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## COMPREHENSIVE STUDY ABOUT SOLUBILITY ENHANCEMENT TECHNIQUES

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### ABSTRACT

Solubility is an important parameter for dosage form. According to BCS Classification Class II drug has low water solubility effects its dissolution and bioavailability of drug. The various methods are used to improve solubility of drug by chemical modification and physical modification such as solid dispersion, co solvent method and cyclodextrin encapsulation. This study is important to understand the difference between various methods used to enhance solubility. It is useful to reduce toxicity by reducing dose of drug. To improve absorption and dissolution of drug to achieve better therapeutic response. The solubility of a drug molecule plays a vital role in its bioavailability, as the aqueous solubility of poorly water soluble drugs (BCS class II) molecule in gastrointestinal fluid often causes unsatisfactory bioavailability, poorly aqueous soluble drugs often requires high dose in order to reach therapeutic plasma concentration. After oral administration of any BCS class II drug to be absorbed must be present in the form of aqueous solution at the site of absorption.

**Keywords:** Sertaconazole, Cyclodextrin, Solubility, absorption, bioavailability, toxicity

## INTRODUCTION

**Solubility:** Solubility is defined as the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent [1]. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure [2]. The of solubility of a substance in a specific

solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution [3]. Solubility is not same with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction [4].

Solubility Expression [5]

Table 1: Solubility Expression

Definition	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1 -10
Soluble	From 10 -30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000 -10,000
Insoluble	Greater than 10,000

**BCS Classification:** The low solubility and dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause less bioavailability [6]. In the Biopharmaceutical Classification System (BCS) Class II drugs are those are having

low aqueous solubility and high membrane permeability and therefore, solid dispersion technologies are particularly promising for enhancing the oral absorption and bioavailability of BCS Class II drugs [7, 8].

Table 2: BCS classification of Drugs

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

### Classification

Any drug is said to be poorly soluble when [9]

1. Aqueous solubility <100µg/ml.
2. Poor dissolution: Intrinsic dissolution

rate <0.1mg/cm<sup>2</sup>/min,

3. High molecular weight: (>500), Self association and aggregation.
4. High crystal energy

### Techniques to overcome poor solubility [10-16]

I. Physical Modification	II. Chemical Modifications:
<ol style="list-style-type: none"> <li>1. Particle size reduction               <ol style="list-style-type: none"> <li>a) Conventional method</li> <li>b) Micronization</li> <li>c) Nanosuspension</li> </ol> </li> <li>2. Modification of the crystal habit               <ol style="list-style-type: none"> <li>a) Polymorphs</li> <li>b) Pseudo polymorphs</li> </ol> </li> <li>3. Complexation               <ol style="list-style-type: none"> <li>a) Physical mixture</li> <li>b) Kneading method</li> <li>c) Co-precipitate method</li> </ol> </li> <li>4. Inclusion Complex Formulation Based Techniques               <ol style="list-style-type: none"> <li>a) Lyophilization/Freeze-drying Technique</li> <li>b) Microwave irradiation method</li> </ol> </li> <li>5. Solubilization by surfactants               <ol style="list-style-type: none"> <li>a) Microemulsions</li> <li>b) Self micro emulsifying drug delivery system</li> </ol> </li> <li>6. Drug dispersion in carriers               <ol style="list-style-type: none"> <li>a) Solid solutions</li> <li>b) Solid dispersions                   <ol style="list-style-type: none"> <li>i. Fusion Process</li> <li>ii. Solvent Method</li> <li>iii. Fusion solvent method</li> <li>iv. Spray drying</li> <li>v. Lyophilization (Spray Freeze Drying Method)</li> </ol> </li> </ol> </li> </ol>	<ol style="list-style-type: none"> <li>1) Salt Formation</li> <li>2) Co-crystallization</li> <li>3) Co-solvency</li> <li>4) Hydrotropy</li> <li>5) Use of novel solubilizer</li> <li>6) Nanotechnology</li> </ol>

**Solid Dispersion Method [17]:** Solid dispersion shows a reduction in particle size and an increase in surface area of poorly water-soluble drugs, resulting in improved solubility, dissolution rate, and oral bioavailability [18, 19].

#### Merits of solid dispersion [20-22]

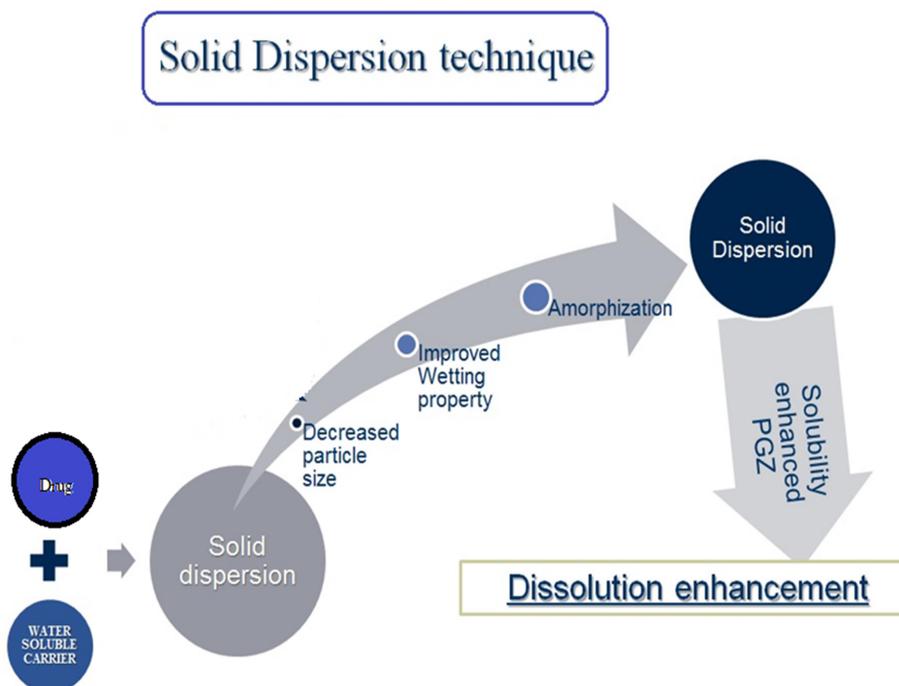
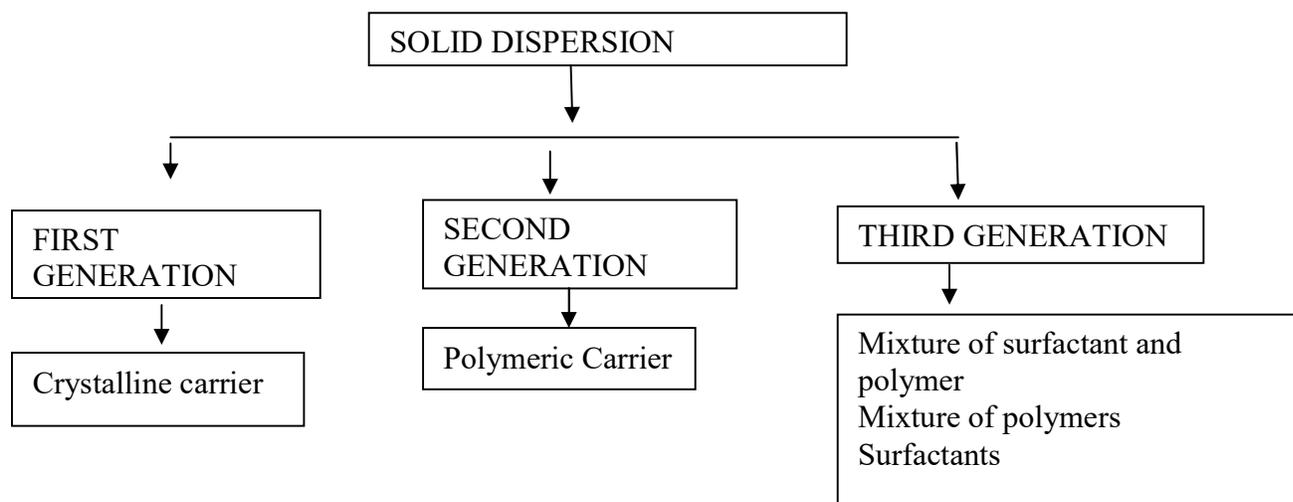
- Increased wet ability during solid dispersion, results in enhancing the solubility. Here the carriers play the key role to improve the wet ability of the solid particles.
- In solid dispersion method, the particles are having high degree of

porosity. Increase in porosity influence carrier properties and increase drug release profile [23].

- Amorphous state of drug leads to enhancement in drug. By using solid dispersion method, drugs are presented as supersaturated solutions, which are considered to be meta stable Polymorphic form [23]
- Particle size reduction in solid dispersion leads to increase → surface area which cause increase in dissolution rate hence improved bioavailability [24].

**Demerits of Solid Dispersions: [25]**

- Stability problem of vehicle and drug.
- Physicochemical properties reproducibility.
- Method of preparation is expensive.
- Difficult to prepare solid dispersions in a dosage form [25].

**Classification of Solid Dispersion: [26]****Figure: Solid Dispersion Process**

### 1.3: Molecular Encapsulation with cyclodextrins:

Cyclodextrins beta or gamma and various derivatives have ability to enhance solubility to form molecular inclusion complex with hydrophobic drug. Oligosaccharides

produced from starch are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guests, outside the host molecules is relatively hydrophilic [27].



Figure: Cyclodextrin Encapsulation

#### CO-Solvency Method:

Solubility of poorly aqueous soluble drugs in pharmaceutical liquid formulations can be enhanced by using co-solvent. Co solvents are the mixtures of miscible solvents often used to water which can dramatically change the solubility of poorly aqueous soluble drugs [28].

#### Micronization Method:

In this process size of drug particles should be reduced to 1 to 10 microns by using spray drying method also named as micro milling [29].

#### CONCLUSION:

The solubility of a drug molecule plays a vital role in its bioavailability, as the aqueous solubility of poorly water soluble drugs (BCS class II) molecule in gastrointestinal

fluid often causes unsatisfactory bioavailability, poorly aqueous soluble drugs often requires high dose in order to reach therapeutic plasma concentration. After oral administration of any BCS class II drug to be absorbed must be present in the form of aqueous solution at the site of absorption

The bioavailability may be enhanced by increasing solubility and dissolution rate of the poorly water soluble drugs in gastrointestinal fluid. The Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity Researchers are still working to resolve this issue and till now researchers have used different solubilisation methods such as solid dispersion, co-solvent method,

co-crystallization methods, Microencapsulation (Beta cyclodextrin) method, hydro trophy etc. The endeavour of the present study is to improve solubility, bioavailability with reduced dose and toxicity of widely used anti fungal drug.

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