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A review of drug delivery system: Solid dispersion

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ABSTRACT
Solid dispersion, defined as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to improve dissolution of purely water soluble drug to enhance their bioavailability. Poor water solubility is one of the major problems for the various types of drugs and various approaches have been introduced for the inhancement of solubility of such drug the solubility behavior of drug remains one of the most challenging aspects in formulation development. The number of poor water soluble compounds has dramatically increased. Currently only 10-12% of new drug candidates have both high solubility and high permeability. More 60-65% of potent drug products suffer from poor water solubility solid dispersion have attracted considerable interest as an efficient means for improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. Compared to conventional formulation such as tablets or capsules, solid dispersion which can be prepared by various methods have many advantages. Few of the aspects are to be considered for the preparation of solid dispersions, such as selection of carrier and methods of physicochemical characterization. In the review, and over view on solid dispersions in general will be given with emphasis on the various types of the solid dispersions, manufacturing process, characterization, advantages, disadvantages and the application of the solid dispersions, challenges in formulation of solid dispersion dosage forms, and various types of marketed preparations.

Keywords : Solid dispersion, carrier, solvent carrier, characterization, poorly water soluble, bioavailability.

I. INTRODUCTION

The oral route of drug administration is the most common and preferred route of delivery due to convenience and ease of ingestion. From a patients prospect, swallowing a dosage form is a comfortable means of taking medication as a result, patient compliance is more effective with orally administered medications as compared with other route of administration, for example, Parenteral route. Although the oral route of administration is preferred, in case of many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. After administerising a drug orally, if firstly dissolves in gastric media and then permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with a poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agent include-

Enhancing solubility and dissolution rate of poorly water soluble drugs and enhancing permeability of poorly permeable drugs. Solubility is a predetermined and rate limiting step for absorption

All poorly water soluble drug are not suitable for improving their solubility by salt formation the dissolution rate of particular salt is usually different from that of parent compound. Potential disadvantage of salt form include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water soluble drug, epigastric distress due to high alkalinity. Use of co solvent to improve dissolution rate pose problems such as patient compliance and commercialization.

Advantages of solid dispersions

- To reduced particle size.
- To improve wettability.
- To improve porocity of drug
- To decrease the crystalline structure of drug into amorphous form.
- To improve dissolvability in water of a poorly water of a poorly water-soluble drug in a pharmaceutical.
- To mask the taste of the drug substance.
- To prepare rapid disintegration oral tablets

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- To obtain a homogeneous distribution of the small amount of drugs at solid state
- To stabilize unstable drugs.
- To dispense liquid or gaseous compounds.
- To formulate a faster release priming dose in a sustained release dosage form.
- To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble.

Disadvantage of Solid Dispersion :-

The advantage of solid dispersion are enlisted below:

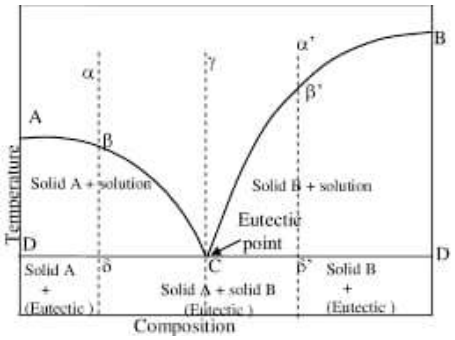
- Polymers used in solid dispersion can absorb moisture and cause phase seperation
- difficulty in pulverization and sifting because of the tacky and soft nature.
- It cause s reproducibility of physicochemical characteristics.
- Poor stability of dosage form
- laborious and expensive method of preparation.
- aggregation, agglomeration and air adsorption during formulation.
- Decrease in dissolution rate with aging ford.
- Poor scale-up for the purpose of manufacturing .

Classification of Solid Dispersion

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

1. Eutetic 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 fine crystals of the two components.



2. Solid Solutions

Depending on the Miscibility, The two types of Solid solutions are

a. 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.

b. Discontinuous solid solutions

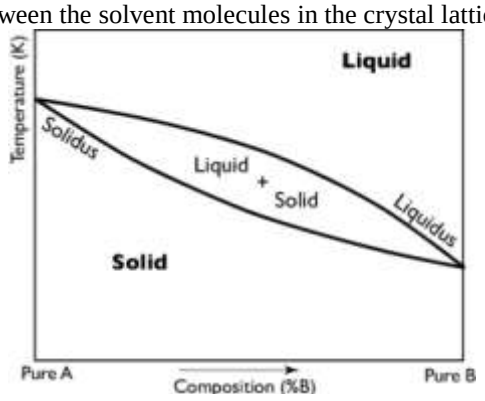
In discontinuous solid solutions, the solubility of each of the component in the other component is limited in nature.

c. Substitutional crystalline solution

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

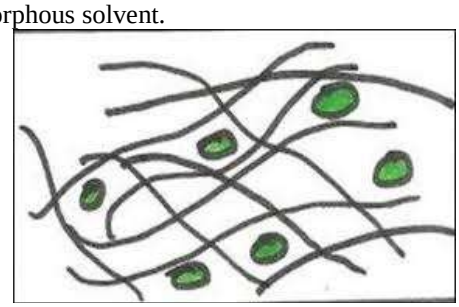
d. Interstitial Crystalline solid solution

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



3. Amorphous solid solutions

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



4. 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.

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Classification of solid dispersion on the basis of recent advancement

1. First generation solid dispersion

These solid dispersions are prepared by using crystalline carriers. Urea and sugars were the first crystalline carriers that were used in the preparation of solid dispersions. These have a disadvantage of being thermodynamically unstable and they do not release drug at a faster rate.

2. Second generation solid dispersion

These solid dispersions are prepared using amorphous carriers instead of crystalline carriers. The drug is molecularly dispersed in the polymeric carrier. The polymeric carriers are divided into two groups:

Synthetic polymer – povidone, plyethylene glycols and polymethacrylates.

Natural polymers – hydroxypropylmethylcellulose, ethyl cellulose, starch derivatives like cyclodextrin.

3. Third generation solid dispersion

These solid dispersions contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These achieve the highest degree of bioavailability for the drugs that are having poor solubility. The surfactants being used in the third generation solid dispersion are having poor solubility. The surfactants being used in the third generation solid dispersion are such as insulin, poloxamer 407 etc.

4. Fourth generation

The aim of solid dispersion is for solubility enhancement and extend release in a controlled manner in this system the poorly water soluble drug is dispersed in either water soluble carrier or water insoluble carrier the water soluble carrier used in solid dispersion is ethyl celluse eudragit, HPC, polyethylene oxide, carbomer.

Mechanism of solid dispersion

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

1. Carrier-controlled Release

Corrigan (1986) provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG. He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford (1985) who noted that the dissolution rates of a range of drugs in a single carrier. Prepared under comparable conditions, were identical in most cases. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer.

2. Drug-controlled release

Sjokvist and Nystrom (1991) measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to reconcile these contradictions Sjokvist-Saers and Craig (1992 used a homologous series of drugs [para-aminobenzoates] in PEG 6000 in an attempt to interrelate the solid state structure, drug solubility and dissolution rate. These noted that tere was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behavior as drug-controlled dissolution as opposed to carrier-controlled dissolution. Here the dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated the particles and the possibility of improved wetting and decreased agglomeration.

Common Materials Used In Preparation of Solid Dispersions :

There are several materials the can be used as hydrophilic carries in preparation of solid dispersion. Some examples are briefly discussed below.

1) Polyethene glycols (PEGs)

Polyethene glycols (PEGs) are polymers of ethylene oxide, with a molecule weight falling in the range 200-300,000. For the manufacture of solid dispersion, PEGS with a molecular weight 1500-20,000 are usally empolyed .PEGs have many avantage including high aqueous solubility ,low cost , low toxicity and low ,elting points (below 65 degree celcius) making them suitable

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carriers for prepration of solid dispersions by melting method.

2) polyvinylpryrrolidone (PVP)

Polymerization of vinyl pyrrolidone leads to polymers of molecular weight ranging from 2500 to 300,000, They are inert ,safe , highly water solubale and soluble in wide variety of solvents including alchol. The main disadvantages of PVPs are hygroscopicicty and high melting points (above 265 degree celsius) making them more suitable for prepration of solid dispersion bysolvent-based methods instead of heatin-based methods.

3) Urea

It is the end product of protein metabolism and can also be synthesized by chemical reactions. It is highly water-soluble, soluble in many common organic solvents and has a moderate melting point (132-135 °C) making it suitable for preparation of solid dispersions by different methods.

4) Sugars

Although sugars have high aqueous solubility, they have many drawbacks regarding their use as carriers in solid dispersions. Most of them have high melting points making them problematic in the preparation of solid dispersions by heating methods. They are also poorly soluble in most organic solvents creating problem in preparation of solid dispersions by solvent methods. Despite these draw backs, mannitol and sorbitol were reported to be used as carriers for many drugs.

5) Poloxamers

Poloxamers are poly (oxyethylene)-poly (oxypropylene) copolymers, with trade names as Supronic, Pluronic or Tetronic. They have been introduced in 1950 and were since then very famously used in diverse pharmaceutical applications. They are composed of two hydrophilic chains of polyethylene oxide (PEO) sandwiching one hydrophobic polypropylene oxide chain (PPO). They are classified according to the proportions of hydrophilic andhydrophobic chains including poloxamer 124, 188, 237, 338 and 407 as the most common types. They are used as gelling agents, surfactants, stabilizers and hydrophilic carriers. They are soluble in different solvents and have low melting points (52-57 °C) making them suitable carriers for preparation of solid dispersions by different methods.

6) Polymethacrylates

They are synthetic cationic and anionic polymer of dimethylaminoethylmethacrylates, methacrylic acid, and methacrylic ester in varying ratio. Mostly used in oral tablet and capsule formulation as film coationg agent for drug release modification. Also used as binder in both aqueous and organic weight granulation process.

7) Emulsifier

Emulsifier act by two principle mechanism: Improvement in drug weightability and enhancement in drug solubility. Increase in drug weightability result into higher drug dissolution rate.

Selection of carrier :

Solid dispersion should have following criteria for selection of carrier :

- A carrier should be freely soluble in water with high rate of dissolution
- It should be non toxic
- It should be inert.
- It should be able to enhance the aqueous solubility of a drug.
- It should posses chemical compatibility

1. First generation carriers

Eg.Urea, sugar, organic acid.

2. Second generation carrier

Eg. PEG, HPMC, starch derivative

3. Third generation carrier

Eg. Poloxamer 408, Twin 80

Selection of solvent:

Solid dispersion should have following criteria for selection of solvent :

- Both drug and carrier must be dissolve.
- Water base system are used.
- Ethanol can be used as an alternative.
- Toxic solvent to be avoid. Eg. Chloroform and dichloromethane.

METHODS OF PREPARATION :-

There are various methods of preparation of solid dispersion which has been reported in literature. Preparation methods mainly include the mixing of a carrier with the drug at molecular level. During the preparation of solid dispersion formation of different phases and de-mixing is observed. Therefore it was observed that extent of phase separation can be prevented by Rapid cooling procedure. Phase separation can also be prevented by maintaining the driving force for phase separation low for example by keeping the

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mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Various techniques for preparation of solid dispersion are as following:

- Melting methods
- Solvent methods
- Solvent evaporation
- deposition method
- Solvent deposition
- Supercritical fluid method
- Kneading method
- Lyophillization technique
- Hot melt extrusion
- Use of co-solvents
- Melt solvent method

1. Melting Method

It is also known as Fusion Method. In this method carrier is selected on the basis of preliminary solubility studies. Firstly the carrier is melted in a china dish at 550 - 600 C and the drug is added into the melted carrier with constant stirring. After this the melted mixture is cooled rapidly and stored in desiccators for 24 hours. The solidified mass is crushed pulverized and sieved through mesh for the desired product. Advantages:

• The main advantage of direct melting method is its simplicity and economy.

• In addition melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier

Disadvantage:

• This method can be applied only when the drug and the carrier are compatible and they mix well at heating temperature.

• Degradation of drug and carrier can occur during heating process,

• Phase separation can occur. When drug is slowly cooled, crystalline form is obtained whereas rapid cooling yields amorphous solid dispersion.

2. Solvent Evaporation Method

The drug and carrier are selected in particular ratios and dissolved in common solvent with constant stirring. The solution is evaporated continuously under pressure to obtain dry mass. The dried mass is pulverized and passed through sieve and stored in desiccators. Two challenges are mainly faced during formulation by solvent evaporation method mainly:

To dissolve both drug and carrier in same solvent despite of different polarity.

• To minimize drug particle size in solid dispersion, the drug and carrier has to be dispersed in solvent as fine as possible.

Advantages

• Thermal decomposition of the drugs can be prevented because of low temperature required for organic solvents to evaporate.

3. Solvent Evaporation Deposition Method

The drug and carrier are weighed and transferred into a solvent system. After complete dissolution a water insoluble carrier or an adsorbent is added into the above solution. After the ternary system had been completely mixed, the solvent is evaporated in water bath at 800 C and solid dispersion obtained is crushed, pulverized and sieved and stored in desiccators.

4. Solvent Deposition

The drug is weighed and dissolved in a solvent system. After complete dissolution, an adsorbent is added into it. After complete mixing, the solvent is evaporated at 800C. The deposits are dried, crushed and sieved to obtain solid dispersion formed.

5. Supercritical Fluid Method

In this method CO2 is used as either solvent in which either drug or matrix is dissolved or either as anti solvent. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This method does not require any organic solvent due to which it is considered as solvent-free method. However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low w (<0.01wt-%) and decreases with increasing A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved.

6. Lyophillization Technique

In this technique the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion 12

Advantage

• The risk of phase separation is minimized as soon

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as solution is vitrified.

7. Hot Melt Extrusion Method 12

Hot-stage extrusion (HME) consists of the extrusion, 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. A reduction in processing temperature can be achieved by the association of hotstage extrusion with the use of carbon dioxide as a plasticizer, which broadens the application of hot-stage extrusion to thermally labile compounds.

8. Use of Co-solvent

Co-solvency is defined as a process in which the solubility of the drug is increased by addition of water miscible solvents. The added solvents are called as cosolvents.the solublization effect brought about is dependent on the polarity of drug, solvent and cosolvent. Examples of various co-solvents are propylene glycol, polyethylene glycol, ethanol etc. The co-solvents basically enhance the solubility in of the drug and reduce difference between polarity of the drug and water system thereby enhancing the solubility. The mechanism involved in solubility enhancement by co-solvency is reduction in interfacial tension between aqueous solution and hydrophobic solutes and reduces the contact angle between liquid and solid.

9.Melt-Solvent Method

In this method the drug is dissolved in liquid solvent. The solution so formed is incorporated into the melted polymer without removing liquid solvent

Approaches to overcome the common objection arise from solid dispersion

1. To prevent crystallization and phase separation
2. Surfactant and emulsifier reduce crystalanity by improving missability of drug
3. Surface active agent can also increase the solubility of drug and also increase drug weitability

Characterization of Solid dispersions

• Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR mostly used for to characterize drug-polymer (carrier) compatibility study. Its main application is to study the solid state interaction between drug and polymer.

• Differential Scanning Calorimetry (DSC)

It is a powerful technique used for to study amorphous content. It also detect endothermic and exothermic peak. It also studies whether the drug was incorporated into the polymer (carrier) or not on the basis of melting point.

• Powder X-ray Diffraction (PXRD)

It is mostly useful for to characterize whether the solid dispersion is amorphou crystalline. Sharper peak indicate more crystalinity.

• Scanning electron microscopy

It is used for to characterize particle morphology.

Limitations :

1. Problem related to dosage form.
2. Problem related with scale up and manufacturing
3. Problem related to stability.
4. Method of preparation
5. Physicochemical property

Evaluation of Physicochemical properties of solid dispersion

1. Phase solubility study
2. Drug content
3. Drug saturation study

Application of Solid Dispersion :-

1) It depends the solubility of ineffectively solvent drugs and alcohol these lines builds the dissolution rate ,which upgrades the absorption bioavailability of the drugs.

2) For stabilization of the unstable drugs against different deterioration system like hydrolysis, oxidation and so on.

3) Masking of unsetting taste and smell of drugs.

4) To stay away from bothersome incompatibilities.

5) To get a homogeneous dispersion of a restricated amount of drug in solid state.

6) Dispensing of liquid (up to 100%) or gaseous compound s in solid dosage.

7) Formulation of sustained release dosage form.

MARKETED SOLID DISPERSION PRODUCTS

• Troglitazone solid dispersion is marketed by Parke Davis

• Gris-PEG® solid dispersion of griseofulvin marketed by Novartis.

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DRUG	BRAND NAME	CARRIER	MANUFACTURE
Itraconazole	Sporanox	HPMC	Janssen Parmaceutical, Inc,USA
Tacrolimus	Prograf	HPMC	AstellasPharma,US Inc.
Lopinavir	Kaletra	PVP	Abbot Labarotaries, USA
Nabilone	Casamet	PVP	Meda pharmaceuticals Inc.,USA
Nimodipine	Nimotop	PEG	Bayer Ltd.,USA
Fenofibrate	Fenoglide	PEG	Santarus,Inc
		HPMC	
Nifedipine	Afeditab	PVP OR Poloxamer	Elan Corp,Ireland
Nabilon	Cesamet	PVP	Lilly USA
Griseofulvin	Gris PEG	PEG	Novartis , Switzweland
Griseofulvin	Gris PEG	PVP	VIP Pharma,Denmark
Itraconazole	Onmel	HPMC	Stiefel
Nivaldipine	Nivadil	HPMC	Fujisawa pharmaceut-Ical Co.,Ltd.
Verapamil	Isoptin SR –E	HPC /HPMC	Abbot laboratories, USA
Verapamil	Isoptin SRE -240	Various	Soliqs,Germany
Etravirine	Intelence	HPMC	Tibotec,Yardley
Etravirine	Incivo	HPMC	Janssen Therapeutics, Belgium
Tacrolium	LCP-Tacro	HPMC	Lifecycle Pharma, Denmark
Tarolium	Prograf	HPMC	Fujisawa pharmaceuti-Cal Co., Ltd
Itraconazole	Onmel	HPMC	Stiefel
Telaprevir	Incivek	HPMC	Vertex
Torcetrapib	Torcetrapib	HPMC	Pfizer,USA

II. CONCLUSION

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These include methods like spraying on sugar beads and direct capsule filling.

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