# A review on Solubility enhancement of poorly soluble drugs by solid dispersion method

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## Abstract

*The solubility concerns for the new medicine's focused drug delivery impact the delivery of several current drugs. At least 40% of new drugs developed for the pharmaceutical industry have low water solubility. More water solubility and higher bioavailability of such medications are hence the primary challenges facing scientists. Therefore, in order to get around these issues and promote dissolving, it is beneficial to form solid dispersion using carriers that have great water solubility. Therefore, it is discovered that solid dispersion techniques are a useful way to increase a drug's solubility factor if it has low water solubility. For limited commercialization, the review emphasizes the many aspects of the solid dispersion type, rationale, benefits, limitations, and production processes.*

***Keywords:*** *Solubility, Solid dispersion, Method of preparation, Generation, Solution.*

## Introduction

Solubility is an important physicochemical factor that affects both drug absorption and therapeutic efficacy. Inadequate solubility in water can cause formulation development to fail. The primary cause of the drug's insufficient bioavailability is its slow rate of dissolution and poor solubility in aqueous solution. Today, a great deal of hydrophobic carriers is being investigated, and they are demonstrating noteworthy improvements in solubility. The majority of medication substances on the market today are innovative, but one of the most challenging challenges in drug research is still finding ways to make hydrophobic drug substances more soluble and dissolve. For oral medications, dissolution of the drug in an aqueous media such as stomach fluid is crucial for improved absorption and bioavailability. Polymer matrix with different sources can therefore be employed to advance the bioavailability of weakly water-soluble substances such as class II and IV medications in the biopharmaceutical categorization system. To overcome this issue, a number of solubility augmentation techniques have been suggested [1].

Solving the solubility issue and increasing the solubility and dissolution rate of poorly soluble drugs through the solid dispersion method is the best way to get around these issues. Hence solid dispersion is one of the best techniques. To improve a poorly soluble drug's rate of dissolution, soluble nature, and oral bioavailability. Pharmaceutical research has two main areas of focus that aim to improve the oral bioavailability of the active agent. These include increasing the permeability of poorly permeable drugs and improving the solubility and rate of dissolution of poorly water-soluble drugs [2, 3].

## Solubility

A chemical substance's capacity to dissolve and create a homogeneous solution in a liquid, gaseous, or solid solvent is referred to as its solubility. The solubility of a material is primarily influenced by the solvent used, temperature, and pressure. To measure how soluble a material is in a certain solvent, one may look up its saturation concentration [4], which is the point at which pouring more of a substance does not increase the amount of substance in the solution.

## Importance of solubility: -

Oral ingestion is the most practical and widely used method of drug delivery because it is simple to administer, has a high patient compliance rate, is economical, and has minimal sterility requirements,

**Table 1. USP and BP solubility criteria: -**

| 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 |

and allows for dosage form design flexibility. Because of this, many generic drug manufacturers are more likely to create oral pharmaceutical products that are bioequivalent [5]. There are various ways to express a drug's solubility, including percentage, parts, molality, molarity, mole fraction, and volume fraction. The solubility equilibria in pharmaceuticals are of great importance.

The Biopharmaceutical Classification System (BCS), developed by the FDA, classifies medications into four groups according to their solubility and permeability (Table 2) [6]. Drugs in classes II and IV have solubility issues. [7, 8]. Therefore, enhancing a drug's solubility will also enhance its bioavailability for BCS Class II and Class IV drugs. [9].

**Table 2. Biopharmaceutical Classification System [10, 11]**

| Class | Solubility | Permeability | Example of drugs |
|---|---|---|---|
| Class 1 | High solubilty | High permeability | Benzapril etc. |
| Class 2 | Low solubility | High permeability | Valsartan,Nimesulide etc. |
| Class 3 | High solubility | Low permeability | Gabapentine,Atropine etc. |
| Class 4 | Low solubilty | Low permeability | Furesomide, Meloxicam etc. |

**Solid dispersion**

Solid dispersion formulation is a highly effective technique for improving solubility. Chiou and Riegelman define solid dispersion systems as the solid dispersion of active ingredients in an inert carrier or matrix through fusion, solvent, or melting-solvent methods. The drug is hydrophobic, whereas the matrix is hydrophilic. Solid dispersion can be classified into simple eutectic mixtures, solid solutions, glass solutions and suspensions, amorphous precipitation in a crystalline carrier, and compound or complex formations. [13]

**Table 3. Materials used as carrier for solid dispersion [10, 12]**

| Sr.no | Materials Used As Carrier | Examples |
|---|---|---|
| 1. | Sugars | Dextrose, sucrose, galactose, sorbitol, maltose, xylitol mannitol, lactose |
| 2. | Acids | Citric acid, succinic acid |
| 3. | Polymeric materials | Povidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan. |
| 4. | Insoluble or enteric polymer | HPMC phthalate, eudragit L100, eudragit S100 |
| 5. | Surfactants | Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans |
| 6. | Miscellaneous | Pentaerythritol, Pentaerythrityl tetra acetate. |

**Solid dispersions can be divided into the following four generations according to the carrier used: [14]**

**First generation**

In the first generation, solid dispersions were used as carriers. In this generation, crystalline carriers like sugars and urea are utilized. The disadvantage of the first generation is that the carrier is crystalline. Thermodynamically stable, but slower drug release compared to amorphous form. [15]

**Second generation**

In the second generation, amorphous polymers are typically used as carriers. [16] Polymers can be synthetic or natural, including polyethene glycols (PEG), povidone, polyvinyl pyrrolidine, and polymethacrylates.
Ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and starch derivatives like cyclodextrins and hydroxypropyl cellulose. [17]

**Third generation**

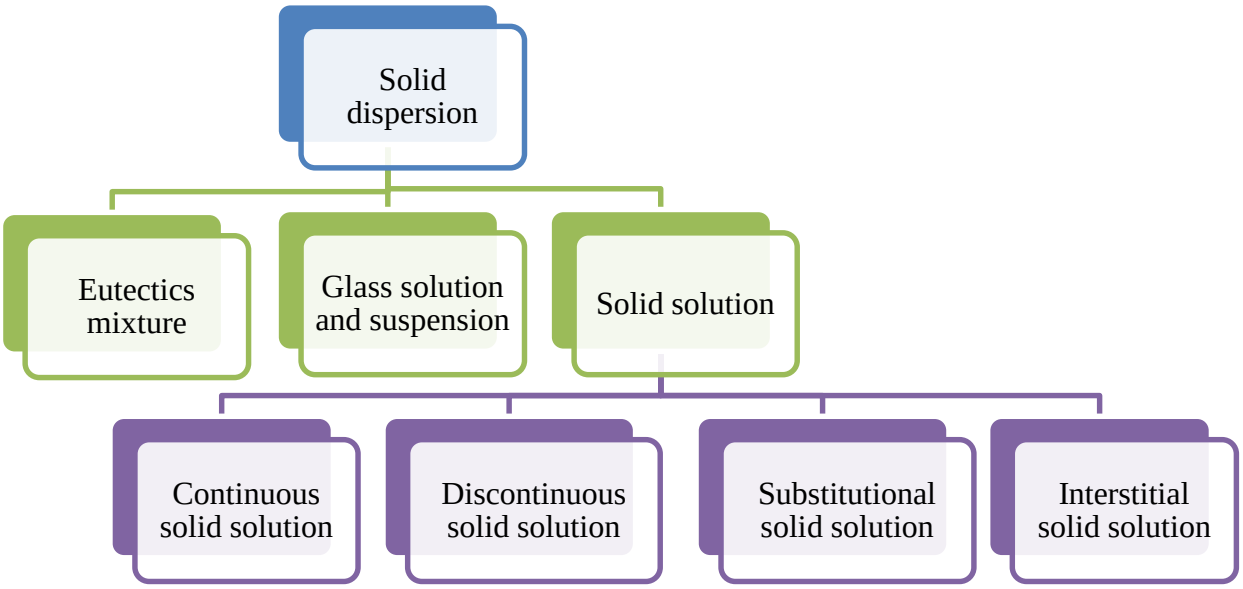
It has been demonstrated that employing a carrier with surface active agent qualities can improve the dissolution profile. In order to achieve a high purity level of the polymorphic and to increase in vivo bioavailability, it was found that the use of surface-active agents such as poloxamer 407, compritol 888, ATO, inutec SP1, gelucire 44/14, and insulin as carriers was effective. [18]

**Fourth generation**

The term "controlled release solid dispersion" refers to this kind of dispersion. Drugs with a short biological half-life and poor solubility in water are present in it. Water-soluble or insoluble water carriers are the two types of carriers that are employed. In controlled release solid dispersion, the two goals are to improve solubility and provide controlled drug release. Among the water-soluble carriers used in controlled-release solid dispersion are hydroxypropyl cellulose, eudragit, and ethyl cellulose. [19]

**Types of solid dispersion**

**Based on the arrangement of their molecules. The following types of solid dispersions can be distinguished:-**




**Eutectics mixture**

This combination is made up of two totally miscible liquid compounds that are just slightly miscible solid compounds. The process involves quickly solidifying the combined melt of the two chemicals, resulting in a fully liquid miscible product with little solid-solid solubility.

A system of this kind is physically combined with its two crystalline constituents in an intimate thermodynamic manner. [20]

## Glass solution and suspension

Glass suspensions, which contain precipitated particles, are suspended in glass solvent, whereas glass solutions are homogenous glassy systems in which a solute is dissolved in a glass carrier. Examples of carriers that produce glass solutions and suspensions include urea, citric acid, polyethene glycol, polyvinyl pyrrolidine, and sugars including galactose, sucrose, and dextrose. In these systems, the lattice energy is low and the melting point is not sharp. [20]

### Solid solution

Solid solutions are similar to liquid solutions in that they have just one phase,
regardless of the quantity of constituents. When it comes to solid solutions, the medication's particle size has been whittled down to the molecular dimensions, the smallest possible size.[21] and the carrier's dissolving rate influences the dissolution rate. Categorized either first by their miscibility (continuous vs. discontinuous solid solutions) or second by the distribution of solvate molecules in the solvendum (interstitial, amorphous, substitutional).

### Continuous solid solution

All ratios of the constituents in a continuous solid solution are miscible. Theoretically, this suggests that the bonding strength between the molecules of each individual component is smaller than the bonding strength between the two components. These kinds of solid solutions, however, have not yet been documented in the pharmaceutical industry [22].

### Discontinuous solid solution

The solubility of one component in the other component is restricted in discontinuous solid solutions. According to Goldberg et al., the phrase "solid solution" should only be used when the mutual solubility of the two components is greater than 5% due to practical issues. [23]

### Substitutional solid solution

Only when there is a size difference of less than 15% between the solvent and solute molecules may substitution occur. [34] In classical solid solutions, the solvent molecules can be replaced by the solute molecules in the crystal lattice or they can fit into the spaces created by the solvent molecules. [22]

### Interstitial solid solution

The soluble particles in interstitial solid solutions occupy the spaces created by the solvent molecules in the crystal lattice. Therefore, the diameter of the solute molecule should be smaller than 0.59 times that of the solvent molecule. [24]

### Advantages of solid dispersion

1. **Particle size reduction**

   Using different carriers in solid dispersion results in smaller drug particles, improving solubility and bioavailability.

2. **Particles with Better Wettability**
   The drug's wettability is improved by the carrier. Carriers primarily affect the drug's dissolution profile through co-solvent effects or direct dissolution.
3. **Particles with increased porosit**y
   It has been discovered that the particles in solid dispersion have a higher degree of porosity. It is dependent on the characteristics of the carrier. In contrast to solid dispersions containing reticular polymer, which have a greater dissolving rate, those containing linear polymer create bigger and more porous particles. The medication release profile is enhanced as the porosity of the solid dispersion particles increases. [25]
4. **Drug in amorphous state**
   In the amorphous condition, crystalline medicines with low water solubility are more soluble. [26] Drug release can be improved by employing the drug in its amorphous condition, which requires no energy to break up the crystal lattice during the dissolution.[27] Medicines in solid dispersions appear as supersaturated solutions following system breakdown. It is believed that if medicines precipitate, they will be in a metastable polymorphic form with better solubility than the most stable crystal form.[28]

## Disadvantages of solid dispersion

1. Even though solid dispersions are highly skilled, their usage in commercial goods is limited mostly because to the risk of them transitioning from an amorphous to a crystalline form.
2. The majority of polymers used in solid dispersion have the ability to absorb moisture, which can cause phase separation, crystal development, or the transition from an amorphous to a crystalline form.
3. With age, the crystallinity of solid dispersions changes and the dissolving rate decreases.
4. Solid dispersions are poorly scaled for production applications.Patients with cancer should continue to take anticancer medications during therapy.
5. Because it may enhance drug mobility and encourage drug crystallization, the impact of moisture on the amorphous medicines' storage stability is likewise a serious worry.
6. During storage, solid dispersions are susceptible to changes in humidity and temperature because of their thermodynamic instability.
7. Amorphous solids must be stabilized in the solid state in order to reach their full potential.
8. These elements may enhance the overall mobility, lower the glass transition temperature, or interfere with the drug-carrier interaction, causing the drug's solubility and rate of dissolution to decrease, all of which may encourage phase separation and crystallization of solid dispersion.[29 30 ,31]

## Application of solid dispersion

1. It is mostly useful for achieving a uniform dispersion of a tiny quantity medication in a solid condition.
2. It helps stabilize the unstable medication.[32]
3. It can also be utilized to create soluble drugs with prolonged release by utilizing insoluble or poorly soluble carriers.

4. It is employed for the solid dosage state dispensing of both liquid and gaseous compounds.
5. Solid dispersion systems like solid solutions and eutectic mixtures are supplied by polymorph.
6. A sustained dosage form for the quick release initial dose is possible. [33,34]

**Methods of preparations**

A variety of solid dispersion techniques are employed to improve the solubility of drugs that are poorly soluble, and they are as follows: -

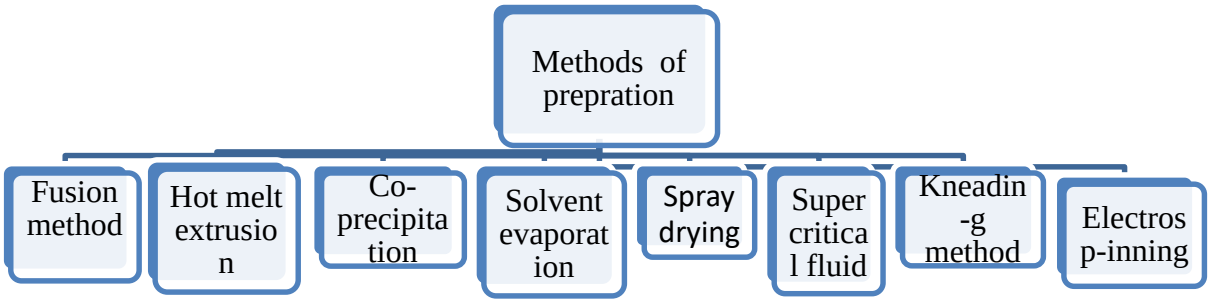



**Fig No. 1. Various methods of solid dispersion preparation [35]**

**Fusion method**

In 1961, Sekiguchi and Obi introduced the fusion process, which is often referred to as the melt method. After heating a physical mixture of medication and polymer to a molten state, the combination is cooled and solidified while being vigorously stirred. The solid mass is ground, pulverized, then sieved to get the appropriate particle size. In spite of its wide spread use, Using this method to create solid dispersions has a number of disadvantages. These short comings consist of a lack of miscibility of medication and polymer at heating temperature. To get around this problem, surfactants might be utilized. Lower manufacturing temperatures are preferred as pharmaceuticals and polymers need to be thermally stable at melting temperatures as well. The fused mixture must also be impervious to phase separation and recrystallization. [35]

**Hot melt extrusion method**

The hot-melt extrusion method is a modernized version of the fusion process in which the extruder causes strong mixing of the components. In comparison to the classic fusion approach, melt extrusion has the capacity to shape the molten drug-polymer combination into implants, pellets, or oral dose forms. [36] The pharmaceutical industry uses the hot-melt extrusion technology to create a variety of dosage forms, including sustained-release pellets. The hopper is loaded with the drug carrier mix, which the extruder then conveys, mixes, and melts. [37] This approach is cost-effective and produces heat quickly and uniformly. [38]

**Co-precipitation method**

Formulating solid dispersions (SDs) of PWS medications that are poorly soluble and have high melting points in organic solvents that cannot be controlled by melting or other solvent techniques is a suitable option. Using an ant solvent that causes the medication and polymer to precipitate, this method dissolves the medication and polymers entirely in an organic solvent. The remaining solvents are subsequently removed by filtering out and washing off this suspension. Micro precipitated bulk powder is the term used to describe the co-precipitation material that is obtained following filtration and drying (MPD). [39]

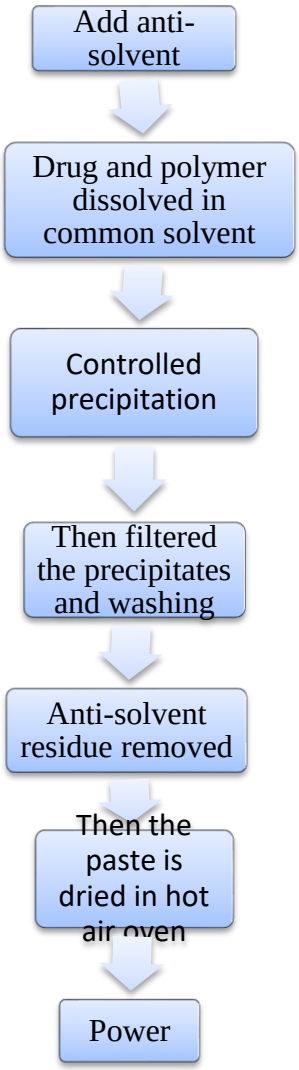



**Fig No. 2. Co-precipitation process [40]**

**Solvent evaporation method**

In the solvent-based method, the medication and carrier molecule are thoroughly dissolved and distributed using an organic solvent. [41, 42] To create a homogeneous liquid, use an organic solvent such as dichloromethane, acetone, or chloroform. [43]

It can be difficult to find a common solvent for the medicine and carrier, and it might take a while to completely remove the solvent from the product. Furthermore, the performance of the product may vary significantly depending on appropriate adjustments to the concentrations employed for solvent evaporation. Moreover, significant amounts of solvents are often needed, which might result in toxicological issues. [41, 42] Because of their enhanced wetting, enhanced bioavailability, and reduced crystallinity, the produced solid dispersions exhibited better dissolving.

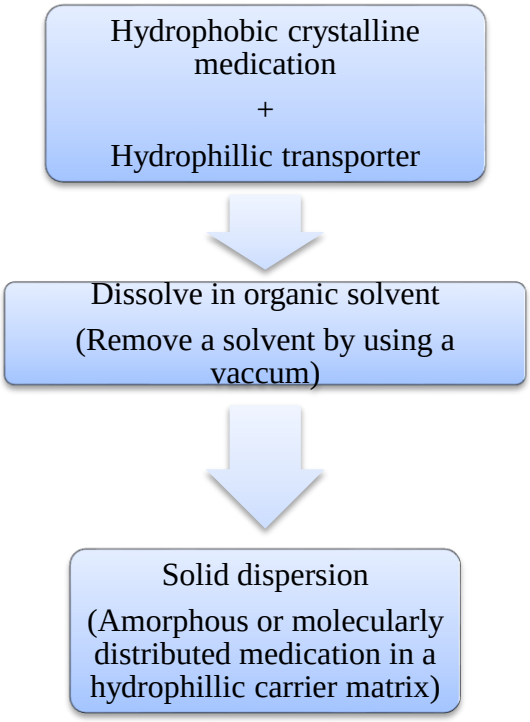



**Fig No. 3. Preparation of solid dispersion by solvent evaporation technique [44]**

**Spray drying method**

This method makes it possible for the solvent to evaporate very quickly, which speeds up the process of turning an active pharmaceutical ingredient (API)-polymer solution into solid API-polymer particles. This method involves spraying the medication and polymer solution as small droplets into a chamber with regulated humidity, heat, and airflow to cause the solution to evaporate. After the product has finished drying, it is separated using air as a drying medium. Through a protruding spout, the particle size produced by spray drying will change the droplet size to satisfy advanced application or processing requirements. [45] This process involves dissolving the medication and polymer in an organic solvent before spraying the mixture into the heated chamber through a nozzle. Owing to the elevated temperature, the solvent evaporates, resulting in the finest possible powder particles. [46, 47]

**Supercritical fluid method**

It has been frequently noted that carbon dioxide (CO2) can be used instead of typical solvents. Because carbon dioxide combines the low viscosity and high diffusivity of the gas and liquid density, it is a suitable supercritical fluid. [48] Initially, a nozzle is used to spray

the drug/carrier combination into the expansion vessel once it has been solubilized in the supercritical CO2. The sprayed particles are creating SD of the target size at a quick pace. When CO2 is employed as an anti-solvent, an organic solvent is used to introduce the drug/carrier combination. Following the mixture's expulsion into the tank, supercritical CO2 quickly evaporates the organic solvent, creating SD particles. [49,50]

**Kneading method**

A solvent is added to a mixture of carefully weighed Medicine and carriers, and the mixture is vigorously kneaded. [51] The carrier and medicine are crushed together to make a thick paste with minimum organic solvents such alcohol, acetone, or water.[52] The medication and polymers are triturated in a pestle and mortar while the liquid which might be water or a hydroalcoholic mixture is added dropwise in the kneading procedure. Due to the kneading action, this causes slurry to develop and the size of the particles to decrease, increasing the bioavailability. After that, the mixture is dried and put through a mesh screen to ensure that all of the components are uniform. [53] The kneading procedure is cost-effective but limited by residual solvent. [54]

**Electrospinning method**

Solid fibers are created by the electro spinning method, which involves delivering a melt or polymeric fluid stream via a millimeter-scale nozzle. [55] Nanotechnology and solid solution/dispersion technologies are combined in the polymer industry's electrostatic spinning process. [56, 57] This technique is used in the pharmaceutical industry [58, 59] A conducting capillary attached to a reservoir holding a polymeric solution and a conductive collective screen were subjected to an electric field throughout this procedure. This method has been used to make itraconazole/HPMC. [60]

**Characterization of solid dispersion: -**

The application of solid dispersions is mostly recognized for improving bioavailability and dissolving rate. Standard dissolve techniques, which require the use of USP dissolution test equipment, can be used to evaluate the increased dissolution rate. Finding the drug's and the polymer's physical states, such as their degree of crystallinity and crystalline or amorphous state, is another parameter examined in the case of solid dispersion. [61] To characterize solid dispersions, a variety of analytical and experimental techniques are employed. Various approaches such as thermal methods, spectroscopic methods, microscopic methods, micro thermal analysis, macroscopic techniques, etc. can be employed for characterization. [62]

**These are a few different techniques for characterizing solid dispersion:**

1. Physical state examination
2. Surface microscopy
3. Structure elucidation
4. Drug carrier interactions
5. Dissolution rate
6. Stability

**1. Physical state examination**

Powder X-ray diffraction, differential scanning calorimetry, hot stage microscopy, and humidity stage microscopy.

**2. Surface microscopy**

Hot stage microscopy, polarized light optical microscopy, and scanning electron microscopy.

**3. Structure elucidation**

Fourier transforms infrared spectroscopy and solid state nuclear magnetic resonance spectroscopy.

**4. Drug carrier interactions**

Nuclear magnetic resonance spectroscopy, Fourier transforms infrared spectroscopy, and differential scanning calorimetry.

**5. Dissolution rate**

Dissolution studies, dynamic solubility studies.

**6. Stability**

Differential scanning temperature measurement, nuclear magnetic resonance spectroscopy to and Fourier transform infrared spectroscopy.

## Conclusion

One useful strategy to improve the solubility and bioavailability of drugs that are poorly soluble in water is the solid dispersion technique. So, it is necessary to resolve a few issues pertaining to the drug's stability and flow characteristics. The greatest and alternate method for increasing the solubility of the weakly water soluble BCS-II medication is to use a solid dispersion with a synthetic or natural carrier that is less toxic, biocompatible, and more readily available. Employing solid dispersion and carefully selecting the carrier to increase the release rate and oral bioavailability of poorly soluble water-soluble medications. Delaying or reducing the drug's release pattern is also a possibility.