bonded complexes with the drug
- economical.

Carrier used in solid dispersion

Nature of carrier	Name of carrier
Sugars	Dextrose, Sorbitol, Sucrose, Fructose, Maltose, Galactose, Xylitol, Mannitol and lactose.
Acids	Citric acid, Tartaric acid, Succinic acid.
Polymeric materials	Polyvinylpyrrolidone (PVP), polyethylene glycol (PEG 4000,6000), Hydroxyl propyl methyl cellulose .
Insoluble or enteric polymer	Hydroxypropylmethylcellulosepthalate, Eudragit RL , eudragit L 100, eudragit S1000.
Surfactant	Polyethylene stearate, poloxamer 188, tweens and spans.
Miscellaneous	nicotinic acid, succinamide, dextrin's , gelatin, polyvinyl alcohol, urea, cyclodextrins

MECHANISM OF BIOAVAILABILITY ENHANCEMENT

Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms:

- Reduction in particle size
- Improvement in wettability and dispensability
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles.

Methods of preparation of solid dispersions:

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

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilisation techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (Scf) technology

METHODS OF PREPARATION OF SOLID DISPERSION:

1. 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. The advantage is its simplicity and economical nature

2. **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.

3. 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

4. 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 thermo labile drugs as the mixture of the drug and carrier is subjected to elevated temperature for about 1 min.

5. Lyophilisation:

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

6. Melt Agglomeration technique:

In this technique binder is use as carrier. There are two method of preparation of solid dispersing, first is by spraying the drug on melted binder plus exipients 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.

7. 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 use 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 lead to formation of uniform fibre in nano diameter. This process all depend on rate of feeding surface tension and electric force used.

8.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.

Various methods for characterization of solid dispersions and its significance

Characteristics	**Methods used**	**Significance**
Physical state examination	Differential scanning calorimetry, Powder X-ray diffraction, Hot stage microscopy, Humidity stage microscopy	To find out physical state of sample, crystallinity and degree of crystallinity of drug, polymer, solid dispersion.
Surface microscopy	Scanning electron microscopy, hot stage microscopy, polarized light optical microscopy	To examine microscopy and crystallinity
Structure elucidation	Solid state nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy	To investigate bonding between drug and carrier e.g. hydrogen bonding
Drug carrier interactions	Differential scanning calorimetry,	To study physical and chemical interactions between

	Nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy	drug and polymer
Dissolution rate	Dissolution studies, dynamic solubility studies	To study rate and extent of drug release
Stability	Differential scanning calorimetry, nuclear magnetic resonance spectroscopy, Fourier transform infrared spectroscopy	To study physical and chemical interactions between drug and polymer during its manufacturing and storage period

Merits of solid dispersion

- Carrier which is used in formulation that reduces particle size so that increases solubility due to high surface area
- When the wettability of drug candidate is increased, the dissolving property also increased. Solid dispersion increases the wettability of drug
- Solid dispersion is responsible for increasing porosity of drug. This characteristic of drug is also responsible for improving solubility
- Solid dispersion is responsible for converting insoluble drug into the amorphous state which is responsible for higher degree of dissolution.
- The drug candidates in its amorphous state are easy to release because no energy is required for breaking the crystal lattice in dissolution process
- Use of hydrophilic carrier like PEG and use of super disintegrant like croscarmellose sodium is used in manufacturing of oral disintegrating tablet by solid dispersion technique which are responsible for increasing aqueous dissolution.

Demerits of solid dispersion

- Solid dispersion have drawback like poor scale-up for the manufacturing.
- Sometimes it is difficult to handle due to tackiness problem.
- Major disadvantage of solid dispersion technique is instability.
- Reason behind it is that most of the carriers used in formulation are polymers which can easily absorb the moisture due to this phase separation occurs which is responsible for instability.
- Recrystallization of the amorphous drug and/or transitions occurs between polymers responsible for stability problems.

II. CONCLUSION

Therapeutic activity of drug mainly depends on the bioavailability of the drug and ultimately depends on the solubility. Solid dispersion is one of the most important techniques to increase solubility, dissolution, and bioavailability of drug. Oral dispersible tablet have significant advantage of immediate conversion of solid to liquid after administration. The development of oral dispersible tablet by solid dispersion also provides an opportunity for a line extension in market place, for wide range of drugs. Keeping in view the advantages of the delivery system, rapidly disintegrating dosage forms have been successfully commercialized, and because of increased patient demand, these dosage forms are expected to become more permeable.

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