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A Comprehensive Review on Solid Dispersion Technique to Enhance the Solubility and Bioavailability of Poorly Water-Soluble Drugs

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ABSTRACT:

The majority of the time, oral administration of medications to patients is chosen. However, many medications have limited uses in oral delivery due to their low solubility. In the pharmaceutical industry, improving a drug's water solubility is a primary goal. One of the most crucial elements affecting bioavailability and dissolution rate is solubility. By using different polymers, the solid dispersion approach improves the bioavailability and dissolution rate of poorly soluble medicines. In this review, techniques for solid dispersion were examined, along with the characterization of solid dispersions.

Introduction:

The majority of the time, oral administration of medications to patients is chosen. However, many drugs' limited usage in oral administration is a result of their low solubility. Poor solubility primarily affects the rate of medication dissolution and bioavailability. According to solubility and permeability, the medications were divided into four categories by the Biopharmaceutical Classification System (BCS). Drugs that correspond to BCS classes II and IV have poor solubility issues. Enhancing the solubility of these medications that belong to BCS II and IV

is the hardest difficulty. Several methods are employed for this goal, including solid dispersion, particle size reduction (Micronization and Nanonization), salt production, pH adjustment, polymorph and pseudo-polymorph formation, the complexation method, and the use of a surfactant and co-solvent.

Types of solubility:

The ability of a chemical compound known as a solute to dissolve in a solid, liquid, or gaseous solvent and create a homogenous solution of the solute in the solvent is known

as solubility. Fundamentally, a substance's solubility is influenced by the solvent being employed, together with temperature and pressure. When more solute is added, its concentration in the solution does not rise, this is known as the saturation concentration, and it indicates how much of a material is soluble in a certain solvent.¹ The majority of the time, oral administration of medications to patients is chosen. However, many drugs' limited usage in oral administration is a result of their low solubility. Poor solubility primarily affects the rate of medication dissolution and bioavailability. According to solubility and permeability, the medications were divided into four categories by the Biopharmaceutical Classification System (BCS). Drugs that correspond to BCS classes II and IV have poor solubility issues. Enhancing the solubility of these medications that belong to BCS II and IV is the hardest difficulty. Several methods are employed for this goal, including solid dispersion, particle size reduction (Micronization and Nanonization), salt production, pH adjustment, polymorph and pseudo-polymorph formation, the complexation method, and the use of a surfactant and co-solvent.

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Table 1: Solubility criteria as per USP and BP¹

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 and over

Absolute/Intrinsic solubility: Absolute or intrinsic solubility is the highest quantity of solute that may dissolve in a particular solvent under a certain set of temperature, pressure, and pH circumstances. It has a static value.

Saturated solubility: the most solute that can be dissolved in a given solvent before it becomes saturated. The solvent will not dissolve more solute.

The significance of solubility²

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of

dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug product.²

However, the major challenge with the design of oral dosage forms lies in their poor bioavailability. Oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role in other dosage forms like Parenteral formulations as well.³ Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for achieving the required pharmacological response. Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% of NCEs (New Chemical Entities) developed in the pharmaceutical industry are practically insoluble in water.⁴ These poorly water-soluble drugs having slow drug absorption lead to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. The problem of solubility is a major challenge for formulation scientists.⁵ The improvement of

drug solubility thereby its oral bioavailability remains one of the most challenging aspects of the drug development process, especially for oral-drug delivery systems. There are numerous approaches available and reported in the literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as the properties of a drug under consideration, the nature of excipients to be selected, and the nature of the intended dosage form. The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.⁶

As for BCS class II drugs rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.⁷

Biopharmaceutical classification system (BCS)⁸

The Biopharmaceutical Classification System (BCS) was created by Amidon et al. A drug's three main factors that affect absorption—solubility, dissolution rate, and permeability—determine its BCS classification. Drugs were categorized by BCS into one of the following 4 groups: Table 2.

Table 2: BCS Classification of Drugs⁹

Class	Permeability	Solubility	Examples
Class I	High	High	Diltiazem,
Class II	High	Low	Nifedipine, naproxen
Class III	Low	High	Insulin, metformin,
Class IV	Low	Low	Taxol, chlorthiazide

Techniques for improving the solubility of poorly water-soluble drugs⁹

Drug solubility and dissolution rates can be increased by a variety of methods, which can be divided into two categories: physical alterations and chemical changes to the drug ingredient.

Reduction of particle size: A drug's solubility is inextricably linked to the particle size. When a drug's particle size is decreased using a variety of techniques, such as a jet mill, rotor-stator colloidal mill, ball mill, etc., the drug's surface area increases, resulting in improved solubility. However, this technique has limitations, including heat and physical stress on the medicinal product that causes deterioration. Other drawbacks include the restricted ability to regulate crucial end-product attributes including form, size, morphology, surface features, and electrostatic charges. Also, thermodynamically unstable and prone to recrystallization are amorphous regions.^{10,11}

Nanosuspension technology: The development of nanosuspension technology makes it a viable contender for the efficient delivery of poorly water-soluble drugs. It is a surfactant-stabilized sub-micron colloidal dispersion of pure medication particles for topical, oral, parenteral,

or pulmonary delivery. Particle sizes in nanosuspension typically range from 200 to 600 nm, or less than one micron.^{11, 12} There are several ways to prepare a nanosuspension, including media milling, high-pressure homogenization in water, high-pressure homogenization in a non-aqueous medium, and combinations of precipitation and high-pressure homogenization.^{13,14} For a number of medications, such as tarazepide, atovaquone, and amphotericin-B, nanosuspension techniques have been used.¹⁵

Surfactant: Surfactant has been effectively used to increase the solubility of drugs that are poorly soluble. Using a variety of co-solvents and surfactants, Seedhar N et al.¹⁶ investigated how to boost the solubility of enrofloxacin by up to 26 times. Castor oil, lauroylmacroglycerides, and the di-fatty acid ester of low molecular weight polyethylene glycol are examples of frequently used non-ionic surfactants.

Salt formation: The rate at which a certain salt dissolves often differs from that of the parent chemical. In comparison to pure salt, the sodium and potassium salts of weak acids dissolve more quickly. Epigastric discomfort brought on by excessive alkalinity, precipitation as a result of reactivity with air water, and carbon dioxide, and patient compliance are some of the factors limiting salt production.¹⁷

pH adjustment: A pH shift might potentially cause a poorly water-soluble medicine to dissolve in water. The buffer capacity and tolerability of the chosen pH are crucial factors to take into account in order to access the solubility of this technique. The solubility of that medicine is increased by excipients that are soluble and raise the pH of the environment inside the dosage form to a range higher than the pKa of weakly acidic pharmaceuticals. Similarly, excipients that function as alkalizing agents may raise the solubility of weakly basic drugs.¹⁸

Hydrotrophy: A solubilization phenomenon known as hydrotrophy occurs when sodium benzoate, urea, sodium citrate, and sodium salicylate are used to significantly increase the solubility of drugs that are weakly soluble in water.¹⁹ In the presence of nicotinamide and similar chemicals, Rasool AA et al. found that various medicines, including diazepam, griseofulvin, testosterone, progesterone, and 17-estradiol, had improved solubilities.

Solid dispersion: To improve the dissolution and oral absorption of medications that are poorly water-soluble, Sekiguchi and Obi used solid dispersions for the first time in 1961. This process involves dissolving the poorly soluble medication and carrier in an organic solvent, which is then evaporated to produce a solid powder. Soluplus, Poloxamer, HPMCAS, HPMC, and PVP K30 are just a few examples of different polymers that are used, along with water-soluble and water-insoluble ones.²⁰

The mechanism responsible for solubility enhancement from solid dispersion: A number of approaches may be modified to increase the solubilization of poorly water-soluble drugs and further improve their bioavailability. This is the mechanism responsible for solubility enhancement from solid dispersion.

Reduction in particle size

The carrier dissolves when the solid dispersion is exposed to watery solutions, and the medication releases tiny colloidal particles. Poorly water-soluble medications dissolve more quickly due to the increased surface area.²¹

Drugs in an amorphous state

Drugs that are poorly soluble in water and are crystalline in nature often have a greater solubility.²² This is due to the fact that during

dissolution, no energy is needed to break the crystal lattice in its amorphous state.

Highly porous particles

High porosity has been discovered in solid dispersion particles.²³ The medication release profile is accelerated by the solid dispersion particles' enhanced porosity. Porosity increases depending on the characteristics of the carrier; for example, linear polymers produce bigger, more porous particles than reticular particles.

Particles with improved wettability

The improvement in drug wettability has been shown to have a significant impact on the improvement of drug solubility in solid dispersion.²⁴ The wettability property of a medicine can be considerably increased by a carrier with surface activity, such as cholic acid or bile salt, which improves the dissolving profile.

Classification of solid dispersion: Solid dispersion is classified in 3 groups;

First-generation solid dispersions

The creation of eutectic mixtures or molecular dispersion boosted the rate of drug release in first-generation solid dispersion, increasing the bioavailability of weakly water-soluble medicines. The crystalline solid formulation's disadvantage is that the medicine does not release immediately. Urea, sugars, and organic acids are examples of crystalline carriers.²⁵

Second-generation solid dispersions

In the second generation, we utilize amorphous carriers to enhance drug release, similar to completely synthetic Polymers Povidone (PVP), polyethylene glycols (PEG), and polymethacrylates should all be mentioned. cellulose derivatives, such as Hydroxypropyl Methylcellulose (HPMC), ethyl cellulose, or hydroxypropyl cellulose, or starch derivatives, such

IJPPR (2023), Vol. 14, Issue 3

as cyclodextrins, make up the majority of natural product-based polymers.²⁶

Third-generation solid dispersion

In the third generation, we employ carriers with self-emulsifying and surface activity. The surfactants increase the drug's solubility by lowering the rate of recrystallization. Examples include Poloxamer 408, Tween 80, and Gelucire 44/14, which are surface-active self-emulsifying carriers.²⁷

Types of solid dispersion²⁸:

There are three different forms of solid dispersion, which are as follows:

There are two stages in this type: medication and polymer.

Ternary Solid Dispersion

There are three phases of this type: medication, polymer, and surfactant. The most common surfactant employed is Polysorbate 80.²⁹

Dispersion on Solid Surfaces

In this kind, the medication is applied to the polymer's surface, which reduces the drug's particle size and increases its solubility.

Methods of Solid Dispersion: A number of solid dispersion techniques are used to increase the solubility of drugs that aren't very soluble, and they include the following:

Solvent Evaporation Technique³⁰: This procedure involves dissolving the polymer and the medication, both of which have poor solubility issues, in a suitable organic solvent such as dichloromethane, acetone, or chloroform to create a homogeneous liquid. It is then dried using an organic solvent, and the dried mass is then ground into a dry fine powder using a mortar and pestle.

Hot Melt Extrusion Technique³¹: This method involves mixing the medication and the polymer

Review Article

before feeding it into a single screw hot melt extruder. The combination melts and produces extrusions as a result of the heat. It is then triturated to create a powder.

Using the spray drying technique^{32,33}: In this procedure, the medicine and polymer are dissolved in an organic solvent and sprayed into the heated chamber through a nozzle. Due to the high temperature, a solvent is evaporated to get the finest-size particles of powder.

By using the lyophilization technique:³⁴ The process of lyophilization relies on the straightforward physics concept of sublimation. In sublimation, the sample is first dried (in solid form), and then, without previously passing through the liquid stage, it is exposed to the vapor state. The solvent is eliminated during vaporization, which also produces the finest powder particles.

Kneading approach:³⁵ In this approach, a solvent is used to moisten the medication and polymer before they are combined to produce paste in a glass mortar. The mixture is then dried and put through a filter to create powder with tiny particles.

Using the electrostatic spinning technique:^{36,37} Solid fibers are created from a polymeric fluid stream solution or melt that is supplied through a millimetres-scale nozzle. A conducting capillary attached to a reservoir containing a polymeric solution and a conductive collective screen were used in this operation, which entailed an electrostatic field over them. This method has been used to make itraconazole/HPMC.

Inclusion complexes:

Inclusion complexes are created when a non-polar molecule (referred to as the guest) is inserted into the cavity of another molecule or set of molecules (referred to as the host). Cyclodextrins are the

IJPPR (2023), Vol. 14, Issue 3

most popular host molecules. Cyclodextrin is an oligomer that is created when starch is enzymatically broken down by the enzyme cyclodextrin glucosyl transferase (CGT).³⁸

Cyclodextrin inclusion complexes:

In water-soluble polymer/drug-incorporated CD aggregates, the solubilization capacity has improved, requiring less cyclodextrin to solubilize the same quantity of medication. There are several ways to make solid inclusion complexes, including kneading, coprecipitation, neutralization, co-grinding, spray drying, and microwave irradiation.^{39,40}

Table 3: Examples of different polymers used in solid dispersion.⁴¹⁻⁴⁵

Drug	Polymer	Preparation method	Reference
Carbamazepine	Soluplus, Eudragit EPO, HPMC 100, Kollidon VA64, and Affinisol HPMC HME 4000	Hot melt extrusion method	[41]
Azilsartan medoxomil	Affinisol 716G (HPMCAS)	Solvent evaporation method	[46]
Felodipine	Soluplus	Solvent evaporation method	[42]
Simvastatin	Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CCS)	Coevaporation	[43]

Review Article

Eplerenone	Soluplus	Lyophilization technique	[34]
Fenofibrate	PEG 6000	Solvent evaporation Method	[44]
Indomethacin	Poly (2-Hydroxyethyl Methacrylate) (PHEMA)	Solvent evaporation Method	[45]

Solid dispersion's benefits and drawbacks³⁹

a. Advantages:

- **Particle size reduction:** Using diverse carriers in solid dispersion decreases medication particle size, enhancing solubility and bioavailability.
- **Enhance particle wettability:** Solid dispersion enhances particle wettability.
- **Increase porosity:** Linear polymer-containing solid dispersions result in bigger, more porous particles than those made of reticular polymers, which increases the rate of dissolution.
- **Increase solubility and bioavailability by enhancing dissolution.**

b. Disadvantages

- Stability brought on by moisture levels.
- Difficulty putting into dosage form formulation.

Evaluation of physicochemical properties of solid dispersion^{34,40-46}

Phase Solubility Study

The shaking flask technique is utilized when the polymer (carrier) is present. Most of it is done in

accordance with Higuchi and Connors. The medicine is put into a 25 ml container containing a solution of 1%, 2%, 3%, 4%, and 5% polymer in this procedure. It is then placed in an orbital flask shaker for 48 hours at a temperature of 37°C + 0.5°C. After filtering, the sample is examined using a UV spectrophotometer to determine the drug concentration.

Saturation Solubility Study

In 25 ml of distilled water, surplus drug and solid dispersion batch additions are made until the water is super-saturated. It is then placed in an orbital flask shaker for 48 hours at a temperature of 37°C. Then, it is filtered using Whatman filtered paper before being tested by a UV spectrophotometer to determine the drug concentration.

Drug content

A known amount of solid dispersion is dissolved in a liquid and its drug content is then determined using a UV spectrophotometer. The following equation is used to calculate the effectiveness of drug loading and entrapment:

$$\% \text{ Drug loading} = (\text{Weight of drug in solid dispersion powder}) / (\text{Weight of solid dispersion powder}) \times 100 \text{ -----(1)}$$

Characterization of Solid dispersions^{34,36,45-49}

Characterization: Solid dispersion is characterized by using different techniques such as; Differential Scanning Calorimetry, Differential Thermal Analysis, Thermo-Microscopic Methods, X-ray Diffraction, Fourier Transform Infra-Red Spectroscopy (FT-IR), Scanning Electron Microscopy (SEM) and dissolution studies. Different techniques are:

Differential Scanning Calorimetry (DSC):

DSC can be used to determine crystallinity by quantifying the heat associated with the melting

(fusion) of the material. DSC is a well-known technique that measures heat flow into or out of a material as a function of time or temperature.⁴⁵

Differential Thermal Analysis (DTA): In differential thermal analysis, the difference in temperature between the sample and a thermally inert reference material is measured as a function of temperature. With a corresponding deviation of sample temperature from that of the reference any transition that the sample undergoes results in liberation or absorption of energy by the sample. Whether the transition temperature is exothermic or endothermic is shown by plot of the differential temperature versus the programmed temperature. In constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution obtained is the main advantage of this technique. A sample size of less than 1 mg can be used.⁴⁶

Thermo-Microscopic Methods: In this method to study the phase diagrams of binary systems hot stage microscope is used. The physical mixture or dispersion (approx. 1 mg) on a slide is heated at the rate of 1-5°C per minute. The thaw and melting points are then recorded by visual observation. This method requires only a small amount of sample but it is limited to thermally stable compounds only. To characterize diflunisal-PEG solid dispersion this technique has been used.⁴⁷

X-ray Diffraction: The X-Ray diffraction method is a very important and efficient tool in studying the physical nature of solid dispersions. Recently, it was used to study binary eutectic systems. The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly different from those of pure components. The biggest drawback of using the diffraction method to study dispersion systems is its frequent inability to differentiate amorphous precipitation from molecular

dispersion if the lattice parameter of the solvent component is not changed.⁴⁸

Dissolution Studies: Dissolution study is carried out to determine the rate and extent of dissolution. The dissolution study of solid dispersion was performed on the USP- type II paddle apparatus at 37±0.20C. Drug was dispersed in medium. Sample was taken time to time, filtered and analyzed for drug contents by measuring the absorbance at suitable wavelength using UV visible Spectrophotometer⁴⁸

Fourier Transform Infra-Red Spectroscopy (FT-IR): FT-IR spectroscopy can be employed to find the possible interactions between the drug and the carrier in the solid state on FT-IR spectrophotometer by the conventional KBr pellet method.⁴⁹

Scanning Electron Microscopy (SEM): SEM is useful in ascertaining the morphology, particle size of solid particles and sometimes polymorphism of drugs. The fine dispersion of drug particles in the carrier matrix may be visualized. The application of the electron microscope technique, however usually limited to chemicals with high resolution.⁴⁹

Conclusion

Drug solubility continues to be one of the most difficult formulation development issues. medication solubility is a prerequisite for medication absorption from the gastrointestinal tract (GIT), and drug dissolution is the rate-determining stage for oral absorption of pharmaceuticals that are weakly water-soluble. The solid dispersion can be employed to increase the medications' solubility.

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IJPPR (2023), Vol. 14, Issue 3
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