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# Solubility Enhancement of Poorly Water Soluble Drugs By Solid Dispersion Technique

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***Abstract:***Solubility and dissolution-related bioavailability issues plague poorly water soluble substances. Orally administered medications account for over 90% of all pharmaceuticals. Pharmacological absorption, bioavailability, and pharmacokinetic profile of orally delivered drug substances are all largely dependent on the compound's solubility in aqueous media. Solid dispersion has been proven to be a superior dose form for medicines with poor water solubility. Solid dispersions in water-soluble carriers have piqued interest as a technique of enhancing hydrophobic medication dissolution rates and bioavailability. solid dispersion, micronization, and salt creation are all important ways for improving the solubility of poorly soluble pharmaceuticals, but each has its own set of limitations and benefits. The basic notion of solid dispersion, numerous forms of solid dispersion, preparation and characterisation methods, advantages, limitations, and applications are all discussed in this article.

**Key words: Dissolution, Bioavailability, Solid dispersion, Carriers, Solubility.**

## I. INTRODUCTION

Because of low and variable levels of absorption, oral bioavailability improvements of such poorly water-soluble medicines frequently demonstrate poor bioavailability. As a result of particle size reduction, slubility and bioavailability of drugs with dissolution rate limited gastrointestinal absorption improve. However, micronizing medications frequently causes particle aggregation and agglomeration, resulting in poor wettability. However, micronizing medications frequently causes particle aggregation and agglomeration, resulting in poor wettability.The use of water-soluble carriers in solid dispersions of weakly water-soluble pharmaceuticals has minimised the occurrence of these issues and improved dissolution.[1]

More than 40% of novel chemical entities (NCEs) generated in the pharmaceutical industry are nearly water insoluble. These medications' weak water solubility, combined with their sluggish absorption, result in inadequate and variable bioavailability, as well as gastrointestinal mucosal toxicity. As a result, improving drug solubility and hence oral bioavailability remains one of the most difficult parts of the drug development process, particularly for oral drug delivery systems.There are several methods for improving

the solubility of poorly water soluble drugs that have been documented in the literature. The approaches are chosen based on factors such as the qualities of the medicine in question, the nature of the excipients to be used, and the nature of the planned dosage form.This review will cover both standard and novel strategies for improving the solubility of hydrophobic medicines in oral pharmaceutical formulations.[2]

## II. Solubility

The solubility of a substance is defined as the maximum amount of that substance that can dissolve in a given amount of solvent or solution at a given temperature.Bioavailability increases as solubility increases. The term "solubility" means:

**Table 1: Definition of Solubility.[3]**

| Definition | Parts of solvent required for one part of solute |
|---|---|
| Very Soluble | < 1 |
| Freely soluble | 1 – 10 |
| Soluble | 10 – 30 |
| Sparingly soluble | 30 – 100 |
| Slightly | 100 – 1000 |
| Very slightly soluble | 1000 - 10,000 |
| Insoluble | > 10,000 |

- **Biopharmaceutical Classification System:** The BCS has proven to be an incredibly effective tool for predicting in vivo performance of pharmacological substances, developing innovative drug delivery systems to suit drug performance in the body, and ensuring bioequivalence of therapeutic products throughout scale-up and post-approval. Because of the many different elements that regulate absorption from the gastrointestinal system 30, formulation scientists have had difficulty developing dose forms, particularly for prolonged release. The pharmacological compounds are classified into four types based on their solubility parameter and biomembrane permeability, and this classification system is known as a biopharmaceutical classification system. Amidon created the BCS in 1995, and it has since become a benchmark in the regulation of bioequivalence of oral medicinal products. The right dosage form and bioequivalence tests, recommending a class of immediate release (IR) solid dosage forms forwhich bioequivalence can be determined using in vitro dissolution tests, and laying out the effect of excipients on drug permeability. Case 1. High solubility-high permeability medications, Case 2. Low solubility-high permeability pharmaceuticals, Case 3. High solubility-low permeability drugs, and Case 4. Low solubility-low permeability drugs are the four biopharmaceutical drug classes.[4]

| I | II |
|---|---|
| III | IV |

High

Permeability

Low

High low

Solubility

**Fig 1: BCS classification system**

## III. Techniques for Solubility Enhancement [5]

### A. Chemical Adjustments

1. Formation of salt
2. Co-crystallization
3. Co-solvency
4. hydration
5. A soluble agent
6. Nanotechnology

### B. Physical Modifications

1. Reduction of particle size

a. Micronization

b.Nanosuspension

2. Changes to the crystal habit

a.Polymorphs

b.Pseudopolymorphs

3. Complexation

a. Use of complexing agent

4. Surfactant solubilization

a. Microemulsions

b. Drug delivery system that self-microemulsifies

5. Dispersion of drugs in carriers

a. Solid dispersions

b. solid solutions

c. eutectic mixes are all examples of solid dispersions.

## A. Chemical Adjustments

1. Formation of salt :is the most popular and effective approach for improving acidic and basic medication solubility and dissolution rates. An acidic or basic medicine is transformed into a salt that has a higher solubility than the original drug. Aspirin, theophylline, and barbiturates are examples.

2. Co-crystallization :The use of co-crystals, also known as molecular complexes, is a new strategy for improving medication solubility. Co-crystals are crystalline materials that are held together by non-covalent forces and consist of two or more molecular (and electrically neutral) species. It can be made by evaporating a heteromeric solution, grinding the ingredients together, or sublimation, melt growth, and slurry production. It's becoming more popular as a substitute for salt production, especially for neutral chemicals.

3. Co-solvency :It is generally known that adding an organic co-solvent to water changes the solubility of medications substantially. Water solubility is poor for weak electrolytes and non-polar molecules, but it can be enhanced by changing the polarity of the solvent. Co-solvent is a solvent that is used to boost solubility. Solvent mixing is another name for this process.

4. hydration :The presence of a large amount of additives causes an increase in solubility in water. It enhances solubility by complexing hydrophobic agents (Sodium benzoate, sodium alginate, urea) with the solute. Sublimation of theophylline using sodium acetate and sodium alginate, as an example.

5. A soluble agent :Various solubilizing compounds can help improve the solubility of poorly soluble drugs. PEG 400, for example, improves hydrochlorothiazide solubility.

6. Nanotechnology :Nanotechnology will be utilised to increase the solubility of medications that are now ineffective. Nanotechnology is the study and application of materials and structures at the nanoscale level, which is defined as 100 nanometres (nm) or less. Oral bioavailability increase via micronization is insufficient for many new chemical entities with low solubility because micronized products have a small effective surface area for dissolving, hence the next stage was nanonization.

## B. Physical Modifications

**1. Reduction of particle size :**Size reduction procedures using various milling processes are well established, and they are a typical aspect of formulation development. This can be accomplished primarily through micronization and nanosuspension. he surface area of a particle increases as its size decreases, resulting in an increase in solubility. For particle size reduction, the Sonocrystallisation process is sometimes utilised.

**2. Changes to the crystal habit :**Polymorphism refers to an element's or compound's capacity to crystallise in several crystalline forms. Drug polymorphs are chemically identical, but their physical features, such as solubility, melting temperature, density, texture, and stability, differ. Amorphous forms of drugs are always better than crystalline forms due to the higher energy and increased surface area. Order for the dissolving of various medication solid forms. Amorphous polymorph > Metastable polymorph > Stable polymorph.

**3. Complexation:**The association of two or more molecules to generate a non-bonded entity with a well-defined stichiometry is known as complexation. London forces, hydrogen bonding, and hydrophobic

interactions are all used in the complexation process. Chelates, such as EDTA and EGTA, molecular complexes, polymers, inclusion complexes, and cyclodextrins, are examples of complexing agents.

**4. Surfactantsolubilisation:** Surfactants are compounds that have polar and non-polar parts. A hydrocarbon segment is usually coupled to a polar group in most surfactants. An anionic, cationic, zwitterionic, or non-ionic polar group can exist. Small polar molecules can accumulate in the micelles' hydrophobic centre when they are added. This solubilization process is critical in both industrial and biological operations. The inclusion of surfactants reduces surface tension but increases medication solubility in organic solvents.

## IV. Solid disperaion

A solid dispersion is a collection of solid goods made up of at least two separate components, usually a hydrophilic matrix and a hydrophobic substance; the matrix might be crystalline or amorphous. Because the medication can be disseminated molecularly, in amorphous particles (clusters), or in crystalline particles, six different types of solid dispersions can be recognised depending on their molecular arrangement. Furthermore, specific combinations can be found in the same sample; some molecules are clustered, while others are molecularly distributed. Interestingly, the designation of solid dispersions in distinct research is depending on the manner of preparation. However, because different preparation procedures can produce the same subtypes or distinct subtypes from the same preparation process, it can be argued that solid dispersions should preferably be labelled according to their molecular arrangement. Furthermore, the molecular arrangement, not the method of manufacture, determines the properties of solid dispersions. As a result, terminology that indicate the molecular configuration in the solid dispersion must be used. Understanding the molecular structure will help you better understand the properties and behaviour of solid dispersions.[6]

## V. Classification of Solid dispersions

Different forms of solid dispersions (SDs) can be recognised based on their molecular arrangement. Table 2 lists all of them.

**Table 2: Classification of solid dispersions in six subtypes**

| Solid Dispersion | Type | Matrix * | Drug ** | Remarks | No. of phases | Reference |
|---|---|---|---|---|---|---|
| I | Eutectics | C | C | the first type of solid dispersions prepared | 2 | 7 |
| II | Amorphous precipitations in crystalline matrix | C | A | rarely encountered | 2 | 8 |
| III | Solid solutions | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Continuous solid solutions | C | M | miscible at all compositions, never prepared | 1 | 7 |
| | Discontinuous solid solutions | C | M | partially miscible | 2 | 8 |
| | Substitutional solid solutions | C | M | molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinous: 2 phases even though drug is molecularly dispersed | 2 | 7,8 |
| | Interstitial solid solutions | C | M | drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG. | 2 | 7 ,8 |
| IV | Glass suspension | A | C | particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix | 2 | 8 |
| V | Glass Suspension | A | A | particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type | 2 | 7, 8 |
| VI | Glass solution | A | M | requires miscibility/solid | 1 | 8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP | | |

*: A: matrix in the amorphous state
C: matrix in the crystalline state
**: A: drug dispersed as amorphous clusters in the matrix
C: drug dispersed as crystalline particles in the matrix

## VI. Advantages of Solid Dispersion

The following are some of the reasons why solid dispersion is used to increase solubility:

### 1. Reduction in particle size :

When a molecular dispersion is created, the polymer/carrier dissolves in a solvent, resulting in a fine dispersion of the medication in the medium. This results in a large surface area, which increases the dissolution rate and bioavailability.

### 2. Improves wettability of particles:

The drug wettability improvement observed in solid dispersions1 makes a significant contribution to improving medication solubility. After the development of a solid dispersion, it is seen that carriers with no surface activity have increased activity, whereas carriers with surface activity have a considerably higher increase in dissolution rate.

### 3. Particles with higher porosity

The porosity of particles increases in solid dispersion, which is mostly dependent on the polymer characteristics used. Reticulated polymers produce higher porosity than linear polymers. As a result, the medication release profile increases.

### 4. Drugs in amorphous state

Amorphous drugs have a higher solubility than crystalline drugs. Because no energy is required to break up the crystal lattice during the dissolving process, it is usually possible to improve drug release by utilising the medication in its amorphous state.[9]

## VII. Disadvantages of solid dispersion

The following are some of the technique's limitations:

1. Drug and vehicle stability
2. Difficulty incorporating it into a dosage form
3. Time-consuming and expensive preparation process
4. Reproducibility of physicochemical parameters[10]

## VIII. Applications of solid dispersions (SDs)

1. It improves the solubility of weakly water soluble medicines, increasing the dissolution rate and hence the drug's absorption and bioavailability.
2. The solid dispersion protects the unstable medications from degradation processes such as hydrolysis and oxidation.
3. The solid dispersion of certain medications decreases their negative effects.
4. The solid dispersion conceals the drug's disagreeable taste and odour, as well as avoiding unwanted incompatibilities.
5. In the solid state, the solid dispersion achieves a homogenous distribution of a little amount of medication.
6. The solid dispersion aids in the dispensing of liquid or gaseous chemicals in solid dosages (up to 10%).
7. The sustained release dosage forms are created using solid dispersion.
8. The solid dispersion can be employed as a prodrug, reducing the inactivation of medicines such as morphine and progesterone in the pre-systemic circulation.
9. Polymorphs can be transformed into isomorphous, solid solution, eutectic, or molecular addition compounds in a given system.[11]

## IX. Materials Used As Carrier For Solid Dispersions :

Because the dissolving rate of one component from the surface is modified by the other component in a multiple component mixture, the carrier chosen has an impact on the dissolution characteristics of the dispersed medicament. As a result, a water-soluble carrier allows the medicine to be released from the matrix more quickly. A poorly soluble or insoluble carrier causes a drug's release from the matrix to be slower. Faster drug release can be accomplished from matrix if the active agent is a minor component in the dispersion. Table 4 lists the many carriers used to prepare solid dispersions.[12]

**Table 3: Materials used as carrier for solid dispersion**

| Sr .no. | Category | Carriers | Example |
|---|---|---|---|
| **1** | Sugars | Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose | Rofecoxib from sorbitol and mannito |
| **2** | Acids | Citric acid, succinic acid | Felodipine, rofecoxib from citric acid |
| **3** | Polymeric materials | Polyvinyl pyrrolidone(PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose | Temazepam , felodipine, etoricoxibrofecoxib from PEG 4000 & 6000 and |

| | | | |
|---|---|---|---|
| | | (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan | troglitazone and rofecoxib from PVP K3 |
| **4** | Insoluble or enteric polymer | Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100, eudragit RL, eudragit RS | Indomethacin from eudragit E100 |
| **5** | Surfactants | Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans | Felodipin and rofecoxib from poloxamer 188 |
| **6** | Miscellaneous | Pentaerythritol, pentaerythrityltetraacetate, urea, urethane, hydroxy alkyl xanthins | Rofecoxib from ur |

## X. Ideal qualities of a carrier for solid dispersions[13]

High solubility in water promotes wettability and dissolving.

ii) Improved stability and a high glass transition point (Tg).

iv) Low water consumption (reduces Tg)

Drug soluble in common solvent (solvent evaporation technique)

v) Low melting point (melting process);

vi) Ability to produce a solid solution with the medication

vii) Ability to preserve medicine from moisture

viii) Good compressibility and flow index

## XI. Methods Of Preparation Of Solid Dispersions

1. Solvent evaporation method
2. Modified solvent evaporation method
3. Sovent-melting (melt evaporation )
4. Melting /Fusion method
5. Co-precipitation method
6. Melt Extrusion Method
7. Kneading method
8. Co-grinding method
9. Gel entrapment technique

10. Spray-Drying Method
11. Lyophilization Technique
12. Electrospinning
13. Supercritical fluid method
14. Dropping method solution

## 1. Solvent evaporation method

The physical mixture of the drug and carrier is dissolved in a common solvent, which is then evaporated until only a transparent, solvent-free film remains. The film is then dried to maintain a consistent weight.The fundamental advantage of the solvent approach is that due to the relatively low temperatures necessary for the evaporation of organic solvents, thermal degradation of medications or carriers can be avoided. However, there are several drawbacks to this procedure, such as 1) the increased preparation cost. 2) The difficulty in eliminating liquid solvent completely. 3) The potential negative impact of solvent traces on chemical stability 4) The choice of a typical 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.

## 2. Modified solvent evaporation method

With continuous stirring for a period of time, the drug is dissolved in an organic solvent at its saturation solubility. A suitable amount of water is used to suspend the polymer (up to wet mass of polymer). The medication solution is put into the polymer suspension at the same time. The solvent has completely evaporated. The resulting mass is dried.

## 3. Sovent-melting (melt evaporation )

The medication is dissolved in an organic solvent after it has been precisely weighed. The solution is mixed into the mannitol melt and quickly chilled before being placed in a desiccator to dry completely. The solidified material is crushed, pulverised, and sieved. The advantages of both the fusion and solvent evaporation procedures are combined in this technique. It is limited to medications having a low therapeutic dose from a practical standpoint (less than 50 mg).[14]

## 4. Melting /Fusion method

This method entails preparing a physical mixture of a medication and a water soluble carrier and directly heating it till it melts. The melting slurry is then immediately solidified in an ice bath while being vigorously stirred. Crushed, pulverised, and sieved solids are the ultimate product. The procedure can be modified by pouring a thin layer of homogeneous melt onto a ferrite plate or a stainless steel plate and cooling it with air or water flowing on the opposite side of the plate. Furthermore, a super-saturation of a solute or medication in a system can frequently be achieved by rapidly cooling a melt from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The immediate solidification process stops the solute molecule in the solvent matrix. When applied for simple eutectic mixtures, the quenching process produces a substantially finer dispersion of crystallites.[15]The melting approach has the advantage of being a cost-effective and solvent-free process; nevertheless, it is not suited for drugs or carriers that are unstable at fusion temperature or

evaporate at higher temperatures. To avoid oxidative destruction of the medicine or carrier, some solutions include heating the physical mixture in a sealed container or melting it under vacuum or in the presence of an inert gas such as nitrogen. This approach was used to make solid dispersions of albendazole and urea, for example.

## 5. Co-precipitation method

The required amount of medication is added to the carrier solution. The system is kept agitated by magnetic fields and is shielded from light. To prevent the loss of the structural water from the inclusion complex, the produced precipitate is vacuum filtered and dried at room temperature.[16]

## 6. Melt Extrusion Method

This method produces solid dispersion by hot-stage extrusion with a co-rotating twin-screw extruder, which is made up of active ingredient and carrier. In the dispersions, the drug concentration is always 40% (w/w). In the pharmaceutical sector, the melt extrusion process is used to make a variety of dosage forms, such as sustained-release pellets.[17]

## 7. Kneading method

The carrier is penetrated with water and turned into a paste in this manner. The drug is subsequently added and kneaded for a specific amount of time. The kneaded material is then dried and fed through a machine. if required, through a sieve.

## 8. Co-grinding method

A physical mixture of drug and carrier is blended for a period of time at a specific speed in a blender. Steel balls are then introduced to the slurry in the chamber of a vibration ball mill. Pulverize the powder combination. The sample is then collected and stored in a screw-capped glass vial at room temperature until it is needed. This approach was used to make solid dispersions of chlordiazepoxide and mannitol, for example.[18]

## 9. Gel entrapment technique

To make a clear and translucent gel, hydroxypropyl methyl cellulose is dissolved in an organic solvent. The medicine, for example, is then sonicated for a few minutes to dissolve it in the gel. Under vacuum, the organic solvent evaporates. Mortar is used to reduce the size of solid dispersions before sieving.[19]

## 10. Spray-Drying Method

The spray drying approach involves dissolving or suspending the medicine and polymer in a common solvent or solvent mixture, then drying them in a hot air stream to remove the solvent. The solvent quickly evaporates due to the huge surface area of the droplets, and a solid dispersion forms within seconds, which may be fast enough to phase separate.

**11. Lyophilization Technique**

a small amount of cyclohexanol was used to dissolve several solid dispersions The solution was then rapidly solidified by pipetting small amounts onto the inner surface of a cold flask spinning in a -50°C methanol bath with a Pasteur pipette. The flask was linked to the lyophilizer's vacuum adaptor after obtaining a particular layer thickness. After that, the solvent was sublimed at 8-10 mmHg and condensed onto a -75°C condenser. When the solvent was removed completely, the powder residue was discovered to be a porous, light, and fluffy material. The medication is subjected to low heat stress during the production of the SDs, which is an essential benefit of freeze drying.[20]

**12. Electrospinning**

Solid fibres are created by electrospinning from a polymeric fluid stream solution or melt fed through a millimeter-scale nozzle. A high electrostatic field is applied to a conductive capillary attached to a reservoir containing a polymer solution or melt and a conductive collection screen in this method. Charge species accumulating on the surface of a pendant drop collapse the hemispheric shape into a conical shape when the electrostatic field intensity is increased up to but not surpassing a critical value (commonly known as Taylor s cone). When the critical value is exceeded, a charged polymer jet is expelled from the cone's apex (as a way of relieving the charge built-up on the surface of the pendant drop). The electrostatic force carries the ejected charged jet to the collection screen. The charged jet's thinning during its course to the collection screen is due to the Coulombic repulsion force. The charged jet's thinning down is limited. The charged jet is dried as the viscosity rises. This approach has a lot of potential for making nanofibers and controlling the release of medicines because it is the easiest and cheapest. It can also be used to make solid dispersions in the future.

**13. Supercritical fluid method**

Carbon dioxide is employed as anantisolvent for the solute but as a solvent for the organic solvent in supercritical fluid antisolvent techniques. Various writers used different acronyms to describe micronization processes: aerosol solvent extraction system, compressed fluid antisolvent precipitation, gas anti-solvent, solution improved dispersion by supercritical fluids, and supercritical antisolvent. The SAS procedure entails spraying a solution containing the solute and an organic solvent into a continuous supercritical phase that is flowing at the same time. Although a small quantity of carbon dioxide remains trapped inside the polymer after the process is complete, using supercritical carbon dioxide is advantageous since it is much easier to extract from the polymeric materials when the process is complete; it provides no harm to the patient. Furthermore, carbon dioxide's ability to plasticize and swell polymers can be used, and the process can be carried out at room temperature. Furthermore, supercritical fluids are utilised to reduce the melting temperature of the dispersed active ingredient, lowering the temperature of the melt dispersion process. The solubility of the lighter component (dense gas) in the developing phase (heavier component) is the cause of this decrease.[21]

### 14. Dropping method solution

The dropping method is a new method for creating spherical particles from melted solid dispersions that was created to aid in the crystallisation of various substances. This methodology may be able to overcome some of the problems that other systems have. A solid dispersion of a melted drug-carrier mixture is piped and then placed onto a plate, where it hardens into spherical particles for laboratory-scale production. It's possible that using carriers that solidify at room temperature will help with the dropping process. The dropping method not only makes the production process easier, but it also increases the rate of dissolution. It doesn't require organic solvents, thus it doesn't have any of the issues that come with solvent evaporation.[22]

## XII. Characterization of solid dispersion

In solid dispersions, the medication in the matrix can take on a variety of molecular configurations. The molecular arrangement in solid dispersions has been studied using a variety of approaches. The most effort, however, has gone into distinguishing between amorphous and crystalline materials. There are a variety of approaches for detecting the amount of crystalline material in a dispersion.

**1. Drug -carrier miscibility**

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

**2. Drug carrier interactions**

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

**3. Physical Structure**

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

**4. Amorphous content**

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- Powder X-ray diffraction

**5.Stability**

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

**6. Dissolution enhancement**

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media[23]

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