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A REVIEW ON INCLUSION COMPLEXES FORMULATION AND CHARACTERISATION

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ABSTRACT

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water-soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. Poorly water-soluble compounds have solubility and dissolution related bioavailability problems. The present review deals in detail about solid dispersion technology and its manufacturing techniques at laboratory and industrial level. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. This article reviews historical background of solid dispersion technology, limitations, classification, and various preparation techniques likes Inclusion complexation with cyclodextrins, Size reduction technology, Functional polymer technology and Solid dispersions etc. with its advantages and disadvantages. This review also discusses the recent advances in the field of solid dispersion technology.

KEYWORDS: Inclusion, Dispersion, Complex, Solubility, Polymers.

INTRODUCTION

Solubility is defined in *Quantitative terms* as the concentration of the solute in a saturated solution at a certain temperature. In *Qualitative terms*, solubility may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent.

The solubility of a drug may express as Parts, Percentage, Molarity, Molality, Volume fraction and Mole fraction. *Solubility* is an important determinant in drug liberation and absorption and hence plays a key role in its bioavailability. For a drug to be absorbed, it must be present in the form of an aqueous solution at the site of absorption. *Solubilization* may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic components (Babu, 2010; Lachmann, 2008).

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. When combined with the *in vitro* dissolution characteristics of the drug product, the BCS considers three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms1. It classifies drugs into four classes (Fig. 1)

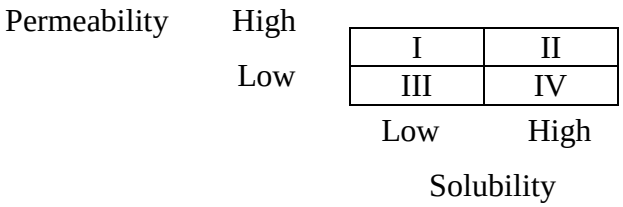

Fig. 1: Biopharmaceutical classification system.

Poorly water-soluble drug candidates often emerge from contemporary drug discovery programs, and present formulators with considerable technical challenges. (Sharma, 2009; Yu, 2002) A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption (Goldberg, 1966) Therefore, pharmaceutical researchers' focuses on two areas for elution rate of poorly water-soluble drugs and (ii) Enhancing permeability of poorly permeable improving the oral bioavailability of drugs include: (i) Enhancing solubility and disso drugs (Amidon, 1995; Das 2012). Chiou and Riegelman defined the term solid dispersion as "A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures". Sekiguchi and Obi suggested that the drug presented in a eutectic mixture in a microcrystalline state, after few years Goldberg et al. reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution (Sharma, 2011). Solid dispersion means a group of solid products consisting of at least two different components, generally a hydrophilic inert

carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most commonly used carriers for the preparation of SDs are different grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol, sugars, and urea. (Mooter, 1998; Habib, 2000). In order to receive solid dispersions with the desired dissolution properties, the carrier material has to fulfil certain criteria which favour the dissolution of the solid dispersion in aqueous media like high wettability by and solubility in water (Nora, 2005)

Approaches for Solubility Enhancement of Poorly Water Soluble Drug (Sharma, 2011)

1. Micronization
2. Crystal habit of drug
3. Solubilization and complexation- use of surfactant and cyclodextrin
4. Salt formation
5. Solid dispersion

Advantages of Solid Dispersions

Particles with reduced particle size

Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium (Leunner,2000) A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug (Prabhu, 2005).

Particles with improved wettability

The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate (Das 2012).

Drugs in amorphous state

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process (Das, 2012; Pokharkar, 2006).

Disadvantages

1. As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
2. As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.
3. Toxic effects on renal, central, nervous, hepatic, and CVS system as well as cell lysis and localtissue irritation.
4. High tonicity leads to cell lysis or tissue necrosis. (Mukherjee, 2012)

Eminent Properties of Solid Dispersions

Solid dispersions are promising drug delivery forms which offer the possibility to disperse a hydrophobic drug in a hydrophilic matrix and thereby improve the dissolution behavior and the bioavailability of the drug. Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. The various aspects such as composition and molecular weight of carrier, drug crystallinity, particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability (Sharma, 2009).

Higher Porosity of Drug Particles

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the properties of carriers used, 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 and hence bioavailability (Leuner, 2000).

Reduced Dug 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. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

Improved Wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. The powder surface composition is expected to play an important role in the wetting process, as it influences the overall hydrophobicity of the powder. In particular, high surface coverage of hydrophobic drug is assumed to give poor wettingproperties with large contact angles. The amount of drug at thepowder surface is further believed to significantly influence dissolution and physical drug stability. The importance of contact angles and wettability on dissolution rate is discussed in several studies (Dahlberg, 2008).

Drugs in Amorphous state

It is well known that utilizing the amorphous form of a drug is a useful approach to improve the dissolution behavior and bioavailability of poorly water-soluble active pharmaceutical ingredients. Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. 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. 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. For drugs with low crystal energy (low melting temperature or heat of fusion) the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them (Sharma, 2009)

Classification of Solid Dispersions

SDs can be classified into simple eutectic mixtures, solid solutions, and physical mixtures of microcrystalline drug dispersed in carriers. A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only tovery a limited extent in the solid state. A eutectic mixture of a sparingly water soluble drug and a highly water-soluble polymer or carrier may be regarded thermodynamically as an intimately blended

physical mixture of its two crystalline component and these components are assumed to crystallize simultaneously in very small particulate sizes and thus increases the rate of dissolution of a poorly water-soluble drug. Solid solution consists of a solid solute dissolved in a solid solvent. In solid solution, particle size is reduced to molecular level. Solid solutions of lower drug concentrations generally give faster dissolution rate, and the drug dissolution improves markedly with an increase in molecular weight of a water-soluble polymer such as PEG (Sekiguchi,1961) Solid solutions can be further classified into three categories based on their miscibility into continuous versus discontinuous solid solutions. Asshown in Figure 1, the solid molecules may be dispersed in the solvent in three fashions these are: (i) substitutional crystalline; (ii) interstitial crystalline; and (iii) amorphous solid solutions (Das 2012)

CARRIERS

Many water-soluble excipients are employed as carriers of solidsolutions/dispersions.

1. Poloxamers.
2. Polyethylene Glycol (PEG)
3. Polyvinyl Alcohol (PVA) Crospovidone (PVP-CL)
4. Polyvinylpyrrolidone-Polyvinylacetate Copolymer (PVPPVA)
5. Cellulose Derivatives.
6. Polyvinylpyrrolidone (PVP)
7. Hydroxypropylmethylcellulose (HPMC)
8. Hydroxypropylcellulose (HPC)
9. Carboxymethylethylcellulose (CMEC)

Preparation of Solid Dispersions

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 and these methods are discussed below.

Fusion Method

The fusion method is sometimescalled melt method, which is correct only when thestarting materials are crystalline. Therefore, the more general term “fusion method” is preferred. In this method the drug was melted in a carrier and after cooling the dry mass obtained was pulverized and sieved to obtain powder. Cooling of the drug-carrier melt was done on ice

bath with continuous stirring until the dry mass was obtained (Sekiguchi,1961) The main advantages of this method are its simplicity and economy. In addition melting under vacuum or blanket of an inert gas such as nitrogen may be used to prevent oxidation of drug or carrier material. a major disadvantage is thatthe method is only applied when the drug and matrix arecompatible and when they mix well at the heatingtemperature. When the drug and matrix are incompatible two liquid phases or suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion and this problem can be prevented by using surfactants.

Kneading method

To Cyclodextrin small quantity of water is added in a mortar and mixed it until a uniform paste is obtained to this drug was slowly added. Kneading is continued with the aid of the ethanol as co solvent until a homogenous paste of the mixture is formed. The slurry was kneaded for 30min and then dried in hot air oven for 40oc for 24 hrs and the dried complex was pulverized in to a fine powder and passed through sieve no 60 and stored in an air tight containers (Jyothi, 2013).

Solvent Evaporation Method

Drug (b-carotene) and carrier (PVP) were dissolved in a common solvent (chloroform) and solvent was evaporated to form the solid mass. Basically, this solvent evaporation method involves two steps and these are:(i) preparation of a solution containing both matrix material or carrier and drug and (ii) the removal of the solvent resulting in the formation of the solid mass. Nature of the solvent used and the rate and temperature of evaporation of the solvent are the critical factors which can affect the formed mass (Das) One of the major advantages of this method is that thermal decomposition of the drugs can be prevented as low temperature is required for the evaporation of the organic solvents. This method has several disadvantages these are: (i) high cost of preparation, (ii) difficulty in selecting a common solvent for both the drug and carrier and complete solvent removal from the product can be a lengthy process, and (iii) crystal forms are difficult to reproduce (Chiou, 1971; Sharma, 2007).

Spray Drying

Spray drying method consists of dissolving or suspending the drug and polymer in a common solvent or solvent mixture and then drying it into a stream of heated air flow to remove the

solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed within seconds, which may be fast enough to phase separation.

Lyophilization (freeze drying)

Singh et al., in 2011, dissolved some selected solid dispersions in a minimum amount of cyclohexanol. Then this solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After achieving a certain layer thickness, the flask was attached to the vacuum adaptor of the lyophilizer. The solvent was then sublimed under a pressure of 8-10mmHg and condensed onto a -75°C condenser. When the solvent was completely removed,they found that the nature of the powder residue was porous, light and fluffy mass. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the SDs. (Singh,2011).

Hot-melt extrusion

Many advantages of hot melt extrusion over conventional solid dosage form manufacturing picked the interest of pharmaceutical industry and researchers for the useful technology to prepare novel drug delivery system. This technique employs the uses of extruders which consists of conveying system, for transportation and mixing of materials, and die system, which shapes the melt into required shape like pellets, granules, or powder. In this method solvents are not used therefore, it is environmentally friendly, economical and no residual solvent in the final product. This method has several disadvantages these are: (i) high shear forces may produce high local temperature in the extruder therefore it may create a problem for heat sensitive materials, (ii) just like traditional fusion method, miscibility of drug and carrier matrix can be a problem. Some examples of pharmaceutically approved polymeric materials which are used in hot-melt extrusion include vinyl polymers (polyvinylpyrrolidone (PVP) PVP-vinyl acetate (PVP-VA), polyethylene oxide (PEO), Eudragit® (acrylates), Polyethylene glycol (PEG) and cellulose derivatives.

Electrostatic Spinning Method

Electrostatic spinning method involves the introduction of a liquid into an electric field whereby the liquid is caused to produce fibres. After being drawn from the liquid the fibresharden, which may involve mere cooling, chemical hardening or evaporation of solvent, and then hardened fibres may be collected upon a suitably charged surface. Tubular products comprising polyurethane fibres can be prepared by this electrostatic spinning method.

Coating on sugar beads using fluidized bed-coating system

This method involves a fluidized bed-coatingsystem, wherein a drug-carrier solution is sprayed ontothe granular surface of excipients or sugar spheres toproduce either granule ready for tableting or drug-coatedpellets for encapsulation in one step. The method can beapplied for both controlled- and immediate-release soliddispersions.

Supercritical Fluid Technology

This technique consists of dissolving the drug and the inert carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This SCF technology provides a novel alternative method of preparation of small particles with higher surface area, free flowing property, and a very low content of residual organic solvent and this technology also avoids most of the drawbacks of the traditional methods (Das, 2012)

Characterization of Solid Dispersions (Sharma, 2011)

The methods that have been used to characterize solid dispersions are summarized in Table 1. Among these, the most important methods are thermo analytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug) solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to differentiate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiatebetween solid solutions and solid dispersions (Table 1).

Methods for the characterization of solid dispersions
Dissolution testing
Thermoanalytical methods : differential thermoanalysis and hot stage microscopy
Calorimetric analysis of the solution or melting enthalpy for calculation of entropy change
X- ray diffraction
Spectroscopic methods, e.g. IR spectroscopy
Microscopic methods including polarization microscopy and scanning electron microscopy

CONCLUSION

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Most of the promising newer chemical entities are poorly water soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drug's poor water solubility.

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