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SHORT DISCUSSION ON SOLID DISPERSION: SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

The phenomenon of dissolution of solid phase in liquid phase to obtain a homogenous system is known as solubility. Many drugs, in particular, have poor solubility in water but we also know that water is the chief solvent of choice to be used for liquid pharmaceutical formulations. And thus, this poorly solubility ultimately affects the therapeutic plasma concentrations and also the bioavailability of the drugs. To ameliorate the dissolution of poorly water-soluble drugs as well ultimately ameliorating their bioavailability, the dispersion of one or more active pharmaceutical ingredients in a carrier that too at solid-state is used. This phenomenon is known as Solid dispersion. This solid dispersion is mainly applied to improve the solubility, dissolution rates as well as bioavailability of poorly soluble drugs. Various solid dispersions techniques have been described briefly in this review article. These techniques include the kneading method, adjustment of pH, co-precipitation, co-solvency, etc. In this article, further, we have studied the formulations, merits, and demerits as well as the characterization of the solid dispersions.

KEYWORD: Solubility; Solid dispersion; dissolution; solubility enhancement.

1. INTRODUCTION

The most compatible route of drug administration for the patient is seen to be the oral route of drug administration due to its ease of ingestion. This means the patient feels more comfortable with oral ingestion than other routes. Yet many drugs are not compatible to be administered via the oral route of administration. The reasons for this can be their limited absorption in a way resulting in its poor bioavailability which mainly happens due to low solubility and dissolution rates. Thus, to make a drug compatible for its oral drug administration, the main way is to enhance its solubility thereby increasing its dissolution rate.[1]

A group of solid products can be defined as solid dispersion if it contains at least two different components and these can be a hydrophobic matrix and a hydrophilic matrix (crystalline or amorphous).[2] This hydrophilic matrix behaves as a carrier and dissolves when the solid dispersion is exposed to aqueous media. As a result, the drug gets released as fine colloidal particles thereby enhancing the solubility as well as the dissolution rate of drugs.[3]

Table 1: Examples of commercially available solid dispersion.[3]

Drug	Manufacturer	Brand name	Dosage form	Carrier
Nabilone	Valeant	Cesamet	Tablet	PVP
Itraconazole	Janssen	Sporanox	Capsule	HPMC
Nifedipine	Elan	Afeditab	Tablet	Poloxamer/PVP
Tacrolimus	Fujisawa	Prograf	Capsule	HPMC
Verapamil	Abbott	Isoptin SR-E	Tablet	HPC/HPMC

PVP - polyvinylpyrrolidone; HPC - hydroxypropylcellulose;
HPMC – hydroxypropylmethylcellulose

The solid dispersion technique was firstly used by Sekiguchi and Obi by demonstrating the faster absorption of a drug named sulfathiazole. This was achieved by the formation of eutectic mixtures with a water-soluble carrier. Lyophilization has also been suggested for molecular mixing in which the carrier and the drug can be co-dissolved in cyclohexanol, frozen,

and then sublimed under vacuum to specifically obtain a lyophilized molecular dispersion.[4]

As mentioned above, solubility acts as a major key factor for a drug's oral bioavailability, Noyes-Whitney equation gives the dissolution rate of a drug and also ways to improvised the rate of poorly soluble drugs with respect to minimizing the limitations to oral drug 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, $\mathbf{C_s}$- is the solubility of the compound in the dissolution medium, **C** -is the concentration of drug in the medium at time t and **h** - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.[5]

Advantages of solid dispersion

1. To improve dissolvability in the water of a poorly water-soluble drug in a pharmaceutical, improve wettability and improve the porosity of the drug.
2. To increase dissolution rate and extent of absorption.
3. Transformation of liquid form to solid form.
4. It is more efficient than the particle size reduction technique.[5]
5. To reduce particle size
6. To formulate a faster release priming dose in a sustained release dosage form.
7. To formulate sustained release dosage or prolonged-release regimens of soluble drugs using poorly soluble or insoluble carriers.
8. To mask the taste of the drug substance.
9. To prepare rapid disintegration oral tablets.
10. To obtain the homogenous distribution of a small number of drugs at solid-state.
11. To stabilize unstable drug.[3]

Disadvantages of Solid Dispersion

1. Major disadvantage is their instability. It shows changes in crystallinity and a decrease in dissolution rate with aging.
2. Temperature and moisture have a more deteriorating effect on solid dispersions than on physical mixtures.
3. Reproducibility of its physicochemical properties.
4. Its formulation into dosage forms
5. Difficulty in handling because of tackiness.[7,8]

2. BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Biopharmaceutical Classification System

A drug is orally active and if it dissolves into the gastrointestinal (GI) fluids, then permeates the gut wall, passes through the liver without being inactivated, and finally enters the systemic blood flow. But amongst the various obstacle insolubility is the major problem for highly lipophilic and poorly water-soluble new chemical entities. Amidon *et al.*, classified active compounds into four classes according to their solubility and permeability. This is known as the Biopharmaceutical Classification System (BCS).[9]

2.1 Class I: compounds with high solubility and high permeability so their bioavailability will depend on the gastric emptying rate.

2.2 Class II: compounds have low aqueous solubility and high permeability so the dissolution will be the rate-limiting step.

2.3 Class III: compounds have sufficient solubility but poor permeability and hence the absorption rate will be determined by passage through the gut wall.

2.4 Class IV: compounds have both low solubility and low permeability, the rate-limiting step will differ case by case.[10]

Table 3: Solubility – Permeability Chart.[11]

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

3. COMMON METHODS USED FOR PREPARATION OF SOLID DISPERSION

1] Fusion method/ Hot melting method
2] Solvent method
3] Melting solvent method (melt evaporation)
4] Supercritical fluid method
5] Electro spinning method.
6] Solvent evaporation method
7] Melt agglomeration method
8] Lyophilization Techniques
9] Spray-Drying method
10] Dropping method solution
11] Melt extrusion method
12] Gel entrapment technique
13] Kneading technique
14] Co-precipitation method
15] Co-grinding method

3.1 Fusion Method / Hot Melting Method

The melting method was first used in 1961 by Sekiguchi and Obi.[12] The melting method in which a physical mixture of a drug and hydrophilic carrier (polymer) is heated directly until they melt at a temperature slightly above their eutectic point. Then, the melt is cooled and then solidified rapidly in an ice bath with the help of stirring. The final solid mass is crushed and sieved.

The advantages of the fusion method / hot melt method are it is simple and economical. Several drug Solid dispersions have been prepared using this method such as furosemide[13], albendazole[14], and paclitaxel[15]. The fusion method/ melting method is used to improve the solubility of poorly soluble anticancer drugs. For example, to improve the solubility of prednisolone, a Solid dispersion was prepared by the melting method

using PEG 4000 and mannitol as the carriers. The results showed that at weight ratios of the drug: PEG 4000 (1:4) and drug: mannitol (1:7), the release of drug from the Solid dispersion (~85%) increased in comparison with the pure drug (~50%). In a study for improving the release of paclitaxel from poly(ε-caprolactone) (PCL)-based-film, a Solid dispersion of paclitaxel was prepared by the melting method using poloxamer 188 and PEG as the carriers and was then incorporated into poly(ε-caprolactone) (PCL) films. Drug released from Solid dispersion was higher than that from the pure drug, with over 90% of drug released from the Solid dispersion after 1 h at a weight ratio of drug: poloxamer 188.

3.2 Solvent Method

In the solvent method, the physical mixture of the drug and carrier (polymer) 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.

Advantages

1] Solvent method is the thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required further evaporation of organic solvents.

Disadvantages

1] The higher cost of preparation.
2] The difficulty in completely removing liquid solvent.
3] The possible adverse effect of traces of the solvent on the chemical stability
4] The selection of a common volatile solvent.
5] The difficulty of reproducing crystal form.
6] In addition, supersaturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.[16]

3.3 Melting Solvent Method

In the melting solvent method, the preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent-free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol 6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also, the liquid solvent used may affect the polymorphic form of the drug, which precipitates the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.[17]

3.4 Supercritical Fluid Method

This is the supercritical 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 re-crystallized at great, with reduced particle size. The flexibility and precision offered by the supercritical fluid process allow micronization of the drug particle, within the narrow range of particle size obtained to the submicron level. The current supercritical fluid processes can demonstrate and create the nano-particular suspension of particle 5-2000 in diameter. The spraying of the solution was done which is composed of the solute & the organic solvent into a continuous supercritical phase following concurrently.[18]

3.5 Electro Spinning Method

Electro spinning method is a process in which solid fibres are produced from a polymeric fluid stream solution or melt delivered through millimetres-scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical Value, a charged polymer jet is ejected from the apex of the cone. The ejected charge jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried.

Advantages

1] This technique has tremendous potential for the preparation of Nanofibers and controlling the release of biomedicine.
2] Process is simplest, the cheapest.
3] This technique can be utilized for the preparation of solid dispersions in the future.

Disadvantages

1] Less economical for all the drugs and carriers.[19]

3.6 Solvent Evaporation Method

The solvent evaporation method is a simple way to produce solid dispersions where the drug and carrier are solubilized in a (volatile) solvent. The solvent is later evaporated. Tachibani and Nakumara (1965) were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under a vacuum to produce a solid solution. The method was then taken up by Mayersohn and Gibaldi (1966). With the discovery of the solvent method, many of the problems associated with the melting method were solved and for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers

began to make solvent based methods more and more problematic. For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions (Leuner and Dressman 2000).[20]

3.7 Melt Agglomeration Method

Melt agglomeration method in which a binder plays the main role it acts as a carrier. In melt agglomeration method, the drug, binder, and other excipients are heated to above the melting point of the binder. Alternatively, a dispersion of the drug is sprayed onto the heated binder . For example; A diazepam SD was prepared by melt agglomeration method in a high shear mixer to improve the dissolution rate. In this preparation, lactose monohydrate was used as the binder and was melt agglomerated with PEG 3000 or Gelucire 50/13. The binder was added by either pump-on or melt-in procedures. Use of melt agglomeration resulted in a high dissolution rate at a lower drug concentration. The dissolution rates were similar between pump-on and melt-in procedures. In addition, the SD of diazepam containing Gelucire 50/13 showed higher dissolution compared with the SD containing PEG 3000.[21]

3.8 Lyophillization Techniques

Lyophilization technique In this technique the drug and carrier are dissolved in a common solvent, frozen and sublimed to attain a lyophilized molecular dispersion.[22,23]

3.9 Spray-Drying Method

This method was developed in 1920 in which the manufacture of milk powder was one of the first applications of spray drying. Presently, this technique is having great utility in pharmaceutical industry owing to rapid drying and specific characteristics such as particle size and shape of the final product. In this method atomization of suspensions or solutions into fine droplets is done and drying of particles that may lead to the formation of solid particles.[24] This process permits production of fine, dust free powder.[25,26]

3.10 Dropping Method Solution

The dropping method, developed by Ulrich et al., (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is a pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process but also gives a higher dissolution rate. It does not use organic solvent and, therefore, has none of the problems associated with solvent evaporation.[27]

(a) Non-ionic (neutral).
(b) Ionic (including anionic or cationic).
(c) Amphoteric electrolyte (ampholytic) comprising both acidic and basic groups.
(d) Zwitterionic (polybetaines) consisting of both anionic and cationic groups in each structural repeating unit.

3.11 Melt Extrusion Method

This method is meanly preferred for the thermolabile drug. The drug and carrier are mixed 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.[28,29]

3.12 Gel Entrapment Technique

Hydroxyl propyl methyl cellulose is dissolved in an organic solvent to form a clear and transparent gel. Then drug for example is dissolved in the gel by sonication for few minutes. An organic solvent is evaporated under a vacuum. Solid dispersions are reduced in size by mortar and sieved.[27] In this method, the carrier is permeated with water and transformed to paste. The drug is then added and kneaded for a particular time. The kneaded mixture is then dried and passed through a sieve if necessary.[27]

3.14 Co-Precipitation Method

A required amount of drug is added to the solution of the carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature to avoid the loss of the structured water from the inclusion complex.[19]

3.15 Co-Grinding Method

In the co-grinding method in which physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw-capped glass vial until use. Ex. Chlordiazepoxide.[27]

4. APPLICATION OF SOLID DISPERSION IN PHARMA INDUSTRIES

The application of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. In their early paper on the use of solid dispersions, Chiou and Riegelman 70 observed that "It is believed that this relatively new field of pharmaceutical techniques and principles will play an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms."

- Increases oral bioavailability of poorly water-soluble drugs.
- Solid-state suitable for oral delivery.
- No change in chemical properties of the drug.
- Relatively simple processing techniques.
- Uses conventional equipment.

- Increases dissolution due to metastable solid state.
- Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored. Such a technique may be used:
- To obtain a homogeneous distribution of a small amount of drug in solid-state
- To stabilize the unstable drug.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate a sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compound. The following products have been developed by solid dispersion and these products were successfully launched in the market.

5. CONCLUSION

Solubility is the most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of the drug is the rate-determining step for oral absorption of the poorly water-soluble drugs, which can subsequently affect the in vivo absorption of the drug. Currently, only 8% of new drug candidates have both high solubility and permeability. Because of the solubility problem of many drugs, the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs.

From this review, it is clear that solid dispersion technology is one of the advanced approaches to resolve the problem of the solubility of poorly water-soluble drugs. Solid dispersion systems have been considered an 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 the formulation of dosage forms have been gradually resolved with the advent of alternative strategies. These technologies are expected to form a basis for the commercialization of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the near future.

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