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THE COMPREHENSIVE REVIEW ON SOLID DISPERSION TECHNOLOGY

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ABSTRACT

Solid dispersions is drawn attention and interest of researchers for improvement and enhancement the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersions is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. Solid dispersions modify the dissolution properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage forms. This review highlights on definition, types, method of preparation, characterization advantages and disadvantages of the solid dispersion.

INTRODUCTION TO SOLID DISPERSION

The rate limiting or defining step in the absorption process of any therapeutically active agent is its aqueous solubility. Solubility as well as dissolution is the main core factor of pharmacokinetic and biopharmaceutical considerations in not only in dosage form development but also in therapy of any therapeutically active agent. But, as the synthetic drug design approach is growing successfully to deliver many promising lead compounds for most of the pharmacological categories, they are also taking the molecules towards bulkier structures. Thus, increased bulk shows increased hydrophobic character in the molecule makes it very poorly soluble and inadequately bioavailable. As a result, more than 40% of new candidates entering the drug development pipeline fail because of non-optimal biopharmaceutical properties.[1] Oral bioavailability of depend on drugs solubility as well as

dissolution rate, therefore development of novel approaches are needed to increase dissolution of drugs with water solubility. Many methods are available to enhance solubility & dissolution characteristics including surface-active agents, salt formation, addition of solvent and many more. In this study polyethylene glycol was selected and solid dispersion was prepared by the method of solvent evaporation.[2]

The improvement in oral bioavailability of poorly water-soluble drugs remains the most challenging task of drug development. Even though few technologies like salt formation, particle size reduction etc commonly have been used to increase dissolution rate and thereby absorption as well as bioavailability of such drugs, but these technologies having few practical limitations such synthesis of appropriate salt forms of weakly basic and weakly acidic drugs may often not be practical and also it is not feasible for neutral compounds.[3,4] In many cases of salt formation due to formation of aggregates in gastrointestinal tract from salts an increased dissolution rate in the may not be achieved.[5] Although particle size reduction to practical limit obtained by various common methods such as grinding, controlled crystallization, pearl milling etc. is commonly used to increase dissolution rate. The utilization of very fine powders develops charges which makes then unsuitable in dosage forms because of poor wettability and handling difficulties due to charge development.[6]

A practical method was developed by Sekiguchi, etal with the bioavailability enhancement of poorly water-soluble drugs can be overcome many of the limitations, which was called and termed as “Solid Dispersion”.[7,8]

For conventional dosage forms like capsules and tablets, the dissolution rate is controlled & limited by the size of the particles formed after disintegration. For conventional dosage forms higher particle sizes are preferred for ease of formulation, handling and manufacturing although usual lower limit an average particle size of 5 µm. In case of a solid dispersion or a solid solution, the gastrointestinal fluid is get saturated as a portion of the drug dissolves immediately and the remaining drug precipitates out as oily globules or fine colloidal particles of submicron size. Solid dispersion approach is one of the most active areas of research and development in the pharmaceutical due to increase in the bioavailability of poorly water-soluble drugs.[9,10]

Definition

Solid dispersion is the approach in which dispersing one or more therapeutically active ingredients in an inert matrix in the solid state to achieve altered solid state properties, an enhanced dissolution rate or sustained release of drug and improved stability.[11]

Types of Solid Dispersions

A) Simple Eutectic Mixture

It is mixture of a poorly aqueous soluble drug in freely water-soluble carrier. These are usually prepared by melt fusion method. When this system come in contact with water, the highly soluble carrier dissolves leaving the drug in a microcrystalline state which gets rapidly solubilize. The increase in surface area is mainly responsible for enhancement in rate of dissolution.[12]

B) Solid Solutions

It consists of a solid solute dissolved in solid solvent. Solid solutions are generally prepared by solute and carrier is dissolved in a common volatile solvent such as alcohol. By flash evaporation solvent is allowed to evaporate. So a mixed crystal containing amorphous drug in crystalline carrier is formed. Such formed dispersions are known as "Co-evaporates" or "Co-precipitates".[13,14]

These can be classified in various types according to crystalline structure of the solid solution or the two components extent of miscibility.

(i) Continuous solid solutions
(ii) Discontinuous solid solution
(iii) Substitutional solid solution
(iv) Interstitial solid solution

i) Continuous Solid Solutions

In Continuous Solid Solutions system, the two components are soluble or miscible at solid state in mostly for all proportions. Although theoretically possible, no solid solution of this type has been shown to exhibit faster dissolution.

ii) Discontinuous Solid Solution

Discontinuous solid solution system is contrast to the continuous solid solution. In these type of system only a limited solubility of a solute in a solid solvent. Above eutectic temperature

every component is capable of dissolving the remaining other component to a certain degree.

iii) Substitutional Solid Solution

In substitutional solid solution system, the solute molecules act as substitutes for solvent molecules in the crystal lattice of the solid solvent. These can form a discontinuous or continuous solid solution system.

iv) Interstitial Solid Solution

In interstitial solid solution system, solute molecule acquires or occupies the interstitial space of the solid solvent lattice. This system usually forms only a discontinuous solid solution.[15]

C) Glass Solution

It is a homogenous system in which a vitreous or a glassy carrier solubilizes drug in its matrix. Polyvinylpyrrolidone dissolved in organic solvents and upon evaporation of the solvent; it undergoes a transition to a glassy state.[16,17]

D) Compound or Complex Formation

In this method, during preparation a complex formation takes place between two components in a binary system. The availability of drug from compound or complex depends on the solubility, intrinsic absorption rate of complex and association constant.[18]

E) Amorphous Precipitation

Amorphous precipitation observed when drug precipitates as amorphous form in inert carrier during preparation. In this system generally higher energy state of the drug produces much greater dissolution rates than respective crystalline forms.[19]

MECHANISM OF DISSOLUTION RATE ENHANCEMENT[8,20,21]

In solid dispersion system increase in drug dissolution rate can be attributed to a various factors like polymorphic or crystalline forms, particle size and wettability of drug etc. The mechanism or main reasons proposed for the observed improvements in dissolution from solid dispersion systems are as follows:

a) Reduction of Particle Size

In case of solid solution, amorphous dispersions and glass solution, particle size is reduced. This causes increase in the surface area may result in enhanced dissolution rate. Similarly, it has been proposed that reduce aggregation due to the availability of particles to dissolution

medium as physically separate entities.

b) Dispersibility and Wettability

Due to the surfactant action by carrier material, enhancing effect on the dispersibility and wettability of the drug may occurred, this is due to reducing the interfacial tension between aqueous solvent phase and hydrophobic drug particle, increasing the effective surface area exposed to the dissolution medium. This slow down aggregation or agglomeration of the particles which can reduce rate of dissolution.

c) Solubilization Effect

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

d) Conversion of Polymorphic Nature of Solute

Amorphous state of a substance shows higher dissolution rates than crystalline state due to high energy required to transfer a molecule from crystal lattice of a purely crystalline solid is greater than that required for non-crystalline (amorphous) solid.

SELECTION OF CARRIER

Selection of suitable carrier is one of the most crucial steps in the formulation of solid dispersion for various applications. The properties of selected carrier have a major influence on dissolution of the drug. A substance should possess following characteristics to be suitable carrier for increasing dissolution.[22]:

i. Freely water-soluble with intrinsic rapid dissolution properties
ii. Pharmacologically inertness as well as non-toxic
iii. Having thermal stability preferably for melt method
iv. Solubility in a number of various solvents
v. Ability to enhance the aqueous solubility of the drug
vi. Chemical compatibility and not forming a strongly bonded complex with drug.

POLYMERS USED IN SOLID DISPERSIONS

A variety of polymers is offered as carriers for formulation of solid dispersion. Followings are the few polymers used in solid dispersions are as follows:

A) Polyvinyl Pyrrolidone (PVP)

It has molecular weights ranging from 10,000 to 700,000. It is soluble in common solvents like water, ethanol, etc.

B) Polyethylene Glycols (PEG)

These related to group of compounds with various molecular weight and they are prepared by reacting ethylene oxide with ethylene glycol.

C) Polymers and Surface Active Agent Combinations

By adding surfactants to dissolution medium lowering in the interfacial tension between dissolution medium and drug which altimetly enhances wetting of drug responsible for increase the dissolution and solubility of drug.[23]

D) Cyclodextrins

Cyclodextrins generally used not only for enhancement in solubility, but also for other applications like taste masking, chemical protection and improved handling in manufacturing by the conversion of liquids into solids by entrapment of hydrophobic solute in hydrophilic cavity of Cyclodextrins.[24,27]

E) Phospholipids

Phospholipids are main structural components of cell membranes. These also used as carrier material. Naturally occuring lecithins contain both unsaturated and saturated fatty acids with some exceptions.[28]

Table 2.1: Consists of various materials which used as carrier for solid dispersion by various researchers.

Table 2.1: Materials used as carrier for solid dispersion.

Sr. No.	Category	Examples
1	Polymeric materials	PVP[29], PEG[30], Celluloses like HPMC[31], HEC, HPC, Pectin, Galactomannan, CDs[32]
2	Surfactants	Polyoxyethylene stearate, Renex, Poloxamers[33], Texafor, Deoxycholic acid, Tweens, Spans[34]
3	Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol[35], Lactose[36]
4	Acids	Citric acid, Succinic Acid[37]
5	Insoluble/ enteric polymer	HPMC[38], Phthalate, Eudragits[39]
6	Miscellaneous	Pentaerythritol, Pentaerythrityl tetra acetate, Urea[40]

Methods of preparation of solid dispersions[41,56]

Following are the various methods used for preparation of solid dispersion system.

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

1. Fusion method or Melting method

The fusion or melting method is the preparation of physical mixture by heating directly a drug and a water-soluble carrier until it melted. Then by using ice-bath under vigorous stirring the melted mixture is solidified rapidly. The final solid mass is crushed, pulverized and sieved. This method having some limitations like few substances may degrade or decompose during the fusion process with help of high temperature, it may also cause evaporation of volatile substances during the fusion process at high temperature which can be overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum to avoid loss due to vaporization or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.[41]

2. Solvent method

Drug and carrier is added & dissolved in a common solvent, and then mixture is evaporated until a solvent free clear film is form. These overcome the limitations of other methods by avoiding thermal decomposition of drugs or carriers due to utilization of the low temperatures required for the evaporation of solvents.

However, some disadvantages are associated with this method such as expensive; completely removal of solvent is quite difficult, etc.[42]

3. Melt evaporation (Melting solvent method)

In this method first step the preparation of solution by dissolving drug in a liquid solvent, then in second step adding drug solution in polyethylene glycol and then in third step

evaporation of mixture until a solvent free clear film is remaining. The film is further dried to constant weight. With advantages of both the solvent evaporation and fusion methods these technique also have limited applicability for drugs with a low therapeutic dose or below 50 mg.[43]

4. Melt extrusion method

In this method mixture of drug & carrier is prepared by a twin-screw extruder and co-rotating twin-screw extruder. In this method simultaneously drug and carrier are melt are mix, homogenize, extrude and then shape as dosage forms like powder, tablets, granules, etc. This method is suitable for thermo labile substances because mixture of drug and carrier is subjected to high temperature only for short time. The concentration of drug in solid dispersions is generally 40% weight by weight. The various temperature zones with fixed feeding and screw rate used for processing of solid dispersion.[44,46]

5. Lyophilization Technique

Lyophilization is the molecular mixing method where drug as well as carrier is dissolve in a common solvent, frozen and further sublime to get a lyophilized dispersion. This technique involves transfer of mass and heat from and to the product. This technique may be used as an alternative method for preparation for solid dispersion by solvent evaporation.[47]

6. Melt Agglomeration Technique

By utilizing a high shear mixer solid dispersion are prepared by spraying a dispersion of drug in melt binder on heating binder or by heating drug and excipients to a temperature above the melting point of the binder. In this method binder is used as carrier for preparation solid dispersion. As compare to spray-on procedure with PEG 3000 the melt in procedure gives a higher dissolution peoperties.[48,49]

7. Melt Agglomeration Process

In this process the surfactant are utilize for preparation of solid dispersion. The surfactant plays a crucial role in solubilization. Because of few unique properties of surfactant like manifesting in reduction of melting the active pharmaceutical ingredients, salvation /plasticization, glass transition temperature surfactants have get the attention of investigators for research on solid dispersions.[50,51]

8. Electrospinning

It is a process in which solid fibers are produced from melt passing through a millimeter-scale nozzle or a polymeric fluid stream solution. This process involves the utilization of a strong electrostatic field over a conductive capillary attached to a reservoir containing a polymer solution or melt and a conductive collection screen. This technique has very good potential for the preparation of controlling the release of biomedicine and nanofibres due to its simplicity as well as economical technique which can be used for the preparation of solid dispersions in future.[52,54]

9. Super Critical Fluid (SCF) Technology

In this techniques carbon dioxide are utilize as anti-solvent for the solute. In this process the spraying of solution of solute and of the organic solvent into a continuous supercritical phase flowing simultaneously. Utilization of carbon dioxide as a supercritical fluid is having few advantages like easy removal from polymeric materials after process completion.[55,56]

Characterization of solid dispersion[57,65]

Several techniques is can be used for characterization solid dispersions. However, few of them mentioned as below.

Drug -carrier miscibility

- Differential scanning calorimetry
- Powder X-ray diffraction

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy

Physical Structure

- Surface area analysis
- Scanning electron microscopy
- Dynamic vapor sorption
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Hot stage microscopy
- Humidity stage microscopy
- Polarised light optical microscopy
- Powder X-ray diffraction

Dissolution enhancement

- Dissolution
- Dissolution in bio-relevant media
- Intrinsic dissolution

Stability

- Isothermal Calorimetrys
- Humidity studies
- Dynamic vapor sorption
- Saturated solubility studies

Advantages[66, 67]

The main advantage of solid dispersion technique is fast and enhanced dissolution rates that result in minimization of pre-systemic metabolism and increased bioavailability. Other advantages include conversion of the liquid form of drug into a solid form (e.g. clofibrate and benzoyl benzoate can be incorporated into PEG 6000) which avoiding polymorphic changes in molecule so bioavailability problems are resolved and also protection as well as allow buccal absorption of certain drugs by carrier material against decomposition by saliva.

Disadvantages[68,69]

The limitations of solid dispersion are related to stability issue of dosage form as well as because of tackiness of the few solid dispersion formulations are not easy for handling.

CONCLUSION

With various pharmaceutical particle technologies the poor aqueous solubility of a drug molecule can be solved. The traditional particle technologies such as salt formation, size reduction etc are convenient as well as simple to increase the solubility and dissolution of poorly soluble drugs but these also have limitations and disadvantages for some drugs due to their less efficiency, thermal degradation of drugs due to rise in temperature and formation in

non-uniform sized particles. These limitations & disadvantages cab be resolved by modern novel particle techniques are more efficient methods of formulating poorly aqueous soluble drugs. Solid dispersion is one of that modern novel approaches with main basic principle of enhancement in dissolution & solubility. The use of solid dispersion method for formulation and development is to providing wide applications in enhancement in the dissolution and solubility of the poorly soluble drugs. By considering properties of poorly soluble drug with carrier molecule an appropriate suitable method for preparation of solid dispersion can be selected to formulation of desired dosage form.

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