GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

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An informative review on solid dispersion

Rajiv Kumar *, Avneet Singh, Rajan Salwan, Ritesh Bhanot, Sandeep Rahar and R.K. Dhawan

Khalsa College of Pharmacy, Department of Pharmaceutical Sciences, Amritsar, Punjab, India.

GSC Biological and Pharmaceutical Sciences, 2023, 22(01), 114–121

Publication history: Received on 19 November 2022; revised on 31 December 2022; accepted on 03 January 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.22.1.0498

Abstract

Oral dosage forms are mostly preferred route for administering drugs to patient. But due to the poor solubility many drug has limited used in oral administration. Solubility is a one of the significant factor which affects dissolution rate and bioavailability. Solid dispersion is an effective method of improving the dissolution rate of poorly water soluble drugs and hence its bioavailability. In this study will focus on various methods of solid dispersion preparation, their advantages and major challenges

Keywords: Solubility; Dissolution; Bioavailability; Eutectic mixtures; Lyophilization

1 Introduction

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration for example, parenteral.

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s) and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water-soluble drugs.

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 problem. It is most challenges to enhance the solubility of this 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, formation of polymorphs and pseudo polymorphs, by complexation method, by using surfactant and co-solvent. But among of this approaches solid dispersion is easy and give the high accuracy result of enhancement of solubility.

When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. This increases surface area of dissolution rate and hence bioavailability of poorly water soluble drugs. Drug in soluble hydrophilic carrier improves the dissolution rate by reducing particle size and increasing the particle porosity. Therefore by improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects [1-3].

* Corresponding author: Rajiv Kumar

2 Solid dispersion

Solid dispersion is defined as 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.

2.1 Classification of solid dispersion

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

- 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.

- Solid solutions

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

  - 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.

  - Discontinuous solid solutions

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

Depending on the distribution of the solvates in the solvendum, solid solutions can be of two types:

- 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.

- 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.

  - Amorphous solid solutions

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

  - 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.

Classification of solid dispersion on the basis of recent advancement

2.1.1 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.

2.1.2 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.

2.1.3 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 (4-6).

2.2 Advantages of solid dispersion

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches. Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable.

In molecular dispersions, 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. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability. Solid dispersions also provides particles with improved wettability as it was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability property of drug.

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier.

For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them. Drug is formulated with hydrophilic carrier as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water (7- 11).

2.3 Method of preperation of solid dispersion

Various methods used for preparation of solid dispersion system.

2.3.1 Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

2.3.2 Lyophilization

It is a phenomenon of transfer of heat and mass from and to the product. It is an alternative technique to solvent evaporation in which molecular mixture technique is used where the drug and carrier is dissolved in common solvent, frozen and sublimed.

2.3.3 Melt Agglomeration technique

In this technique binder is use as carrier. There are two method of preparation of solid dispersing, first is by spraying the drug on melted binder plus exipients and other one is melting of binder drug and exipient above the melting temperature of binder used. For using high binder content rotary process might be preferable for controlling temperature. This technique is advantageous in homogenous mixing of drug but larger particle size cause densification and fines cause adhesion of mass.

2.3.4 Electrosipinnig method

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimetre-scale nozzle. In this process, electrostatic field involved over a conductive capillary attaching to a reservoir containing a polymeric solution and a conductive collective screen. Itraconazole/HPMC has been prepared using this technique (12-14).

2.3.5 Melting method

The melting method is suitable for heat stable materials with low melting points. The basic principle of the method consists of melting together the drug and carrier at a temperature slightly above their eutectic point, mixing the liquefied components. It is then cooled to acquire a congealed mass. It is crushed and sieved.

2.3.6 Spray drying method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using spray dryer.

2.3.7 Melt extrusion method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets.

2.3.8 Melting solvent method

It was shown recently that 5-10% (w/w) of liquid compounds could be incorporated into polyethylene glycol 6000 without significant loss of its solid property. Hence, it is possible to prepare solid dispersions by the first dissolving a drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, obtained below 70, without removing the liquid solvent. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol. The polymorphic form of the drug precipitated in the solid dispersion may be affected by the liquid solvent used. Such a unique method possesses the advantages of both the melting and solvent methods. This method involves dissolving the drug in an appropriate liquid solvent and then incorporating the solution formed directly into the melt of polyethylene glycol which is evaporated until a clear solvent free film is obtained. This technique is a combination of fusion and solvent evaporation method.

2.3.9 Supercritical fluid technology

SCF is a substance above its critical temperature and pressure. Critical point represents the highest temperature and pressure at which the substance exists as vapour and liquid in equilibrium. In this technique SCF is used to form solid dispersion of insoluble material/polymer with drug cause increase in dissolution property. It is superior over conventional technique (spray drying, hot melt etc.), in this technique SCF carbon dioxide is mainly used which cause very rapid precipitation of solid mixture giving no time for separation of drug and polymer in preparation of solid dispersion. It form very stable small particle with higher surface area for good flow and low organic solvent residual. In recent Solid dispersion of carbamazepine with PEG-4000 are made using SCF carbon dioxide in precipitation vessel.

2.3.10 Solvent method

This method is also known as solvent evaporation method in which physical mixture of the drug and the carrier is dissolved in common solvent and is evaporated until a clear solvent free film is obtained. The main advantage is that the thermal decomposition of the drug or the carrier can be prevented because the organic solvents require a low temp for evaporation. The disadvantage in this method is difficulty in removing the solvent and higher cost of preparation (15-19).

2.4 Evaluation of physicochemical properties of solid dispersion

2.4.1 Phase Solubility Study

It is carried out in the presence of polymer (carrier) using shaking flask method. It is mostly conducted according to the Higuchi and Connors. In this method, drug is placed in a 25 ml containing 1%, 2%, 3%, 4% and 5% polymer solution. Then it is placed in orbital flask shaker for 48 hrs. at 37 ℃ ± 0.5 ℃ temperature. Then sample is filtered and analysed by UV spectrophotometer for determination concentration of drug.

2.4.2 Saturation Solubility Study

Drug and solid dispersion batches are added in excess quantity in 25 ml distilled water up to its super saturation. Then it is placed in orbital flask shaker for 48 hrs. at 37 ℃±0.5 ℃temperature. Then it is filtered through whatman filtered paper and analysed for determination of concentration of drug by UV spectrophotometer.

2.4.3 Drug content

Known quantity of solid dispersion is dissolved in a solvent and then analysed by UV spectrophotometer for determination of drug content.% drug loading and % entrapment efficiency is calculated by following equation,

% Drug loading = (Weight of drug in solid dispersion powder)/ (Weight of solid dispersion powder) X 100 -----(1)

2.5 Characterization of Solid dispersions

2.5.1 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.

2.5.2 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.

2.5.3 Powder X-ray Diffraction (PXRD)

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

2.5.4 Scanning electron microscopy

It is used for to characterize particle morphology (20-27).

2.6 Polymers used in solid dispersions

2.6.1 Polyethylene glycol (PEG)

These are compounds are obtained from a reaction of ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20,000 are usually employed. As the MW rises, so does the viscosity of the PEG. At MW of up to 600, PEGs are fluid, in the range 800 -1500 they have a consistency that is best described as vaseline-like, from 2000 to 6000 they are waxy and those with MW of 20,000 and above form hard, brittle crystals at room temperature. Their solubility in water is generally good, but reduces with MW. A meticulous advantage of PEGs for the solid dispersions is that they have good solubility in numerous organic solvents. The melting point of the PEGs of interest with an average molecular weight of 4600 (range 4400-4800) is 57 - 61°C and with an average molecular weight of 6000 (range 5000-7000) 60 - 63°C.

2.6.2 Polyvinylpyrrolidone (PVP)

PVP molecular weight ranges from 2500 to 3000000. It is having solubility in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP gets decomposed at high temperature therefore it is not suitable for preparation of solid dispersions prepared by melt method because melting takes place at a very high temperature. PVP can be classified according to the K value, which is calculated using Fikentscher's equation. The temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (Tg) is high; for

example, PVP K25 has a Tg of 1558 °C. For this reason PVPs have only restricted application for the preparation of solid dispersions by the hot melt method. Due to their excellent solubility in an ample variety of organic solvents, they are mostly suitable for the preparation of solid dispersions by the solvent method.

2.6.3 Cellulose derivatives

Hydroxypropylmethylcellulose (HMPC)

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4-32% is derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10000 to 1 500 000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane.

Hydroxypropylcellulose (HPC)

Hydroxypropylcellulose (HPC) exhibits good solubility in a range of solvents, including water (up till 400 °C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37 000 (Type SSL) to 1 150 000 (Type H).4

Carboxymethylethylcellulose (CMEC)

CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. CMECs also dissolve readily in acetone, isopropanol 70%, ethanol 60% and 1:1 mixtures of dichloromethane and ethanol.

Hydroxypropylmethylcellulose phthalate (HPMCP)

HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). They are having a type-dependent solubility in organic solvents. The dissolution rate of griseofulvin at pH 6.8 could be greatly enhanced by incorporating it in a coevaporate of HPMCP.

Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. In pharmaceuticals they are mainly used as coatings to change the release of the drug from the dosage form.

Phospholipids

The complexity of glycerides advances by modification of the terminal hydroxyl with phosphate linked head groups to form phospholipids, common phospholipid head groups include choline, ethanolamine, serine, inositol and inositol phosphate, and glycerol esters. As with the triglycerides, numerous species are possible by various combinations of different head groups and fatty acyl substitution at the first and second positions of the glycerol backbone, fluidity differences are evident as a function of the gel to liquid crystalline transition temperatures. Solubility of phospholipids is intimately linked to the confirmation of the aggregate material rather than strictly a chemical function of the molecule. Monoacyl phospholipids, which tend to form micelles, are usually more readily soluble in aqueous solutions.

Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble and have few, if any, toxicity issues, they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates. Even with these drawbacks, several attempts have been reported to prepare solid dispersions using sugars and their derivatives. Mannitol, which has a melting point of 165-168 °C and decomposes only above 2500 °C, can be employed in some cases to prepare dispersions by the hot melt method.

Organic acids and their derivatives

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin method.

Cyclodextrins

Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment (28-32).

3 Conclusion

Although there was a great interest in solid dispersion systems during the past four decades to increase dissolution rate and bioavailability of poorly water-soluble drugs, their commercial use has been very limited, primarily because of manufacturing difficulties and stability problems. Solid dispersions of drugs were generally produced by melt or solvent evaporation methods. The materials, which were usually semisolid and waxy in nature, were hardened by cooling to very low temperatures. They were then pulverized, sieved, mixed with relatively large amounts of excipients, and encapsulated into hard gelatin capsules or compressed into tablets. These operations were difficult to scale up for the manufacture of dosage forms. The situation has, however, been changing in recent years because of the availability of surface-active and selfemulsifying carriers and the development of technologies to encapsulate solid dispersions directly into hard gelatin capsules as melts. Solid plugs are formed inside the capsules when the melts are cooled to room temperature. Because of surface activity of carriers used, complete dissolution of drug from such solid dispersions can be obtained without the need for pulverization, sieving, mixing with excipients, etc. Equipment is available for large-scale manufacturing of such capsules. Some practical limitations of dosage form development might be the inadequate solubility of drugs in carriers and the instability of drugs and carriers at elevated temperatures necessary to manufacture capsules.

Compliance with ethical standards

Acknowledgments

The authors are grateful to Director and Principal, Khalsa College of Pharmacy for providing support on every step.

Disclosure of conflict of interest

There is no conflict of interest between the Authors.

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