MS.ID-IJPBS-6018
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 13 (1): 41-47
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Review Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Enhancement and Absorption of Poorly Water-Soluble Drug Through GIT

Anannya Bose, Susanta Paul, Indrajit Das and Pranee Roy
Department of Pharmaceutical Technology, JIS University, 81 Nilgunj Road, Agarpara, Kolkata - 700109, India.
124, Basanta Lal Saha Rd, Buroshibtalla, Behala, Kolkata, West Bengal - 700053, Department of Pharmaceutical Technology, JIS University, 81 Nilgunj Road, Agarpara, Kolkata - 700109, India.

Received: 28 Oct 2022 / Accepted: 26 Nov 2022/ Published online: 01 Jan 2023
***Corresponding Author Email:** anannya.bose@jisuniversity.ac.in

Abstract
Solubility is one of the important parameter to attain desired concentration of drug in systemic circulation for pharmacological response to be shown. It is vital to improve the solubility and dissolution rate for poorly soluble drugs since these drugs possess low absorption and bioavailability. About 40% of all new chemical entity has poor bioavailability. Increasing the bioavailability of poorly soluble drugs will be one of the biggest challenges for formulation scientists in the future. This review is intended to discuss thoroughly the various traditional novel techniques like sono crystallization, spray freezing into liquid, pearl milling, solid dispersion, salt formation and pH adjustment etc. for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation and also tried to focus on the polymers used for to achieve solubility enhancement, process of Solubilization and factor effects on it. In this article we focused on, solubility of the drug is the most significant factor and prime requirement for to achieve good bioavailability after the absorption of drug, so it is most critical factor in the formulation development. Bioavailability of poorly water-soluble drugs from gastrointestinal tract (GIT) can be enhanced by formulating the drugs in lipid-based formulations. This formulation can increase the dissolution of poorly water-soluble drugs and facilitates the formation of solubilized phases from which absorption may occur.

Keywords
Poorly water-soluble drug, Gastrointestinal absorption, Formulation, Bioavailability, Drug delivery.

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INTRODUCTION:
The therapeutic efficacy of a drug is determined not only by its bioavailability, but also by its solubility. The greatest concentration of the medicine dissolved in a suitable solvent under certain temperature, pH, and pressure conditions is known as drug solubility

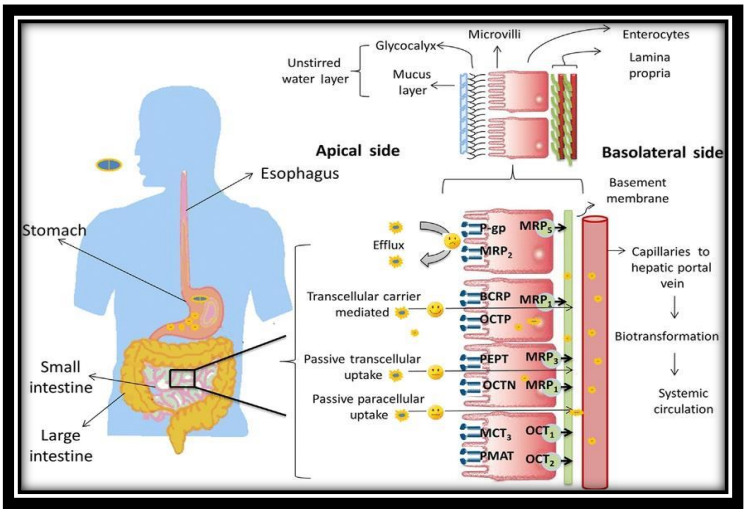

Figure 1: Journey of drug in gastrointestinal tract.

Because solubility is a crucial driver in drug liberation, it also plays a role in bioavailability. For the absorption of any substance at the absorption location, the drug must be in the form of an aqueous solution. Approximately 40% of all novel chemical entities have poor performance bioavailability. Changes in disintegration and dissolving can boost bioavailability. Solubility in water less than 1g/ml will undoubtedly cause a bioavailability issue, affecting the drug's efficacy. The drug's water solubility can be improved using a variety of techniques. Bioavailability can be enhanced by increasing the drug's solubility and dissolution rate in the gastro-intestinal fluids, especially for class II drugs according to the Biopharmaceutics Classification System (BCS)[1].

The Indian Pharmacopeia classified the solubility of drugs in seven classes as listed in Table 1.

Table 1: IP 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 10,000
Practically insoluble	10,000 and over

BCS Classification:

- Class I-High Solubility, High Permeability
  Drugs in class I have a high absorption rate and a high dissolution rate. Because dissolution rate generally exceeds gastric emptying for Class I compounds formulated as immediate release products, nearly 100 percent absorption can be predicted if at least 85 percent of a product dissolves within 30 minutes of in vitro dissolution testing across a range of pH values, in vivo bioequivalence data are not required to ensure product comparability E. g. Metoprolol, diltiazem, verapamil, and propranolol [2]
- Class II -Low Solubility, High Permeability
  Class II drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting Step for absorption apart from at a very high dose number. E.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine [2]
- Class III – High Solubility, Low Permeability
  In this class for drug absorption permeability is rate limiting step. These drugs show a high variation in the rate and amount of drug absorption. e.g., Cimetidine, Acyclovir, Neomycin B, Captopril [2]
- Class IV- Low Solubility, Low Permeability
  Those compounds have a poor bioavailability usually they are not well absorbed over the intestinal mucosa and a high variability is expected with very poor oral bioavailability [2]

IMPORTANCE OF SOLUBILITY:

Because of its convenience of administration, high patient compliance, cost-effectiveness, sterility limitations, and versatility in dosage form design, oral ingestion is the most efficient and widely used mode of drug delivery. As a result, many generic medication manufacturers are more likely to develop bioequivalent oral drug products[3].

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response[4].

Importance of Solubility Enhancement includes

- One of the crucial factors in achieving the desired medication concentration in systemic therapy is solubility for achieving the necessary pharmacological reaction.
- High dosages and high dosage regimens are typically necessary for poorly water soluble medicines in order to following oral treatment, affect therapeutic plasma concentrations.
- The fundamental issue in the development and preparation of is low aqueous solubility both for novel chemical entities and for generic medications.
- For medications taken orally, solubility is a crucial rate limiting factor to achieve their intended effect for a pharmacological reaction, the desired concentration must be in full circulation.
- Water is the solvent of excellent for liquid pharmaceutical formulations.
- Most of the drugs like weakly acidic or weakly basic having poor aqueous solubility.
- Slow medication absorption from poorly water-soluble medicines causes inadequate and gastric
- varying bioavailability and mucosal toxicity.

Importance of lipid-based drug formulation

Because they can improve oral bioavailability of drugs by increasing dissolution and solubility by pre-dissolving drugs in lipid carriers, improving drug permeability in the gastrointestinal tract (GI) by inhibiting P-gp and other efflux transporters, and avoiding the first-pass metabolism of the drug through the lymphatic absorption processes, lipid-based drug delivery systems have become a popular technology.

Drug delivery methods based on lipids have additional advantages. For starters, by minimising irregular absorption, they may be able to lessen the effects of meals and improve the reproducibility of the pharmacokinetic (PK) profile of medications taken orally.

Enhancement of gastrointestinal absorption of poorly water-soluble drug

Drugs that are poorly water soluble can have their bioavailability from the digestive tract (GIT) increased by being formulated in lipid-based formulations. This formulation can speed up the dissolving of pharmaceuticals that dissolve slowly in water and makes it easier to generate solubilized phases from which absorption may take place. The intraluminal processing that lipophilic medications undergo before absorption is most likely to be the cause of their increased solubility in lipid-based systems rather than the given lipid itself.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques

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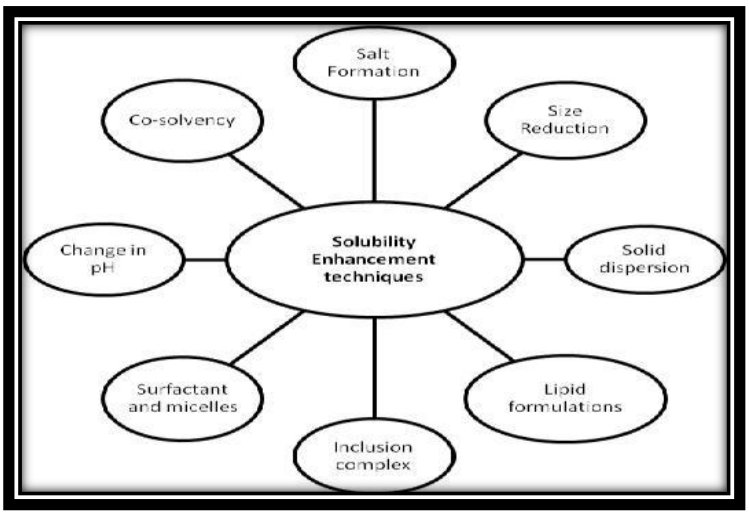

Figure 2 Different solubility enhancements techniques

Physical Modifications —
Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

Chemical Modifications —
Change of pH, use of buffer, derivatization, complexation, and salt formation.

Miscellaneous Methods —
Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

PARTICLE SIZE REDUCTION:
Drug solubility is frequently inversely proportional to particle size; as a particle gets smaller, the surface area to volume ratio rises. Because to the higher surface area, there is more interaction with the solvent, resulting in an increase in solubility.
Another common process for particle size reduction is micronization. Micronization enhances the rate of drug dissolution by increasing the surface area of the drug, but it does not increase equilibrium solubility. The rate of dissolution of these pharmaceuticals is improved by reducing the particle size of these drugs, which results in an increase in surface area. Drugs are micronized using milling techniques such as jet mills, rotor stator colloid mills, and so on. Micronization is not suitable for drugs with a high dose number because it does not change the drug's saturation solubility [5]

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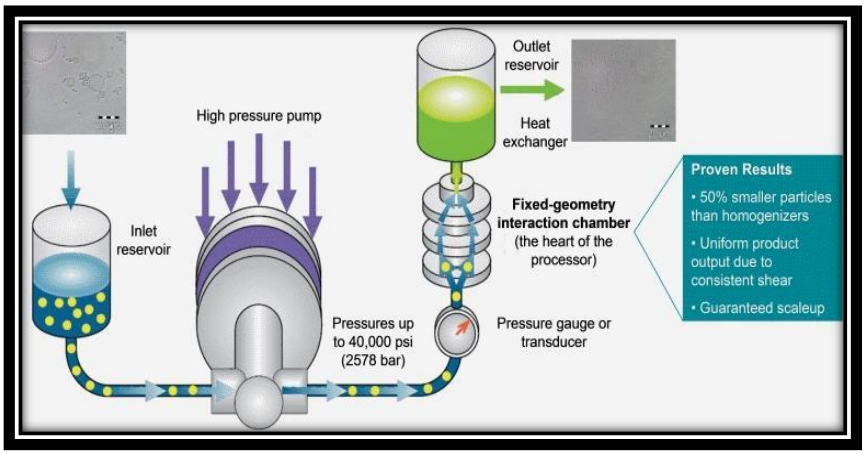

Figure 3 Microfluidizer: Particle Size Reduction Processors

SOLID DISPERSION:
In the early 1960s, Sekiguchi and Obi examined the formation and dissolving performance of eutectic melts of a sulfonamide medication and a water-soluble carrier and proposed the notion of solid dispersions. Solid dispersions are a valuable pharmaceutical approach for improving drug solubility, absorption, and therapeutic efficacy in dosage forms. Solid dispersion is a phrase used to describe a collection of solid goods made up of at least two separate components, usually a hydrophilic matrix and a hydrophobic medication [6].

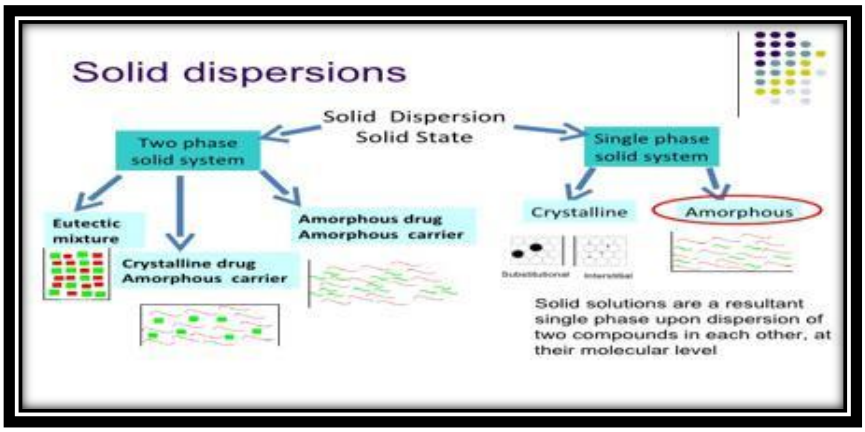

Figure 4 schematic representation of solid dispersion technique

NANOSUSPENSION:

The technology of nanosuspension has been developed as a possible contender for the efficient delivery of hydrophobic medicines. This method is used on pharmaceuticals that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system made up of nano-sized drug particles stabilised by surfactants for oral and topical administration, as well as parenteral and pulmonary delivery. Solid particles in nanosuspensions have a particle size distribution of less than one micron, with an average particle size range between 200 and 600 nm [7][8] .

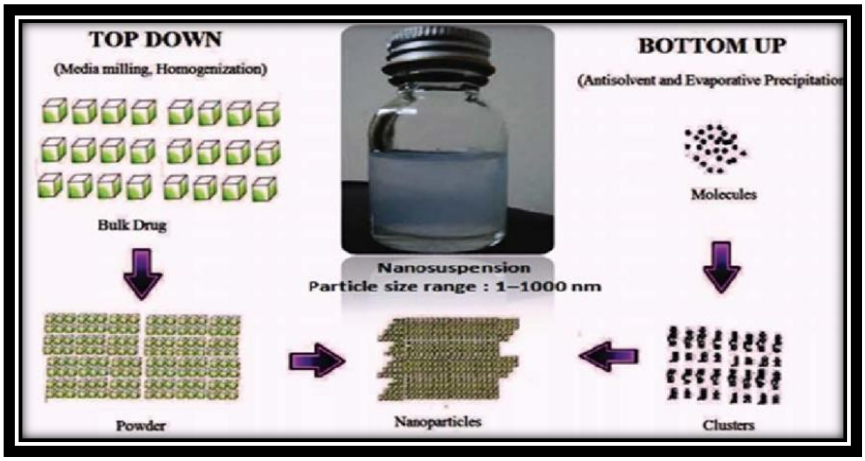

Figure 5 Schematic representation of preparation of nanosuspension

CRYOGENIC TECHNIQUES:

Cryogenic techniques have been developed to increase the pace of drug dissolution by producing nanostructured amorphous drug particles with a high degree of porosity at extremely low temperatures. The type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), nozzle location (above or below the liquid level), and cryogenic liquid composition can all be used to characterise cryogenic inventions (hydrofluoroalkanes, N2, Ar, O2, and organic solvents). Dry powder can be obtained after cryogenic processing using a variety of drying methods such as spray freeze drying, air freeze drying, vacuum freeze drying, and lyophilisation [9-11].

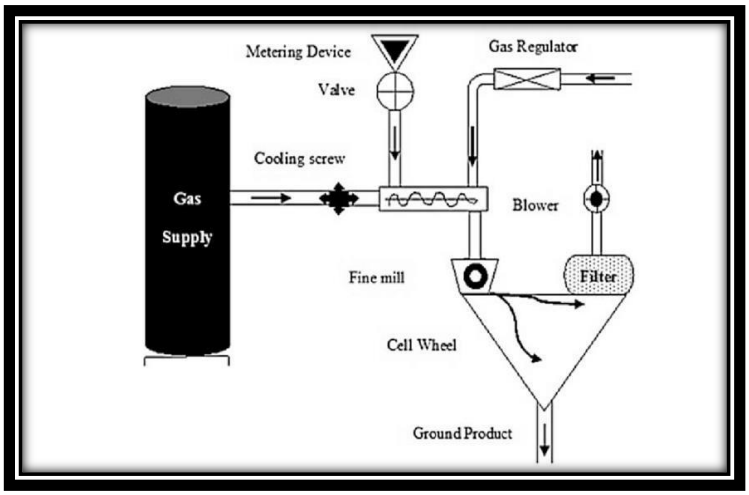

Figure 6 Schematic presentation of cryogenic technology

- ✓ **Spray Freezing onto Cryogenic Fluids**

  Spray freezing onto cryogenic fluids was invented by Briggs and Maxvell. The medication and carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant in this process. To improve the dispersion of the aqueous solution, a sonication probe can be put in the stirred refrigerant [12].

- ✓ **Spray Freezing into Cryogenic Liquids (SFL)**
  Amorphous nanostructured aggregates of drug powder with high surface area and good wettability were created using SFL particle engineering technique. It uses direct liquid-liquid impingement between the automatized feed solution and the cryogenic liquid to achieve strong atomization and, as a result, much faster freezing rates. Following that, the frozen particles are lyophilized to produce dry, free-flowing micronized powders [13].

HYDROTROPHY:

Hydrotrophy is a solubilisation process in which the hydrotropic agent increases the water solubility of the first solute by adding a large amount of second solute. Ionic organic salts, also known as hydrotropic agents, are made up of alkali metal salts of different organic acids. Salts that improve the solubility of a solute in a particular solvent are called to "salt in," while salts that decrease solubility are said to "salt out." A phenomenon known as "hydrotropism" occurs when many salts with large anions or cations that are themselves very soluble in water "salt in" non-electrolytes called "hydrotropic salts." The term "hydrotrophy" refers to the increase in water solubility caused by the presence of a substantial amount of chemicals.The method by which it enhances solubility is more closely linked to complexation, which involves a weak contact between hydrotrophic substances such as sodium benzoate, sodium acetate, sodium alginate, and urea, and poorly soluble medicines[14][15].

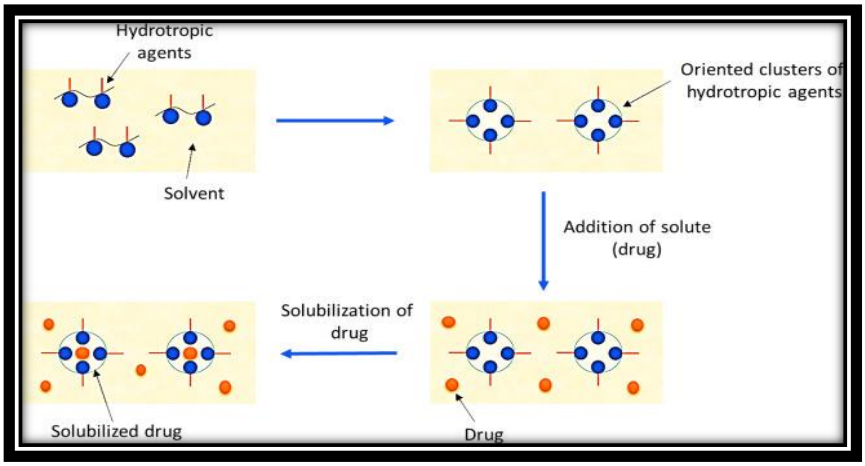

Figure 7 Schematic presentation of hydrotrophy technique

CONCLUSION:

Medication solubility is a prerequisite for drug 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 various methods mentioned above can be employed separately or in combination to increase the solubility of the medicines. The secret to achieving the objectives of a good formulation, such as good oral bioavailability, decreased frequency of dose, and improved patient compliance, combined with a cheap production cost, is proper process selection for solubility improvement. The choice of a method for solubility enhancement depends on the properties of the drug, such as solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour, and so forth. It also depends on the dosage form requirements, such as the formulation of tablets or capsules, strength, immediate, or modified release, and so forth.

ACKNOWLEDGEMENT:

It is my privilege to utilize this golden moment and myself to acknowledge. I consider myself most lucky to work under the guidance of Assistant Prof. Anannya Bose, Department of pharmaceutical Technology, JIS University, Agarpara, Kolkata, I take this opportunity to
express my heartfelt gratitude to my reverend guide.

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