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A REVIEW ON: SOLID DISPERSION METHODS

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ABSTRACT

The improving dissolution rate and enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Therefore increase in dissolution of poorly soluble drugs by solid dispersion technique represents a challenge to the formulation scientists. 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. The different types of solid dispersion based on the molecular arrangement have been highlighted same as practical aspect to be consider for the preparation of solid dispersion, such as selection of carrier and method of physicochemical characterization along with an insight in to the molecule arrangement of the drug in solid dispersion are also discussed.

INTRODUCTION

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, enhance release of drugs from ointment and suppository bases, and improved solubility and stability.The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. This may be achieved by incorporating the drug in a hydrophilic carrier material obtaining products called solid dispersions. Depending on the properties of both, drug and carrier, and depending on their ratio, a solid solution or a solid suspension of the drug in the carrier material may be formed.

The mechanisms involved in solubility and dissolution rate enhancement include transformation of unstable modifications into more stable ones oreven into the amorphous state, reduction of particle size possibly to the molecular level as well as enhancement of wettability and solubility of the drug by the carrier material. However, if a solid dispersion represents a thermodynamically unstable system, it is prone to convert into a more stable state. Especially for substances according to the Bio pharmaceutics Classification System, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug.[1,2]

Solid dispersion, as implied in its name, refers to the solid state where one substance is dispersed into another material. The substances can be mixed completely or partially, containing several phase. Basically in this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. The drug in solid dispersion can be dispersed molecularly, in amorphous particles, or in crystalline particles. The matrix can also be in crystalline or amorphous state. The purpose of making hydrophobic drugs into solid dispersion formulation is to disperse the hydrophobic drug into the hydrophilic matrix so that the hydrophilic matrix can melt prior to the drug in the gastrointestinal fluid.[3]

The different ways of increasing the absorption or bioavailability are:

1. Micronization
2. Use of soluble salt
3. Use of minuscular form of drug adsorb on the insoluble adsorbents
4. Use of surfactants

5. Use of polymorphs
6. Use of hydrates or solvates and
7. Molecular complexation

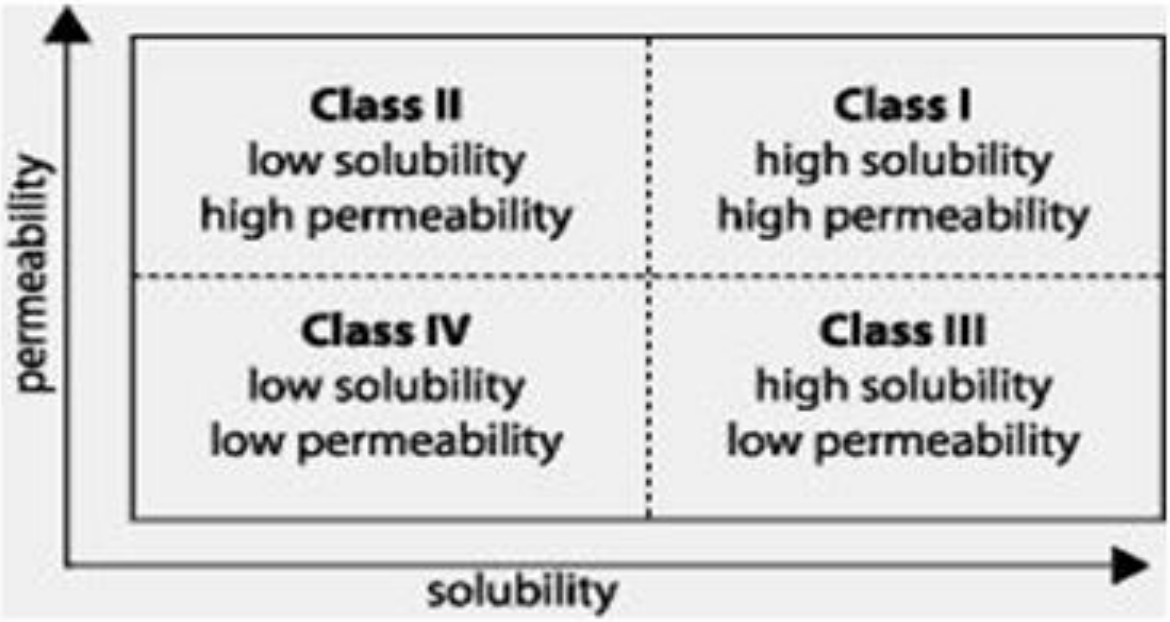
Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition Micronization is a high-energy process, which causes disruptions in the drugs crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different from that of a parent compound. The fusion method can only be applied when drug and matrix are compatible when they mix well at heating temperature. The development of solid dispersions as a practical viable method to enhance bioavailability of poorly water-soluble drugs overcome the limitation of other approaches such as salt formation, solubilization, cosolvency and particle size reduction[17].

TYPES OF SOLID DISPERSIONS [4,5]

• Binary Solid Dispersion: It consists of drug and a polymeric carrier.

• Ternary Solid Dispersion: It consists of drug, a polymeric carrier and a surfactant.

• Surface Solid Dispersion: Surface solid dispersion is formulated with polymers such as polyvinyl pyrrolidone, polyethylene glycol and polyvinyl pyrrolidone-vinyl acetate polymer by fusion technique to improve its solubility. It is appropriate to classify various systems of solid dispersion on the basis of their major fast release mechanisms.



Bio pharmaceutics Classification System, drug substances are classified as follows.[6]

Class I :

High permeability, High solubility

Those compounds are well absorbed and their absorption rate is usually higher than excretion.

Example: metoprolol

Class II :

High permeability, Low solubility

The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found.

Example- Mefenamic acid,

Class III :

Low permeability, High solubility

The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.

Example: cimetidine

Class IV :

Low permeability, Low solubility

Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. Example: hydrochlorothiazide

Example: Hydrochlorothiazide,furosemide.

Different methods of preparation of solid dispersion[7]

Various strategies investigated by several investigators include

- Solvent evaporation,
- Lyophilization (freeze drying),
- Fusion (melting),
- Melt agglomeration process,
- Extruding method,
- Spray drying technology,
- Use of surfactant,
- Super critical fluid technology

ADVANTAGES OF SOLID DISPERSION:

The major advantage of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition.[8]and results in rapid dissolution rates thereby improving the bioavailability of drug. Along with this, the approach may also offer both Particles with reduced particle size 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, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability.[9]

1. PARTICLE SIZE

For hydrophobic drugs, which is in pre-existing solid formulation for tablet, capsule will have large particle size of about 5~100mm in the get after disintegration. It will exhibit low dissolution. There are some limitations in particle size reduction. Drug with solid dispersion show colloidal particles having fine oily globules in the get after disintegration &the drug show high dissolution.[10

2. POROSITY

Drugs having high porosity will release faster compared to low porous drug. Solid dispersion have high porosity so it enhance drug release thereby bioavailability. Solid dispersion containing reticular polymer show less porosity & linear polymer has high porosity.[11]

3. AMORPHOUS STATE

Crystalline drugs which are poorly soluble in the amorphous state show more solubility & increased drug release. In amorphous state no energy is needed to break the crystalline lattice during dissolution.

4.WETTABILITY

Solubility can be enhanced by increasing the wettability. There by increasing the bioavailability.[12]

Disadvantages of Solid Dispersion

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging.[13]

solid dispersions are prepared with water soluble low melting point synthetic polymers such as polyvinyl pyrrolidone, mannitol or polyethylene glycol. These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is

relatively large, around 1:2 to 1:8 (drug/ polymer) ratio An obstacle of solid dispersion technology in pharmaceutical product development is that a large amount of carrier, i.e., more than 50% to 80% w/w, is required to achieve the desired dissolution.[14]

METHODS OF PREPRATION

1. Solvent Evaporation Method

In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a dessicator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented. because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as[15,16]

- The higher cost of preparation.
- The difficulty in completely removing liquid solvent.
- The possible adverse effect of traces of the solvent on the chemical stability
- The selection of a common volatile solvent.

2. FUSION METHOD

Also called melting method. It is so called because it is used for method which use crystalline as starting material. Fusion or Melting method was first introduced by Sekiguchiet al.in 1961.Drug is made to melt in a carrier & the dry mass obtained after cooling were pulverised& sieved. Carriers used include urea, mannitol& PVP/VA-64. It is less expensive & sometimes Nitrogen as inert gas, used to prevent oxidation of drug or carrier material. It is applicable only if the drug & carrier are compatible. It is not effective for thermolabile drugs.[17]

3 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]

4 Hot Melt Extrusion

Hot-melt extrusion (HME) technique represents a novel application of polymer processing technology to prepare pharmaceutical dosage forms. The process involves embedding a drug in a polymer while shaping the composite material to form a pharmaceutical product. This technique is same as the fusion method. The only difference is that in this method, intense mixing of the components is induced by the extruder. High shear forces results in to the high local temperature in the extruder and that can be problematic for heat sensitive materials.[19,20]

5. Super critical fluid technology

These methods use SCFs either as solvent: rapid expansion from supercritical solution (RESS) or anti-solvent: gas anti-solvent (GAS), supercritical anti-solvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. Solution enhanced dispersion by supercritical fluids (SEDS), aerosol solvent extraction system (ASES), supercritical anti-solvent (SAS), gas antisolvent (GAS) and precipitation with a compressed fluid anti-solvent (PCA) are process of micronization. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently.[21]

APPLICATIONS OF SOLID DISPERSION

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. [21,22]

- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release of soluble drugs by using poorly soluble/insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.

CONCLUSION

Solid dispersions are one of the most attractive processes to improve drug's poor water solubility. Solubility is the major criteria for a drug formulation and its therapeutic efficacy.

One of the major techniques to enhance the solubility of drug is Solid dispersion technique. It is a promising technique for the enhancement of bioavailability of poorly aqueous soluble drugs. It aims at improving the dissolution & absorption of drugs by various methods like fusion, solvent evaporation, freeze drying etc. Selection of suitable carrier & preparation method are valid for the better enhancement of bioavailability.

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