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Review Article

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SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS BY SOLID DISPERSION TECHNIQUES: A REVIEW

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ABSTRACT

The solubility enhancement of drug remains one of the most challenging aspects in the formulation development. protein solubility of drug or active ingredients is one of the important parameter to gain desired concentration of drug in the systemic circulation to achieve expected pharmacological response. Solid dispersion is one of the most promising approach for solubility enhancement. According to BCS classification, class II and IV drugs are considered as poorly water soluble. So enhancement of oral absorption and bioavailability of solid dosage forms remains a challenge to a formulation scientists due to their solubility criteria. The focus of this review article on the method of preparation, carrier, solvent use, it also elaborates various factors, advantages, disadvantages, and the application of the solid dispersion.

KEYWORDS: Solid dispersions, solubility, carrier, method of preparation.

INTRODUCTION

The poor aqueous solubility and dissolution rate of API is the one of the major challenge in the pharmaceutical development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[1] Because It is important to improve the solubility and dissolution rate for poorly soluble drugs so these drugs possess low absorption and solubility. Various methods to improve the dissolution of poorly soluble drugs have been reported. Solid dispersion technology has become one of the well-established techniques for solubilization of poorly-soluble drugs. Solubility is defined in quantitative term as the concentration of solute in saturation solution at certain temperature and pressure. Qualitatively it is defined as the spontaneous interaction of two or more substances to from a homogenous molecular dispersion.[2] In this article focuses on the former, in particular, the use of solid dispersion technologies to improve the solubility of poorly water-soluble drug and in turn their oral bioavailability.[3] Solid dispersion (SD) technique has been widely used to improve the dissolution rate, by modifying solubility The term solid dispersions have been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, to enhance oral bioavailability.[4] In the Biopharmaceutical Classification System(BCS) drugs with low aqueous solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. Modified Noyes-Whitney equation gives some idea how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.

$$dC / dt = AD (Cs – C) / h$$

Where,
dC/dt is the rate of dissolution,
A is the surface area available for dissolution,
D is the diffusion coefficient of the compound,
Cs is the solubility of the compound in the dissolution medium,
C is the concentration of drug in the medium at time t,
h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Surface area directly proportional to rate of dissolution, it is increased by decreasing the particle size of drug or by optimizing wetting characteristics.[5]

Advantages of solid dispersion[6,7,8]

- reduced particle size.
- improve wettability.
- improve porosity of drug.
- Enhance solubility and bioavailability of poorly water soluble drugs.
- Easy to produce.
- Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs**.**
- It is easier to produce and is more applicable.
- It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.
- It improves the solubility of the water insoluble drugs (class II).

Disadvantages of solid dispersion[8,9]

- Need to use higher percentage of carrier.
- Reproducibility of physicochemical properties of the drug cannot be regained.
- May lead to physical and chemical instability due to modification of basic structure of drug.
- Handling of the solid dispersions may be difficult due to its tackiness property.

Selection of a carrier

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

- Freely water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.

Selection of solvents

Solvent to be included for the formulation of solid dispersion should have the following criteria:

- It should have complete to dissolved drug and carrier.
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
- Ethanol can be used as alternative as it is less toxic.
- Water based systems are preferred.

Factor affecting solubility[1,6,10]

1. **Temperature:** The solubility of a given solute in given solvent typically depends on temperature. Depending on the nature of the solute the solubility may increase or decrease with temperature. For most solid and liquid, their solubility increase with temperature.

2. **Pressure:** The solubility of liquid and solid in water are not appreciable affected by increased pressure. the solubility of gases significantly increase with pressure. According to Henery's law the increase in solubility of gases is directly proportional to increase in pressure.

3. **Particle size:** The size of solid particle influence the solubility because as particle become smaller, the surface area to volume ratio increases the surface area allows a greater interaction with the solvent.

4. **Polymorphism:** The capacity of a substance to present in more than one crystalline from is known as polymorphism. Polymorphs can vary in melting point. Since the melting point of the solid is related to it's solubility, then polymorph will most likely having different solubility's.

5. **Nature of the solid:** Depending upon internal structure of the solid it may be either crystalline or amorphous. Crystalline structure exhibit low solubility while amorphous forms exhibit higher solubility.

6. **Polarity:** Polarity of both solute and solvent molecules affect the solubility. Generally polar solute molecules will dissolve in polar solvent and non polar solute molecules will dissolve in non-polar solvent.

Types of solid dispersion[5,8,12,15,16]

1. Eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution.

2. Amorphous solid solution

In an amorphous solid solution, the solute molecular are dispersed molecularly but irregularly within the amorphous solvent. This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous from.

3. Solid solutions

In a solid solution the two components are crystallize together in a homogeneous one phase system. The particle size of the drug is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be prepared by two methods. According to the extent of miscibility of the two components, the solid solutions may be classified as continuous or discontinuous.

a) 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.

b) Discontinuous solid solutions

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

c) Substitutional solid solution

It is a one in which the drug molecules substitute for the carrier molecules in its crystal lattice. It is an crystalline structure in which the solute molecules can either substituent for solvent molecules in the crystals lattice into the intrsticies between the solvent molecule.

d) Interstitial solid solution

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

4. Glass solution and suspension

A glass solution is homogenous system in which glass of the carrier solubilized drug molecule where in case of suspension the solute molecules are diapered in carrier.

Methods of solid dispersion

1. Solvent method[6]

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. (Patil et al.,)

2. Kneading method[8]

In this method, suitable proportions of drug and carrier are taken in a mortar to that organic volatile solvents are added. Kneading process can be done for about 30 mins and it is dried until the solvent completely evaporates. For better results, the mixture is placed in desicator for the complete removal of solvent. (Saripilli et al.,)

3. Fusion method[13]

In this method the physical mixture of drug and water soluble carrier are heated directly just above its melting point and drug incorporated into the matrix. the melted mixture is then cooled and solid rapidly on ice bath with vigorous stirring. The final solid mass is then crushed, pulverized and sieved which can be further compressed into tablet. (Yadav Tanwar)

4. Hot melt extrusion[15]

Hot melt extrusion (HME) consists of the extrusion. The extraction is processed at high rotational speed of the drug and carrier, previously mixed, at melting temperature for a small period of time. The resulting product is then collected after cooling at room temperature and milled. (Katta et al.,)

5. Melt Agglomeration process[9]

This technique has been used to prepare Solid Dispersion where the binder acts as a carrier. SD(s) are prepared either by heating the binder, drug and excipients to a temperature above the melting point of the binder or by spraying a dispersion of drug in a molten binder on the heated excipient by using a high shear mixer. A rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a high binder content can be incorporated in the agglomerates. (Ghosh et al.,)

6. Spray drying process[17]

It is a process where a solution of drug substance and carrier is evaporated by spraying the solution as fine droplets into a chamber under controlled condition of heat, humidity and air flow. The medium of drying is mainly associated with hot air and the product is thus separated after completion of drying. (Singh N and Sarangi M. K)

7. Lyophilization technique[18]

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method 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. (Ladan et al.,)

8. Electrospinning method[8]

In this method, the enhancement of poorly water soluble drugs can be achieved by utilization of electrical potential which results in the formation of encapsulated fibers. When adesired amount of potential is applied across the solution of drug polymer it results in the formation of fibers of sub micron range due to domination of electrical force at the interface when compared with the interactive forces (i.e., surfacetension) of drug and carrier. (Saripilli et al.,)

9. Supercritical fluid methods[3]

Supercritical fluid methods are mostly applied with carbon dioxide, which is used as either a solvent for drug and matrix or as an ant solvent. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as "solvent free". The technique is known as Rapid Expansion of Supercritical Solution. (Dhirendra K, Lewis,s.)

Application[11,12,13]

1. To increase the solubility of poorly soluble drugs there by enhance the dissolution rate, absorption and bioavailability.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To mask unpleasant taste and smell and avoid undesirable incompatibilities.
4. To enhance the absorption of drug.
5. To obtain a homogeneous distribution of a small amount of drug in solid state.
6. To stabilize the unstable drug.

CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. Solid dispersion technology most used technique because of less requirement of scale up and also less manufacturing cost. A variety of devices have been developed over the years to enhance the drug solubility and dissolution of the drugs. The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs.

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