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A REVIEW ON SOLID DISPERSION: A SIMPLE AND EFFECTIVE METHOD TO IMPROVE SOLUBILITY OF DRUGS

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Abstract

The oral route is the major route of drug administration to patients. But many of the drugs have limited oral administration due to their poor solubility. Solubility is one of the important factors that affects the dissolution rate and bioavailability of the drugs. Solid dispersion is a simple and effective method for improving the solubility of poorly soluble drugs and increasing its bioavailability.

Keywords: Solid dispersion, Solubility, Bioavailability

Introduction

The oral route of drug administration is most preferred due to ease of convenience and patient compliance. But the major challenge in oral drug bioavailability is the poor solubility of drugs, which leads to decreased dissolution rate and drug absorption. Large doses of drug are needed to get the desired action of the drug and it may also lead to toxicity. This can be overcome by enhancing the solubility, which results in increased dissolution rate and absorption, there by increasing the bioavailability of the drug [1].

Solid dispersion is one of the simple and effective methods for improving the solubility of poorly soluble drugs. Formulation of drug as solid dispersion is more flexible and which offers various processing methods and excipient options [2].

Solid dispersion (SD)

Solid dispersion is the process in which one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid state are prepared by using different methods such as the melting (fusion), kneading, solvent evaporation and melting-solvent method [1].

Advantages of solid dispersion [1]

- Enhance solubility and bioavailability of poorly water soluble drugs
- Easy to produce and more applicable
- Rapid dissolution leads to increased rate and extent of absorption of drugs
- Transformation of liquid form of a drug into solid form
- Enhance wettability of drugs
- Reduce particle size of the drugs
- Improves porosity of the drugs
- Used to mask bitter taste of the drugs
- Converts crystalline form of drug into amorphous form
- Reduce aggregation and agglomeration of drug particles

Disadvantages of solid dispersion [1]

- Instability with ageing
- Difficulty in handling due to tackiness
- Temperature and moisture can deteriorate solid dispersions than physical mixtures
- Moisture absorption leads to phase-separation, converts amorphous form into crystalline form and leads to decreased solubility
- Difficult to merge dosage forms into the formulation

Types of solid dispersions

Solid dispersions can be classified into two:

1) Based on the carrier used
2) Based on the molecular arrangement

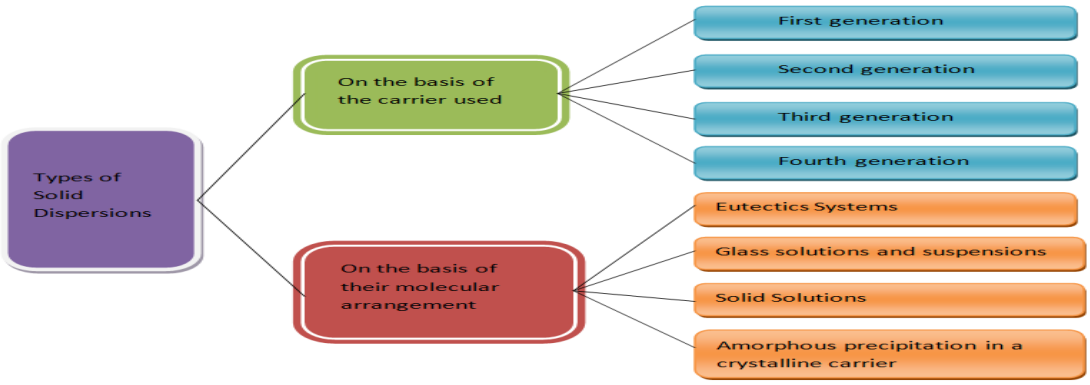

Figure 1 Schematic representation of the solid dispersion types [3]

Based on carrier used [4]

i. **First generation:** Crystalline carriers such as urea and sugars are used in this generation. They are thermodynamically stable, but the drug release is slower than that of amorphous forms.

ii. **Second generation:** These are prepared by amorphous carriers and are usually polymers. The polymers could be following:
   a) Synthetic polymers: Polyethylene glycols (PEG), polyvinyl pyrrolidine, polymethacrylates and povidone.
   b) Natural-based polymers: Ethyl cellulose, hydroxyl propyl methyl cellulose (HPMC). Starch derivatives such as cyclodextrins and hydroxyl propyl cellulose.

iii. **Third generation:** Carriers with surface active properties are used to enhance the dissolution profile. Increased *in-vivo* bioavailability has been revealed by various surface active agents such as poloxamer 407, gelucire 44/14, compritol 888, ATO and inulin.

iv. **Fourth generation:** These are controlled release solid dispersions. It contains poorly water soluble drugs having short biological half-life. The carriers used may be water soluble or water insoluble. Ethyl cellulose, eudragit and hydroxypropyl cellulose can be used as water soluble carriers. Solubility enhancement and extended drug release in a controlled manner are the two main objectives of controlled release solid dispersions.

Based on molecular arrangement [1, 4]

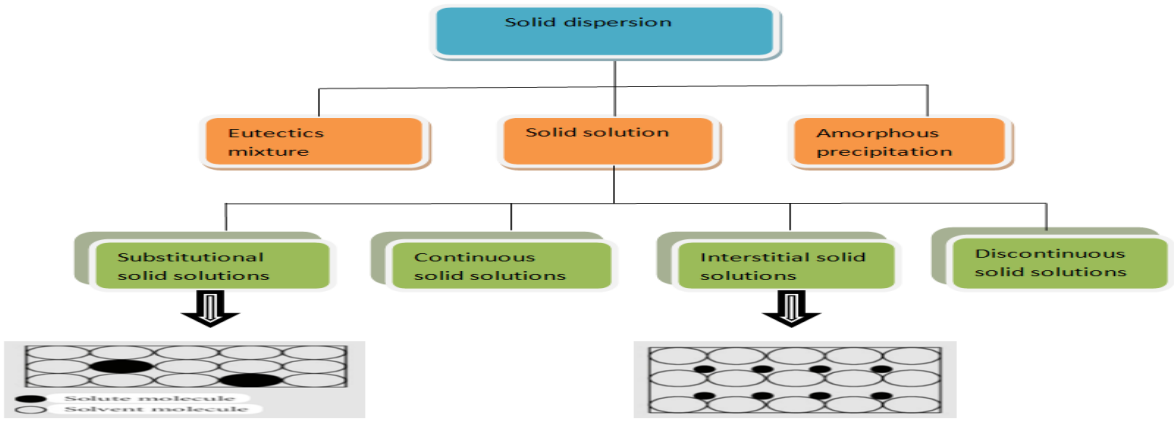

Figure 2 Classifications of solid dispersion [5]

i. **Eutectics systems:** This is a mixture of two compounds in liquid state and are completely miscible, but only a very limited extent in the solid state. The two compounds are melted and rapid solidification of the fused melt gives a product which is completely liquid miscible and a very small solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of two crystalline compounds.

ii. **Glass solution and suspensions:** Glass solutions are homogeneous glassy system contains a solute which is dissolved in a glass carrier. Glass suspensions contain precipitated particles which are suspended in a glass solvent. These systems have low lattice energy and they do not have a sharp melting point. Urea, citric acid, PEG, PVP, sugars such as sucrose, dextrose and galactose are some examples of carriers that form glass solutions and suspensions.

iii. **Solid solution:** In this system, a single homogeneous phase system is formed by the simultaneous crystallization of two components. The particle size of the drug is reduced to its molecular size in the solid solution, and a rapid dissolution rate is obtained than the corresponding eutectic mixture. The solid solution can be classified into two;
   - Based on the level of miscibility of two compounds (continuous or discontinuous)

- Based on how the solvate molecules are circulated (substitutional or interstitial)

a) **Continuous solid solutions:** In this system, the components in all proportions are miscible. Hypothetically it reveals that higher the bonding strength between two components than the bonding strength between molecules of each individual components.

b) **Discontinuous solid dispersions:** The solubility of each component in the other component is limited in discontinuous solid dispersion.

c) **Substitutional solid solutions:** Substitution is possible only when the variability in size of solute molecule is less than 15% or so from the solvent particles.

d) **Interstitial solid solutions:** The interstitial space between solvent molecules in the crystal lattice is occupied by the soluble particles. So the diameter of the solute molecule should be less than 0.59 times than that of the diameter of the solvent molecule and also the volume of solute molecule should be less than 20% as that of solvent molecule.

iv. **Amorphous precipitation in a crystalline matrix:** In the crystalline carrier, instead of simultaneous crystallization of the drug and the carrier (eutectic system), the drug may also precipitate in an amorphous form. Higher energy of drug in the amorphous state produces much greater dissolution rate than the corresponding crystalline form of the drug.

The different solvents used in SD (table no.1) and different carriers used in SD (table no.2) are given below.

Solvent	MeltingPoint (°C)	Boiling Point (°C)	Vapour pressure at 25°C (pka)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Acetic acid	17	118	1.64
1-propanol	-85.8	97.4	2.27
2-propanol	-127	82.4	5.85
1,4-dioxane	12	102	4.92
DMSO	19	189	0.08
Chloroform	-63	62	26.1

Table no.1 Different solvents used in solid dispersions [6]

Sl No.	Category	Carriers
1	Sugars	Dextrose, sucrose, maltose, lactose, galactose, sorbitol, mannitol, xylitol
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), cyclodextrin, pectin, hydroxyl ethyl cellulose, hydroxyl propyl cellulose
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragit L 100, eudragit E100, eudragit RS, eudragit RL
5	Surfactants	Poloxamer188, tweens, spans, deoxycholic acid, polyoxyethylene stearate
6	Miscellaneous	Urea, urethane, hydroxyl alkyl xanthins, pentaerythritol, pentaerythrityl tetraacetate

Table no.2 Different carriers used in solid dispersions [7]

Methods of Preparation [4]

There are various methods for the preparation of solid dispersion and it is difficult to predict the best method which improves the solubility of a poorly water soluble drug. The method is selected based on some factors such as hydrophilicity-hydrophobicity balance of the drug, molecular weight of the drug and the drug dose. So, a trial and error method is the best approach to select a suitable method that improves the solubility of the drug.

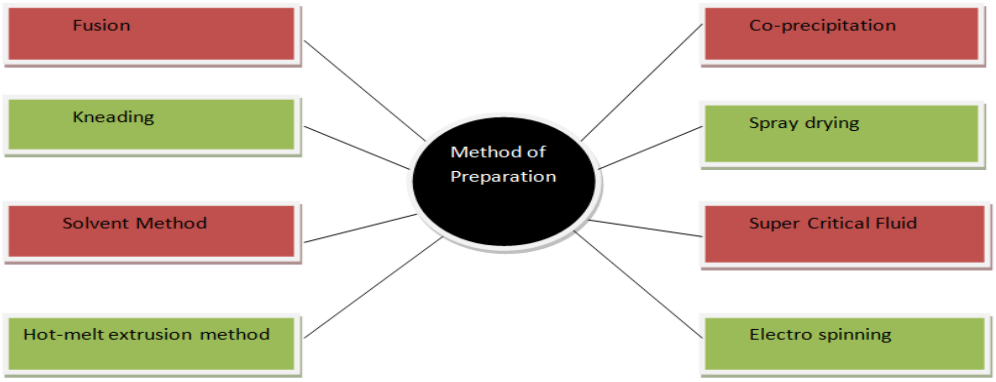

Figure. 3 Various methods of solid dispersion preparation

1) **Fusion**

This method is also known as melt method and was proposed by Sekiguchi and Obi in 1961. In this method, the physical mixture of drug and polymer is heated to get a molten mass. Then it is allowed to cool and harden with vigorous stirring. The solid mass is then crushed, pulverized and sieved to get the desired particle size. This method is more popular, but the lack of drug-polymer miscibility at the heating temperature is the major drawback. But this issue can be avoided by the use of surfactants. In addition, the drugs and polymers should be thermally stable at melting temperatures, lower production temperatures are preffered, and the fused mixture should not undergo recrystallization or phase separation.

SD of spironolactone was developed by using an inert carrier PEG 4000 by fusion method and the solubility was increased from 23.54±1.75µg/ml (pure drug) to 61.73±1.26µg/ml (SD) [8].

2) **Kneading method**

Accurately weighed drug and carrier are transferred into a glass mortar and the mixture is wetted with the dropwise addition of a solvent (water or hydroalcoholic mixture) and is kneaded or triturated with the pestle. The kneading action results in the formation of a slurry and also leads to reduced particle size and increased bioavailability of the drug. The mixture is then dried and passed through the mesh to get content homogeneity.

The dissolution rate of meloxicam was increased by making SD using hydrophilic polymer poloxamer 188 [9].

SD of valdecoxib was prepared using PVP K 30 by kneading method. These are used to prepare fast-dissolving tablets of valdecoxib by using large amounts of superdisintegrants results in greater dissolution profile than commercial tablets [10].

3) **Solvent method**

In this method, both the drug and the polymer are mixed in a single solvent and then the solvent is removed to form a solid dispersion. This method offers molecule-level mixing, which results in the increased solubility and stability of the product. Thermal degradation of the drug and polymer can be avoided by this method, which is usually occurs when the organic solvent is evaporated at lower temperatures. However there are certain issues we have to face while performing this method. The major one is the mixing of drug and polymer in a common solvent. It will be very difficult if there is a large difference in polarity. Surfactants can be used to avoid this issue, but there is a chance of higher amount of surfactant in the final dosage form. It may lead to decreased drug loading capacity and cause problems if they are not well tolerated in the body. It is necessary to evaporate the amount of solvent from the system, which makes it as a costly process. The other major issue is the phase separation, which happens during solvent removal. Drying of solution is commonly attained by vacuum drying and, in some cases, rotary evaporators are also used to get rapid drying. The higher drying temperature leads to increased molecular mobility of drug and polymer, which results in accelerated phase separation.

SD of ibuprofen was prepared using PEG 20000 and poloxamer 407 in different ratios by fusion and solvent evaporation method. Formulations with mixture of hydrophilic carriers showed better dissolution than the individual carriers. Formulation (SDF9) prepared by solvent evaporation showed faster and greater drug release when compared to other formulations [11].

4) Hot-melt extrusion (HME) method

Hot-melt extrusion is an advanced form of fusion method and here the intense mixing of components is done by the extruder. This method has a major advantage over traditional fusion methods: the potential to transform the molten drug-polymer mixture into pellets, implants, and oral dosage forms. The complete miscibility of the drug and polymer in the molten state is a must requirement for this method. The rational selection of compatible polymer and prediction of miscibility can be done by using solubility parameter phase diagrams. The other advantages of hot-melt extrusion method are follows:

- Minimum processing stages because there is no compression of components or drying of products. Therefore, it is an easy, efficient and continuous process.
- Uniform drug particle distribution in the polymer matrix and molecular level dispersion can be achieved by the disaggregation of particles mixed at greater shear rate and temperature.
- It offers continuous manufacturing than traditional fusion method, hence it is suitable for large-scale manufacturing. Widely used polymers in hot-melt extrusion are PVP, HPMC, HPMCAS, vinyl acetate and polyethylene oxide.

Bitterness and solubility problems of azithromycin pediatric preparations can be avoided by eudragit RL PO combined with HME [12].

5) Co-precipitation method (Co-evaporate)

The drug and carrier are weighed accurately. Then the drug is dissolved in an organic solvent and carrier is dissolved in water. After complete dissolution the aqueous carrier solution is transferred into the organic drug solution. Then the solvents are ejected and the dispersion is grinded by a mortar and pestle. Then the powder sieved and dried.

Co-precipitation method has been used to produce amorphous SD of posaconazle having thermal instability and limited solubility [13].

Neil A. Strotman and Luke Schenck studied the opportunities and challenges of co-precipitated amorphous dispersions as drug substance [14].

6) Spray drying

Spray drying is a well known method for making SD of drugs. It is a single step process in which a liquid or a suspension is converted into a dry powder. The method involves more precise control over process factors and which results in powder characteristics such as proper shape, size, density, crystalline forms and flow characteristics. The rapid rate of solvent evaporation leads to greater viscosity and trapping of drug molecules in the polymer matrix. If the poorly water soluble drugs are soluble in some spray-drying solvent, then they can be spray dried into very fine particles. The nature of the prepared solid particles depends on the chemical properties of the drug. Amorphous material, crystalline forms, metastable crystals, or imperfect crystals are formed due to spray drying.

SD of gefitinib prepared by spray drying using HPMC, PVP and eudragit S 100 shows improved mucoadhesive and dissolution properties of the drug [15].

Kaushika Patel et al performed the *in-vitro* and *in-vivo* study of a novel posaconazole oral formulation using spray dried SD [16].

7) Supercritical Fluid (SCF) Method

The supercritical fluids have both liquid and gas characteristics. The materials under supercritical conditions show liquid-like solvent characteristics and gas-like viscosity, diffusivity, and thermal conductivity. The solvent characteristics help in drug / polymer solubilization and the gas-like characteristics increase the fluid mass transport characteristics. This method is widely performed by using supercritical carbon dioxide (CO_2) as a medicine and polymer solvent or used as an antisolvent. In supercritical CO_2, the drug and polymer are dissolved and passed through a nozzle into a low pressure zone, which leads to adiabatic CO_2 expansion and rapid cooling. Therefore, fine particle sizes of the drugs are obtained. This technique is usually known as the rapid expansion of supercritical solutions (RESS). SCF method has the capability to produce nanoparticulate suspensions of particles within 5-2000nm. There is no need for organic solvent and the trace amount of CO_2 trapped inside the polymer does not lead to any harm to the patients. Hence, this method can be called environmental friendly. Propensity of CO_2 to plasticize and swell polymers can also be obtained. But many of the drugs have restricted solubility in CO_2, which limits the use of this technique. Precipitation with a compressed antisolvent, SCF enhanced dispersion, aerosol supercritical extraction system, supercritical antisolvent processes, and gas antisolvent recrystallization are some of the SCF processing techniques to enhance solubility.

SD of albendazole was prepared using Kollidon V A64 by the optimized SCF process. It showed an increased solubility and dissolution at both pH 1.2 and 6.8 [17].

SD of nifedipine was prepared using PVP K30 by SCF technique and the *in-vitro* and *in-vivo* results were combined with SD obtained by kneading method [18].

8) Electrospinning method

This method is widely adapted in polymer industry by incorporating solid dispersion technique into nanotechnology. In this method, a liquid stream of drug / polymer is subjected to a voltage range of 5-30Kv. When the electrical forces is greater than the surface tension of the drug / polymer solution at an air contact, submicron diameter sized fibres are formed. The formed fibres are gathered on a screen to form a woven fabric, or they can be grouped together on a spinning mandrel as the solvent evaporates. Various factors which affect the fibre diameter are surface tension, feeding rate, dielectric constant, and electric field strength. This method is used for the manufacturing of nanofibers and controlling the release of drugs due to its simplicity and cheapness.

SD for poorly soluble drugs is prepared in the form of core-sheath nanofibers by using a coaxial electro spinning process. Different functional groups can be attached in different positions in the core-sheath nanofibers and it gives a unique and specific characteristics for the nanofiber system. The nanofiber

structure has the capacity to increase the dissolution and permeation of a series of poorly water soluble drugs and it could be a novel oral drug delivery system for the future [19].

Dissolution rate of piroxicam was improved by electrospinning technique as a result of electrospun nanofiber formation using PVP [20].

Characterization of solid dispersion [1]

The solid dispersion is characterized by the following different techniques.

1) **Fourier Transform Infra Red Spectroscopy (FTIR)**
   FTIR spectroscopy can be used to find the drug polymer interactions by using conventional KBr pellet method.
2) **Differential Scanning Calorimetry (DSC)**
   DSC is a famous technique which determines heat flow into or out as a function of time or temperature. It can measure crystallinity of the material by quantifying the heat associated with melting (fusion).
3) **Differential Thermal Analysis (DTA)**
   DTA measures the temperature difference between sample and a thermally inert reference material as a function of temperature. If there is any difference in sample temperature to that of the reference, it shows any transition of the sample, which leads to liberation or absorption of energy by the sample. A small amount of sample about 1mg is used for analysis. The graph of differential temperature against programmed temperature shows that the transition temperature is exothermic or endothermic. An increased temperature range is allowed for preparing highly reproducible phase diagram. Higher resolution is an important advantage of this method.
4) **Thermo-Microscopic Methods**
   Here, a hotstage microscope is employed for the detection of phase diagrams of the binary systems. Approximately about 1mg of the dispersion or physical mixture is heated on a slide at a rate of 1-5ºC per minute. By visual examination, the thaw and melting points are determined. This technique needs only a few amount of samples, but it is not applicable to thermolabile substances.
5) **Scanning Electron Microscopy (SEM)**
   SEM is performed to find the morphology, particle size and sometimes the polymorphism of the drug. Carrier matrix with fine dispersion of drug particles may be visualized by this technique. The electron microscope technique is only applicable to chemicals with high resolution.
6) **X-ray Diffraction (XRD)**
   XRD is an essential and efficient technique for identifying the physical nature of solid dispersions. Nowadays, this method is also applied in binary eutectic systems. A marked difference in the spectra or lattice parameters of the pure drug indicates the compound or complex formation. The major disadvantage of XRD is that, when the lattice parameter of the solvent component is unchanged, it mostly fails to differentiate amorphous precipitation from molecular dispersion.
7) **Dissolution Studies**
   It is performed to identify the rate and extent of dissolution. The dissolution study of SD was carried on USP-type 11 paddle apparatus at 37±0.2ºC. The drug was dispersed in the dissolution medium and the sample was collected at specific time periods. An equal amount of fresh media is replaced on each sample collection. Then the sample was filtered and analyzed for drug content by measuring the absorbance at suitable wavelength using UV Spectrophotometer.

Applications of solid dispersion [7]

- Stabilization of unstable drugs against oxidation, hydrolysis, isomerisation, photo oxidation and other decomposition processes
- Dispense liquid or gaseous compounds in a solid dosage

- To formulate fast release primary dose in a sustained release dosage form
- Sustained release of soluble drugs by incorporating with a poorly soluble or insoluble carriers
- To get a homogeneous distribution of small amount of drug in solid state
- Solubility enhancement of poorly soluble drugs by enhancing dissolution rate, absorption and bioavailability
- Reduction of pre systemic inactivation of certain drugs
- Reduction of side effects of certain drugs
- The unpleasant taste and smell of the drugs can be masked
- Avoid undesirable incompatibilities
- Enhancement of drug release from creams, ointments, and gels.

Limitations of solid dispersion [1, 4]

- Difficult to scale-up the manufacturing process
- Stability of the drugs and vehicles
- Method of preparation is laborious and expensive
- Incorporation into dosage forms is difficult
- Reproducibility of physicochemical characteristics
- Storage instability such as crystallization or recrystallization

Conclusion

SD techniques have been proved as an essential method for enhancing the solubility of poorly soluble drugs. But their commercial application is minimum due to some limitations such as manufacturing difficulties and stability issues. Some of the limitations such as incorporation of solid dispersion into formulation of dosage form have been recently overcome by some methods such as spraying on sugar beads and direct capsule filling. By the introduction of some alternative methods, we can resolve the remaining limitations also and the manufacturing of solid dispersion becomes practically feasible.

There should be a need for further study and development in the field of solid dispersion technique in order to avoid limitations and to enhance the solubility of poorly soluble drugs.

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