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Solid Dispersion as Strategy to Improve the Solubility of Poorly Water Soluble Drugs and their Utilization and Consideration during Formulation Development

Mahesh Babanrao Shejul*, R.K. Godge, S.B. Kakad, S.S. Siddheshwar

Department of quality assurance technique, Pravara Rural College of Pharmacy, Pravaranagar, Tal- Rahuri, Dist- Ahmednagar, India

ABSTRACT

Solid dispersions are most promising system to increase the solubility of poorly water soluble drugs. By using reduction in drug particle size in required specification, and due to that improving drug wettability, bioavailability may be todays need. Solid dispersion generally presented as amorphous products, mainly obtained by two major different methods, melting and solvent evaporation. Now days, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility. New manufacturing processes to obtain solid dispersions have also been developed to reduce the drawbacks of the initial process. In this review, it is intended to discuss the consideration during formulation development also role of hydrophobic polymer for solubility enhancement various strategy to inhibit the recrystallization.

Keywords: Solid dispersion, recrystallization, solubility, bioavailability, dissolution rate, hydrophobic polymer.

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***Address for Correspondence:**

Mr. Mahesh babanrao Shejul, Department of quality assurance technique, Pravara Rural College of Pharmacy, Pravaranagar, Tal- Rahuri, Dist- Ahmednagar, India

Introduction

Generally there are various routes for administration of drugs but most of time oral route is preferential for the administration of drug because of the patient convenience. Also taking a medicine by swallowing the drug which is easy for the patient. However in oral route various obstacles are get involve i.e. low absorption of poorly water soluble drug that directly affect the bioavailability of drug.[1]

Solid dispersion is the technique which is used to establish or to increase the solubility and improve the bioavailability of the drug which eventually increases the rate of dissolution in the aqueous media. In an amorphous solid dispersion (ASD), the solubility of the drug substance is improved by disrupting its crystalline lattice to produce a higher energy amorphous form. Compared with other enabling solubilization approaches, an ASD can hold a much higher dose for low-solubility active pharmaceutical ingredients (APIs). ASDs improve bioavailability by maintaining supersaturation in the gastrointestinal (GI) tract. While supersaturation is sustained, the absorption of a compound can be maximized to be greater than that of a saturated solution.[5] In addition, the solubility differences amongst crystalline physical forms (e.g., polymorphs) are eliminated because they are converted to the amorphous form. This is predominantly advantageous for compounds in the research stage when the form is not clearly distinct. ASDs are usually well tolerated in animal disease models and are acceptable to toxicologists as their polymer carriers are derived from GRAS (generally regarded as safe) excipients. Commonly used excipients for forming ASDs are cellulose derivatives such as hydroxypropyl methylcellulose

(HPMC), hypromellose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxy ethyl cellulose, hydroxypropyl cellulose (HPC), cellulose acetate phthalate (CAP), methyl cellulose, carboxymethyl cellulose, ethyl cellulose, carboxymethyl ethyl cellulose, chitosan, cyclodextrin and derivatives, lactose, poloxamers, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-vinyl acetate copolymer (PVP/VA 64), polyvinyl acetate phthalate (PVAP), polymethacrylates (Eudragit E, L, S, FS), and polyethylene glycols (PEG) derivatives.These polymers are biologically inert and minimally absorbed.[6]

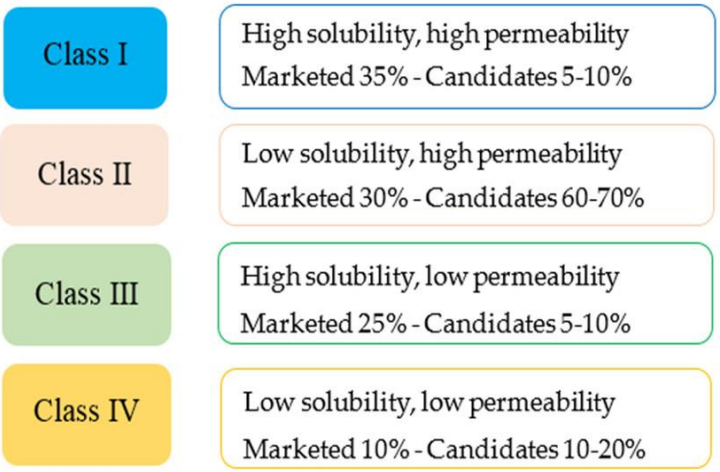
Most of the research of solid dispersion involves the class 2 drugs i.e. having poorly water soluble and highly permeable

to biological membrane. Hence, hypothesis has been that the, rate of absorption will in vivo increase with an increase rate of dissolution. So according to BCS classification, poorly water soluble and highly permeable drugs are promising factor in solid dispersion technology for BCS class 2 drugs.[2]

Now a days lots of research use natural polymer for improving the solubility and bioavailability of the drug. Generally natural polymer used are in the modified form for ex., Guar gum, xanthan gum, hupu gum, locust bean gum which is modified form of natural polymer. Some of the natural polymer having less ability to enhance the solubility of poorly water soluble drugs due its high viscosity and their hygroscopic nature. Herbal drug technologies have the drug utilization of phytoconstituents and bioactive contents in precise manner. In natural product research there is rekindling of discoveries of noval molecule. But there is limited therapeutic potential due to low solubility, bioavailability and instability associated with herbal. Exploration of solid dispersion provides various advantages including enhancement of solubility and bioavailability, protection from toxicity enhancement of stability, sustained release, protection from physical and chemical degradation etc.[2,3]

Solid dispersion is more suitable approach as compared to chemical approach for improving the solubility and bioavailability of drug. Salt formation is limited approach. For example, it is applicable only to the weakly acidic and basic drug and not applicable to neutral drug. In case of prodrug approach parent drug must have specific chemical groups like hydroxyl, carboxylic, amide etc otherwise it can't be converted into prodrug. Formulation approach involves particle size, size reduction, lipid base, solid dispersion, formation of molecular complex, pH adjustment, solubilization. Solid dispersion technique are more effective technique in particle size reduction with concomitant improvement in drug release as compared to micronization or milling process in which limited particle size up to 2 to 5µm. this is insufficient to improve the drug absorption in the small intestine. However the handling of more amorphous powder is very difficult due to their low mechanical properties like low flow, high adhsion and hygroscopic nature etc. solid dispersion are generally prepared by three different methods : 1) solid fusion method 2) fusion melt method and 3) hybrid-fusion method. Hence there is high potential for some important drugs should be formulated into solid dispersion which subsequently provides safe effective and convenient delivery of bioactive constituents in effective and controlled manner.

In 1995 amidon classified active pharmaceutical ingredients into four groups on the basis of their solubility and permeability called as biopharmaceutical classification system. These systems involve mathematical analysis to experimentally determine solubility and permeability of drugs under specified conditions. According to the USFDA i.e. food and drug administration, a drug is considered to be highly soluble when its highest clinical dose strength is soluble in <250 ml of aqueous media at pH range 1- 7.5 at 37.5 ºC. and if absorption of orally administered dose I humans is 90% then it is considered to be highly permeable.



Selection of carriers for Preparation[4]:

The choices of carrier have tremendous impact on solid dispersion. Following criteria should be considered during selection of carrier

- It should have High water solubility: it improves the wettability and enhance dissolution.
- Hugh glass transition time: it improves stability
- Minimal water uptake
- It should be soluble in common solvent with Drug-Solvent evaporation.
- It should have relatively low melting point: for melting process.
- It should be capable of forming solid solution with the drug.
- Particles should have higher porosity which influences carrier properties and increases the drug release profile.
- Drug should be in amorphous state which leads to enhancement in drug release and requires low energy as compare to crystalline state of drug.
- There should be conversion of liquid dosage form into solid form.

Limitations[4]:

- Moisture and temperature can affect the physical mixture of solid dispersion.
- Sometimes tackiness property of solid dispersion makes it difficult to handle.
- Large amount of carrier require achieving better dissolution.

- Many problems encountered during storage of solid dispersion such as phase separation, conversion of amorphous to crystalline form and due to crystal growth there is decrease in solubility.
- Method of preparation is expensive.

Classification[1]:

The type of solid dispersion and its dissolution behavior are strongly influenced by physicochemical properties of drug and carrier and the used production process.

Sr.No.	Types of SD	Matrix	Drug	Remark	No of phases
1	Eutectics	C	C	First type of SD	2
2	Amorphous precipitations in crystal matrix	C	A	Rarely encountered	2
3	Continuous	C	M	Miscible at all composition, never prepared	1
	Discontinuous	C	M	Partially miscible	2
	Substitutional	C	M	Molecular diameter of drug should be 5% differ from the carrier diameter. In that case drug and matrix are substitutional, can be continuous or discontinuous.	1 or 2
	Interstitial	C	M	Can be discontinuous only because molecular diameter of drug differ less than 59% of carrier diameter.	
4	Glass suspension	A	C	Particle size of solid dipsersion is related or depends on rate of cooling and evaporation . Obtained after crystallization of drug in amorphous matrix	2
5	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
6	Glass solution	A	M	it requires miscibility or solid solubility, complex formation or upon fast cooling or evaporation during preparation, many (recent) examples especially with PVP.	1

Method of preparation for Solid Dispersion[7]:

1. Solvent evaporation method
2. Melting / Fusion method
3. Kneading Technique
4. Co-precipitation method
5. Co-grinding method
6. Gel entrapment technique
7. Spray-Drying Method
8. Electro spinning
9. Freeze-drying
10. Supercritical fluid method
11. Melt Agglomeration Process
12. Lyophilisation Technique
13. Dropping method solution
14. Melt Extrusion Method

1. Solvent evaporation method:

In this method, the physical mixture of the drug and carrier 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. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

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, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

Modified solvent evaporation method:

Drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried.

2. Melting /Fusion method:

This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent

matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Advantage of melting method is that, it is economic and solvent less process, however this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at higher temperature. Some of the means to overcome these problems could be by heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

3. 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.

4. Co-precipitation method:

Required amount of drug is added to the solution of 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 in order to avoid the loss of the structure water from the inclusion complex.

5. Co-grinding method:

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 and mannitol solid dispersion was prepared by this method.

6. Gel entrapment technique:

Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

7. 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.

8. Electro spinning:

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. 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 (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged 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 If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

9. Freeze-drying:

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions. An important advantage of freeze drying is that, the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

10. Supercritical fluid method:

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO_2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The use of processes using SCF reduces particle size, residual solvent content, without any degradation and often results in high yield.

11. Melt Agglomeration Process:

The utility of the surfactant systems in solubilisation is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilisation, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.

12. Lyophilisation Technique:

Lyophilisation involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

13. Dropping method solution:

The dropping method, developed by 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 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 solvents and, therefore, has none of the problems associated with solvent evaporation.

14. Melt Extrusion Method:

Solid dispersion by this method is composed of active ingredient and carrier, prepared 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 pellet.

Effect of hydrophillic and hydrophobic polymer on the dissolution of drug:

In recent years there are number of research are carried out, (hai van ngo, toi wei duan, et al.) in this study they used blend of hydrophilic and hydrophobic polymer which both play an important role in influence of dissolution rate of Isradipine while hydrophobic polymer (zein) play both role in inhibition of crystal growth and also helps to increase the dissolution rate. Hydrophobic polymer helps to change the crytal structure into amorphous form that ultimately affect the particle size i.e. reduction in particle size increases the surface area of the particle which helps to increase the rate of dissolution.[8]

Hydrophobic polymers are soluble in organic solvents and practically insoluble in aqueous media, from this study they conclude that both blend of hydrophilic and hydrophobic polymers play important role in modulation of crystalline changes and also they are fairly compatible with each other. Blend of hydrophilic and hydrophobic polymer is recent technique which can be used in the solid dispersion for increase the dissolution rate of drug.

Hydrophilic polymers are a major area of polymer research with prominent fields of application, e.g., in drug delivery[11], self-assembly[12,13], or catalysis[14]. As such, studies regarding hydrophilic polymers are an important part of polymer science. Especially investigations on structure-property relationships of hydrophilic polymers as well as interactions of hydrophilic polymers or the combination with biological entities are a key research area[15,16]. Here, synthetic polymer chemistry opens up new opportunities via novel water-soluble polymer types, architectures or combinations for advanced properties and future applications. Hydrophilic polymers not only feature significant properties in the dissolved state, but also as cross-linked materials, namely in hydrogels. This class of materials presents various interesting properties and tailored shape and size, which is of major interest for biomedical applications as well.[16,17]

Strategy to avoid recrystallization:

Recrystallization is the main disadvantage of solid dispersions. while amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization.

Molecular mobility is a key factor leading the stability of amorphous phases[18], because even at very high viscosity, below the glass transition temperature (Tg), there is sufficient mobility for an amorphous system to crystallize over pharmaceutically relevant time scales,[19,20] In addition, it was postulated that crystallization above Tg would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the suitable conformation, and by the mobility, because this was related to the number of collisions per unit time.

A number of experiments have been carried out to understand the stabilization of solid dispersions. current studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and finding the sub-glass transition beta-relaxation as well as alpha-relaxation[21], which may lead to nucleation and crystal growth[21]. Molecular mobility of the amorphous system depends, not only on its composition, but also on the manufacturing process as declared by Bhugra et al[30]. Solid dispersions exhibit high conformational entropy and lower molecular mobility are more physically stable[19].

Polymers improve the physical stability of amorphous drugs in solid dispersions by increasing the Tg of the miscible mixture, so reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs[20,23]. Meant for a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug[24,25]. For complete miscibility, interactions between the two components are necessary. It is predictable that the majority of drugs contain hydrogen-bonding sites[21], therefore, several studies have shown the formation of ion–dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the interruption of the hydrogen bonding pattern quality to the drug crystalline structure[23] These lead to a higher miscibility and physical stability of the solid dispersions[25,26,27]Specific drug polymer interactions were observed by Teberekidis et al[28], showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions.

Further studies have shown stabilization in systems where hydrogen- bonding interactions are not possible, because of the chemistry of the system [28]. Vippagunta et al[27] concluded that fenofibrate does not exhibit specific interactions with PEG, independent of the number of hydrogen bonds donating groups presented[27]. The same conclusion was achieved by Weuts et al.[29] in the preparation of solid dispersions of loperamide with PVP K30 and PVP VA64, in which, hydrogen bonds were no absolute condition to avoid crystallization.

Considerations during Dissolution

The vehicle composition of formulation is important. Tween 80 at a concentration of 0.2%–0.5% is usually used as a wetting agent in suspensions of crystalline material. though, it reduced the drug release and led to precipitation in a short period of time in the case of an LCQ789 ASD suspension,48 which is consistent with the authors' observations with other research compounds (unpublished data). In another study, Tween 80 at a concentration of 10% was added in an ASD suspension. Formulation because it provided significant solubility improvement for the neat crystalline compound. It was likely that Tween 80 would act like parachute to delay precipitation from the supersaturated solution of ASD. Astonishingly, the solid dispersion crystallized after 3 h in the media with Tween 80, whereas it was stable for more than 6 h when Tween 80 was not present.[31]

When an ASD is dosed at low concentrations, suspending agents, such as methylcellulose, may need to be added.5 though, when ASD is dosed at high concentrations, water or buffer without suspending agent may be used as the amount of polymer released from the ASD can provide as a suspension agent. Water was selected to suspend the LCQ789 ASD, which facilitated formulations of 10, 50, and 120 mg/mL of ASD.[32] When the compound is pH sensitive or the polymer solubility is pH dependent, the pH of the

suspension vehicle and the buffer composition should be carefully selected. The preparation should avoid energetic mixing as it can accelerate reversion to a crystalline form. The powder can be effectively wetted first by adding a minimal amount of suspension vehicle and stirring gently with a spatula.

The dissolution temperature of an ASD formulation is important too. It should be set close to physiological temperature. Although equilibrium solubility increases with elevated temperature and the solubility difference between 25°C and 37°C is usually minimal,[33,34] the solubility of a neat amorphous compound or ASD may decrease with increased medium temperature because crystallization onset may be earlier, crystallization rate may be faster, amorphous material agglomerates may be more extensive, and crystalline precipitation from supersaturation may also occur sooner.[35] Therefore, dissolution at a biologically relevant temperature is necessary for ASD-based formulations, whereas dissolution at room temperature can be acceptable for dosage forms containing crystalline phases.

Conclusion

As from this review, it is comprehensible that the solid dispersion technology is one of the advanced approaches to determine the problem of solubility of poorly water-soluble drugs. So, proceeding to developing a new solid dispersion system for a given drug, it is essential to examine the physio-chemical properties of the drug and carrier that can best fit with each other. Also, the method of preparation and the ratio of carrier to drug also play a vital role in the solubility/dissolution rate enhancement of drug. We have attempted in bringing all the things in progression in this article that how to furnish all these aspects to achieve this goal. So in the novel drug delivery applications, solid dispersion technology will continue to develop in future and solve problems associated with the delivery of poorly water soluble drugs.

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