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ENHANCEMENT OF SOLUBILITY OF POORLY SOLUBLE DRUG THROUGH SOLID DISPERSION: A REVIEW

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ABSTRACT

Solid dispersions are an effective way to improve the dissolution of poorly water-soluble drug to increase their bioavailability. They are defined as the dispersion of one or more active pharmaceutical ingredients in a carrier at a solid state. One of the main issues with many drugs is their poor water solubility, and numerous methods have been developed to improve this solubility. The solubility behaviors of pharmaceuticals continue to be one of the most difficult parts of developing formulations. The delivery of many existing drugs is impacted by the new drug's solubility concerns with regard to targeted drug delivery. At least 40% of new drugs developed for the pharmaceutical industry have low water solubility. Therefore, the main issues facing scientists are to increase the drug's solubility in water and its bioavailability. Therefore, it is advantageous to build solid dispersion with carriers that have strong water solubility in order to overcome such issues and promote dissolution. Therefore, it is discovered that using solid dispersion techniques is a useful way to increase a drug's solubility factor when it exhibits low water solubility. Some of the crucial practical factors that must be taken into account while creating solid dispersions are carrier selection and physicochemical characterization techniques. The main objective of developing solid dispersions is to increase the oral bioavailability and absorption of drugs that are poorly water-soluble. Solubility is an important parameter for attaining the targeted drug concentration in the systemic circulation for pharmacological response. It is the process by which a solid dissolves in a liquid phase to form a homogenous system. The aqueous solubility, dissolution rate, and bioavailability of

poorly water-soluble pharmaceuticals can be improved by a variety of methods, such as hydrotropic, micronization, chemical modification, solid dispersion, complexation, co-solvency, micellar solubilization, and pH adjustment. Technologies for solid dispersion have great promise for enhancing the bioavailability and oral absorption of BCS Class II drug. The focus of this review article on the method of preparation, classification, carrier used, characterization, advantages, disadvantages and the application of the solid dispersion.

Abbreviations: SD: Solid Dispersion; BCS: Biopharmaceutical Classification System; FT-IR: Fourier transform infrared; XRD: X-ray diffraction; DSC: Differential scanning calorimetry; SCF: Super critical fluid Technology.

KEYWORDS: Poorly soluble drug, Solid dispersion, Carrier, bioavailability, Solubility, Biopharmaceutical Classification System (BCS).

1. INTRODUCTION

The oral route of drug administration is the most common and preferred route of delivery due to convenience and ease of ingestion. From the perspective of the patient, taking medication by ingesting a dose form is comfortable.[1] Because of their low levels of absorption, drugs with limited water solubility frequently have poor oral bioavailability.[2] Solubility is a crucial physicochemical property that affects both drug absorption and therapeutic efficacy. Inadequate solubility in water can result in formulation development failure. The main cause behind insufficient bioavailability of drug is its low dissolution rate and low solubility in aqueous media.

Nowadays, a great deal of hydrophilic carriers are being investigated, and their solubility improvement has produced noteworthy outcomes.[3] To increase the oral bioavailability of pharmacologically active substances, pharmaceutical scientists can choose one of two methods: (i) increase the solubility and rate of dissolution of weakly water-soluble pharmaceuticals, or (ii) increase the permeability of poorly permeable drugs.[4] Solid dispersion formulation is used to improve solubility.

According to Chiou and Riegelman, solid dispersion systems can be defined as ‘the dispersion of one or more active components in an inert carrier or matrix at solid state generated by the melting [fusion], solvent, or melting solvent method.[5]

Biopharmaceutical Classification System (BCS) categorized the drugs into four subclasses according to solubility and permeability. BCS class II and IV belonging drugs have poor solubility problems. It is most challenging to enhance the solubility of these BCS II and IV belonging drugs. For this purpose, various approaches are used such as solid dispersion, reduction of particle size (Micronization and Nanonization), formation of salts, alteration of pH, and formation of polymorphs and pseudo polymorphs, by complexation method, by using surfactant and co-solvent. But among these approaches, solid dispersion is easy and gives the high accuracy result of enhancement of solubility.[6] This narrative review focuses on the use of solid dispersion technique and method to improve the dissolution characteristics of poorly water-soluble drug and their oral bioavailability.[7]

Classification of drugs using Biopharmaceutical Classification System (BCS)[8]

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

2. Solubility

The ability of a chemical substance, known as a solute, to dissolve in a liquid, solid, or gaseous solvent and form a homogenous solution in the solvent is known as solubility. Any substance's solubility primarily depends on the solvent employed at a certain temperature and pressure, as demonstrated in table.[9]

Solubility aspect of parameter[10]

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practical insoluble	10,000 and over

3. Solid dispersion[11]

Solid dispersion is defined as the dispersion of one or more active ingredients (Hydrophobic) in an inert carrier (Hydrophilic) at solid state prepared by melting (Fusion), solvent, melting solvent method. The product formed contains different components i.e. a hydrophillic matrix and a hydrophobic drug.

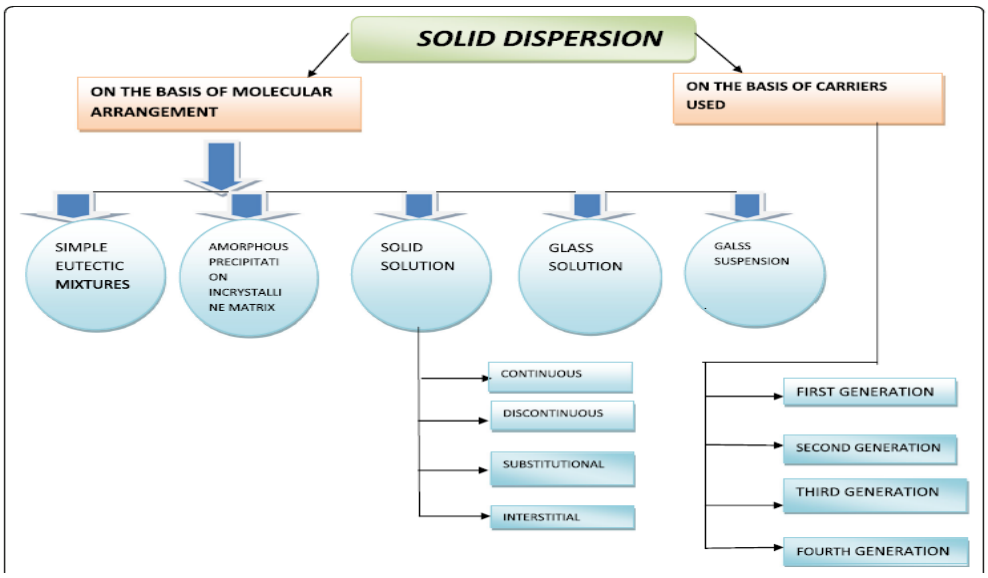

Fig. 1: Classification of solid dispersion.[12]

Classification of solid dispersion

3.1 Depending on the molecular arrangement, Solid dispersions can be of the following types[13]

3.1.1 Eutectic 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 crystals of the two components.

3.1.2 Solid solutions

Depending on the miscibility, the two types of solid solutions are

3.1.3 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.

3.1.4 Discontinuous solid solutions

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

3.2 Depending on the distribution of the solvates in the solvendum, solid solutions can be of two types[14]

3.2.1 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.

3.2.2 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.

3.2.3 Amorphous solid solutions

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

3.2.4 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 characterised 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.

3.3 Classification of solid dispersion on the basis of recent advancement[15]

3.3.1 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.

3.3.2 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, polyethylene Glycols and Polymethacrylates.
- Natural Polymer – Hydroxypropylmethylcellulose, Ethyl cellulose, Starch derivatives like cyclodextrin.

3.3.3 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 such as inulin, poloxamer 407 etc.

3.3.4 Fourth generation solid dispersion

These type of dispersions can be referred as controlled release solid dispersions (CRSD). It contain poorly water soluble drug with a short biological half life. The carrier used are either water soluble carrier or water insoluble carrier. Solubility enhancement and extended release of drug in controlled manner are the two targets in CRSD. The water soluble carriers used in CRSD are ethyl cellulose, Eudragit RS, Eudragit RL, HPC, etc.

4. Carrier[16]

The main determinant of the dissolving characteristics of dispersed drug molecules has been the carrier's qualities. Nonetheless, in order for the carrier to be effective in accelerating the drug's rate of dissolution, it must fulfil the following requirements.

- It should be water soluble with intrinsic rapid dissolution properties.
- It should be nontoxic and pharmacologically inert.
- It should be heat stable with low melting point for melt method.
- It must be soluble in variety of solvents for evaporation in solvent method.
- It must be able to increase the aqueous solubility of drug.
- It must be chemically compatible with drug and should not possess a strong complex with it.
- It must stabilize the supersaturated solution formed after dissolution of solid dispersion in GIT.
- It must have functional groups which are either acceptors or donors for hydrogen bonds, as specific interactions increase the solid solubility of the drug into its carrier.
- It should have high glass transition temperature.

5. Advantages of solid dispersion[17]

- **Reduced particle size**

Since solid dispersions have the smallest particle sizes, the medicine is disseminated in the dissolving media following carrier dissolution. One way to use the solid dispersion principle

is to combine a medication that is not very soluble in water with highly soluble carriers. Therefore, establishing a high surface area that leads to an increased dissolution can improve bioavailability.

- **Particles with Improved wettability**

The drug's wettability is improved by the carrier. Carriers primarily affect the drug dissolving profile by co-solvent effects or direct dissolution.

- **Particles with higher porosity**

It has been discovered that the particles exhibit a greater degree of porosity in solid dispersion. Depending on the carrier's characteristics As solid dispersion having linear polymer which produces larger and more porous particles than those containing reticular polymer which result in an higher dissolution rate. The drug release profile is enhanced by the solid dispersion particles' increased porosity.

- **Drugs in amorphous state**

When in its amorphous form, the crystalline medication, which is poorly soluble in water, exhibits greater solubility. Utilizing the medication in its amorphous form will do this. Higher amorphous compositions can therefore be attained by selecting carriers that have particular interactions with them.

6. Disadvantages of solid dispersion[18]

- The crystalline state of the drug may occur in the undefinable condition; so, strong dispersion is the problem of poor soundness.
- The handling problem arises from the strong scatterings' thickness.
- Strong scattering may breakdown in the presence of moisture and extreme temperatures, which may lead to the formation of valuable stones.
- It is problematic to predict the shelf life of unclear material.
- The hygroscopic nature of the polymers used in strong scattering allows moisture to be retained, which may cause the hazy structure to transform into a crystalline form.
- The main drawback of the solid dispersion is its instability. The physical mixture is more affected by the factors that degrade solid dispersions, such as temperature and moisture, because tackiness makes handling the solid dispersion challenging.

7. Application[19]

- It is mostly useful for achieving a uniform dispersion of a tiny quantity of medication in a solid condition.
- It helps to stabilise the unstable drug.
- It is employed for the solid dose state dispensing of both the liquid and gaseous chemical.
- A sustained dosage form for the fast release initial dose is possible.
- It is also employed in the formulation of soluble drugs with prolonged release by the use of insoluble or poorly soluble carriers.
- In solid dispersion systems, such as solid solutions and eutectic mixtures, polymorphism is given.

8. Method of preparation[20,21,22,23]

1) Melting method
2) Solvent evaporation method
3) Lyophilization technique
4) Melting solvent method
5) Melt extrusion method
6) Melt agglomeration process
7) Spray drying
8) Effervescent method
9) Electrospinning
10) Super critical fluid (SCF) Technology.

1) Melting method

The melting and fusion approach is mixing a medication and a water-soluble carrier physically, then heating the combination directly until it melts. First, the mixture is melted, and then it rapidly solidifies in an ice bath while being stirred vigorously. The last solid mass is pulverised, crushed, and sieved.

2) Solvent evaporation method

This process involves dissolving the mixture, which includes the drug and carrier, in a common solvent, letting it evaporate until a free film remains, and then drying and sieving it again.

3) Lyophilization technique

Heat and mass transfer from the product being prepared occur in this procedure. As a substitute method for solvent evaporation, this method was suggested. This kind of molecular mixing method uses a shared solvent to co-disperse the drug and carrier. After that, it was frozen and sublimed to produce a molecular dispersion using lyophilization.

4) Melting solvent method

Using this process, a set volume of solvent is added, and the melted polyethylene glycol is then heated below 700C to incorporate the solution. High melting point thermolabile drugs are also treated with this technique. However, a restricted medication with a low therapeutic dose is needed (below 50 mg).

5) Melt extrusion method

This method meanly preferred for thermolabile drug. The drug and carrier are mixed together and typically processed with a twin -screw extrusion. The mixture is then simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates are then further processed into conventional tablets.

6) Melt agglomeration process

In this method, the solid dispersion is prepared where the binder rols as a carrier. In addition to this, solid dispersion are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor is the alternative equipment for melt agglomeration. The rotary processer is mainly preferable for high melt agglomeration. Because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates**.**

7) Spray drying

In this method accurately weight amount of drug and lipid carrier are dissolved in methanol to obtain clear solution. This solution is there sprayed on lab scale with the help of dryer, which result in the formation of solid dispersion.

8) Effervescent method

This is the method in which sodium bicarbonate and organic acid such as citric acid or succinic react with the each other to yield effervescence. But when combining of both that increased the dissolution and absorption rate of poor soluble drug**.**

9) Electrospinning

In this process solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter scale nozzle. It mainly involves the application of a strong electrostatic field over a conductive capillary attach to a reservoir containing a polymer solution or melt and a conductive collection screen. With increase in the electrostatic field strength up to but not exceeding a critical value, charge species which accumulated on the surface of a pendant drop, which destabilize the hemispherical shape in to a conical shape. Technique has much more potential for the production of nanofibers and controlling the release of biomedicine, It is simplest the cheapest technique utilized for the preparation of solid dispersion in further.

10) Super critical fluid (SCF) Technology

This is the super critical fluid anti-solvent technique, which involves the use of carbon dioxide as an anti-solvent for the solute.

After this solubilization of drug particles within supercritical fluid they may be recrystallized at great it reduced particle size. The flexibility and precision offered by supercritical fluid process allow micronization of drug particle, within narrow range of particle size obtained to sub-micro level. The current super critical fluid processes have the ability to demonstrate and to create nano-particular suspension of particle 5-2000 in the diameter. The spraying of the solution was done which is composed of the solute & the organic solvent into a continuous super critical phase following concurrently.

9. Characterization of solid dispersion[24,25]

Various methods for characterization of solid dispersion are mention below.

9.1 Drug carrier miscibility

9.1.1 Powder x-ray diffractioon

9.1.2 NMR 1H spin lattice relaxation time

9.1.3 Differential scanning calorimetry

9.2 Drug carrier interactions

9.2.1 Raman spectroscopy

9.2.2 Solid state NMR

9.2.3 FT-IR spectroscopy

9.3 Physical structure

9.3.1 Dynamic vapor sorption

9.3.2 Inverse gas chromatography

9.3.3 Scanning electron microscopy

9.3.4 Surface area analysis

9.3.5 Surface properties

9.4 Amorphous content

9.4.1 Humidity stage microscopy

9.4.2 DSC(MTDSC)

9.4.3 ITC

9.4.4 Hot stage microscopy

9.4.5 Polarised light optical microscopy

9.4.6 Powder X-Ray diffraction

9.5 Stability

9.5.1 Humidity studies

9.5.2 Isothermal Calorimetry

9.5.3 DSC (Tg, Temperature recrystallization)

9.5.4 Dynamic vapor sorption

9.5.5 Saturated solubility studies

9.6 Dissolution enhancement

9.6.1 Intrinsic dissolution

9.6.2 Dynamic solubility

9.6.3 Dissolution

9.6.4 Dissolution in bio-relevant media

10. CONCLUSION

The use of solid dispersions emerges as a promising strategy to address the challenges associated with the poor water solubility of drugs, enhancing their bioavailability and therapeutic effectiveness. The significance of solubility in drug absorption and the development of formulations underscores the critical role that solid dispersions play in pharmaceutical research.

The evolving landscape of solid dispersions holds immense promise for overcoming the challenges posed by poorly water-soluble drugs, ultimately contributing to advancements in drug delivery and therapeutic efficacy. Continued research and innovation in this field will undoubtedly play a pivotal role in shaping the future of pharmaceutical formulations and improving patient outcomes.

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