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Techniques for Enhancing Drug Solubility: A Comprehensive Overview

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Abstract

Drugs with poor solubility have a major impact on their bioavailability, absorption and therapeutic efficacy, which presents a substantial difficulty in pharmaceutical development. This article offers a thorough analysis of numerous approaches to improving drug solubility, including both traditional and modern methods. Modern developments like nanotechnology and amorphous solid dispersions are presented alongside traditional methods like particle size reduction, solid dispersion and pH adjustment. Pharmaceutical researchers may maximise drug performance, guaranteeing improved patient results and broadening the spectrum of effective medicinal molecules, by utilising these solubility enhancement techniques. This article aims to offer valuable insights into solubility enhancement techniques to guide future research and development efforts.

Keywords - Drug solubility, poorly water-soluble drugs, Solubility enhancement, Bioavailability, Nanotechnology

INTRODUCTION

The capacity of a substance to mix with a liquid and the concentration of the dissolved substance in a saturated solution at a given temperature, characterized by a consistent and uniform molecular distribution in terms of quality, are referred to as solubility characteristics.

The highest quantity of a substance that can be incorporated into a defined volume of a liquid is known as its "solubility." That can be characterised both qualitatively and quantitatively.[1]

When the dissolved substance and the liquid are in equilibrium, the mixture is considered to be fully concentrated. To enhance the dissolvability of a poorly soluble medicine and increase its bioavailability, several approaches can be modified. A solubility chart enumerates ions along with their tendency to Form a solid or stay dissolved when combined with other substances. The solubility of a medication can be represented through different concentration metrics, such as ratios, proportions, molarity, molality, volume ratios and mole ratios. [2,3,4]

Solubility Expression [5]

Descriptive terms	Relative amount of solvents to dissolve 1 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	More than 10,000

Table 1: *Solubility Expression*

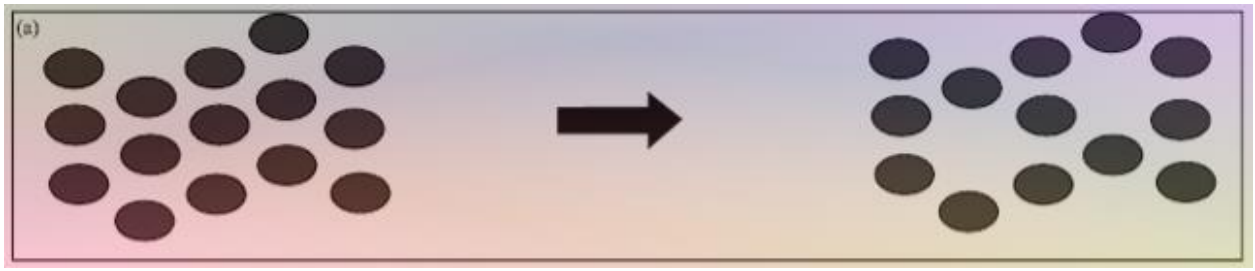
Poor Oral Absorption can happen for several reasons. Here are some possible causes

A drug is considered to have low solubility. Less than 100µg/ml in aqueous solution, Poor dissolution: The intrinsic dissolution rate is less than0.1 mg/cm²/min, High molecular weight: greater than 500, High crystal energy, self-assembly and clustering.[6]

The solubilisation procedure [7]

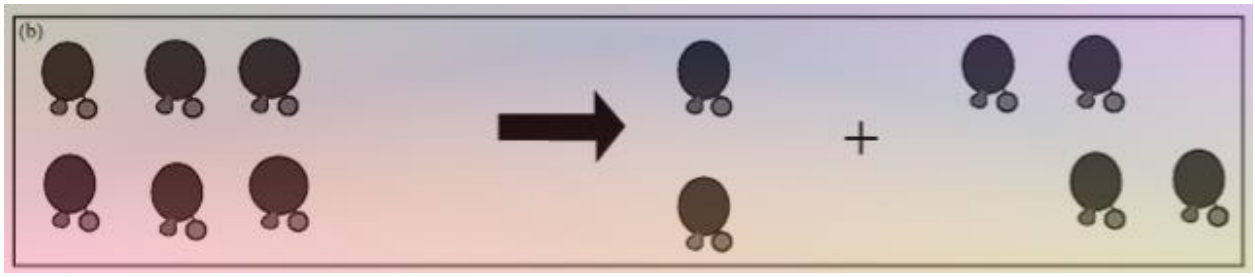
Step 1:

The solubilisation process includes both dissolving ionic or molecular bonds within the solute and separating the connection among dissolving agent & dissolved entity.



Step 2:

Dense molecules separate out of substance



Step 3:

Introduce the solid molecule feed into the solvent cavity.

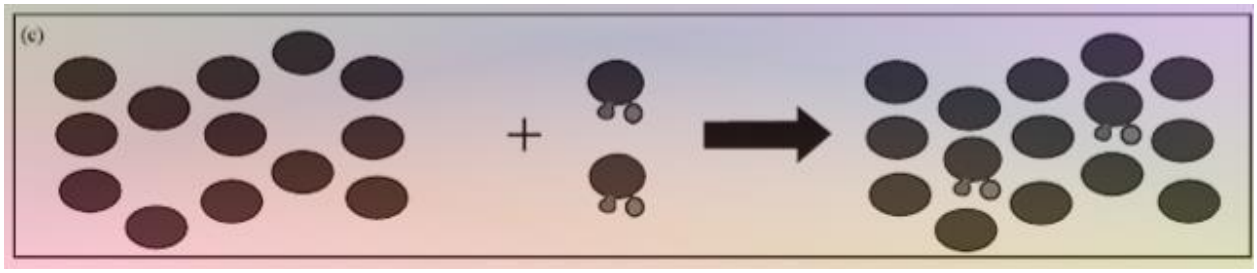


Figure 1*: *The solubilisation procedure Biopharmaceutics Classification System (BCS)

Drugs are categorised into four groups according to the BCS system became stablished via FDA & is based on permeability and dissolvability. Categories II and IV of the system encounter dissolution as the rate-limiting factor for drug absorption due to their poor solubility.

BCS Classification of Drug [8]

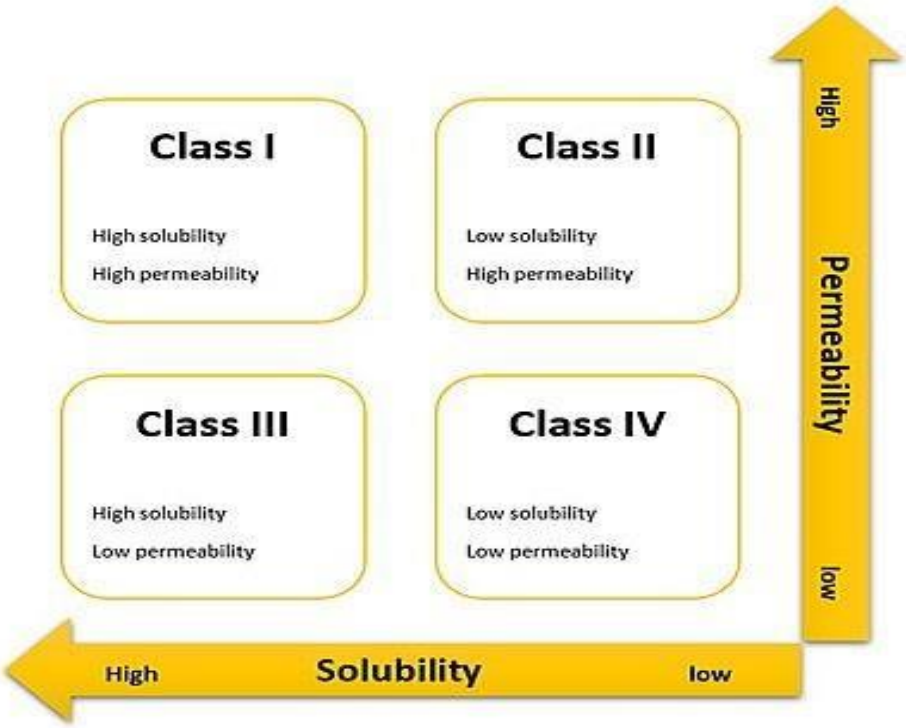


Figure 2: *BCS Classification of drug*

The Importance of Solubility

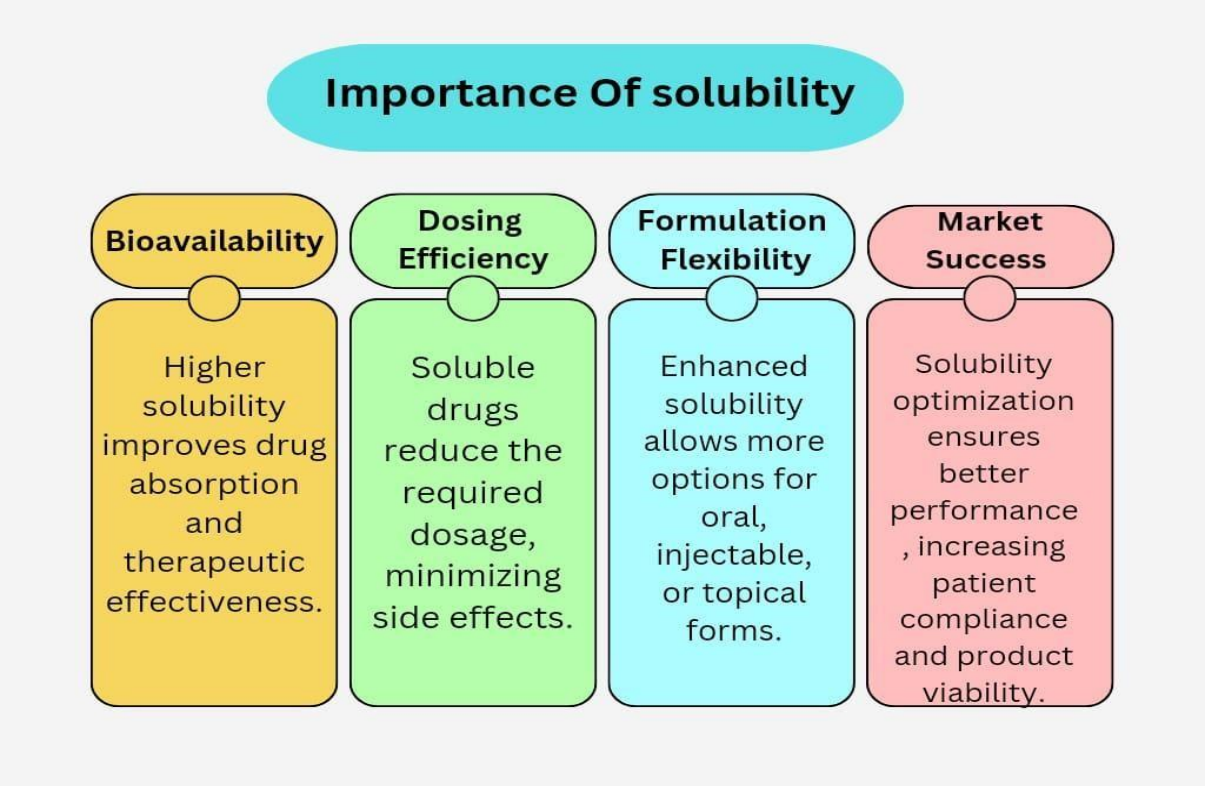


Figure 3: *Importance of Solubility*

Factors affecting Solubility [9]

There are various factors which effect on solubility as follows:

Particle size

Smaller particles dissolve faster than larger ones because their surface area is greater in relation to the solvent, even though the solubility itself remains same. The solubility and particle size relationship can be described using the following formulas.

$$\log \frac{S}{S_0} = \frac{2 \quad \gamma \quad V}{2.303 \quad R \quad T \quad r}$$

Where,

S = Stands for infinitely large particle solubility

So = Stands for suspendability V = Stands for molecular volume λ = Stands for surface free energy r = Stands for radii of small grained T = Stands for thermodynamic temperature

R = Stands for ideal gas constant.

Climate (Temp.)

Temperature impacts solubility. An increase in temperature leads to a rise in solubility as energy is absorbed during the dissolution process. When energy is released during the dissolution process, solubility declines as temperature increases.

Pressure

Gaseous solutes become more soluble with increasing pressure and less soluble with decreasing pressure.

Characteristics of dissolved substance and solvent

Interactions between dissolved substances and the dissolving medium are influenced by concentration and mixing temperature. At ambient temperature, 1gm of lead (II) chloride dissolves in water. Similarly, zinc chloride dissolves in the same amount of water at the same concentration.

Molecular size

The inability to solvate compounds with larger molecular weights and sizes by enveloping them in solvent molecules is the cause of this decrease in solubility.

Techniques for enhancing solubility [10,11]

Techniques to improve solubility can be divided into the following categories:

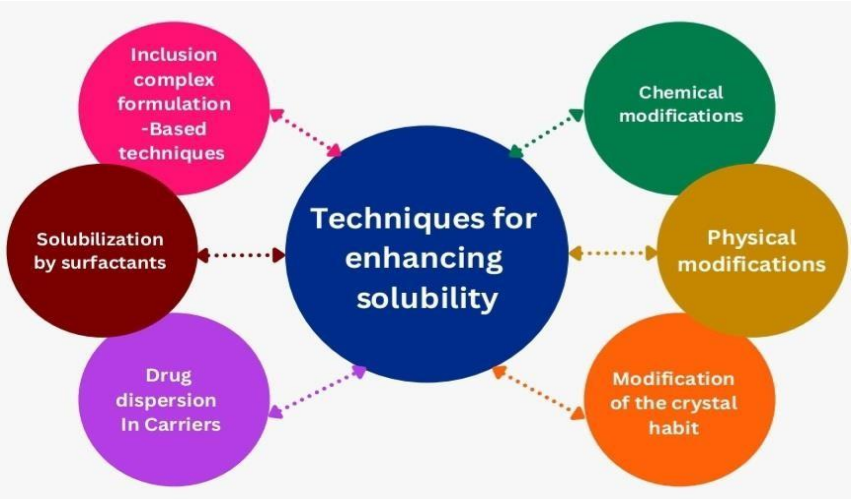


Figure 4: *Techniques for enhancing solubility*

Salt formation

Since many medications can ionize when they react with an acid or base, they can produce salts. In general, medications that are in salt form are more soluble than those that are in neutral form.

Example

Aspirin is more soluble as sodium acetylsalicylate compared to acetylsalicylic acid.

Co-crystallization [12]

Co-crystals are created when a medication and a co-crystal former combine to change the crystalline structure and increase solubility.

Example

Co-crystals of carbamazepine with saccharin or nicotinamide improve its solubility.

PH adjustment

It may be possible to dissolve poorly soluble medications in water by adjusting the PH. These drugs have Parts of the molecule that can undergo protonation or deprotonation. Blood, with a pH of 7.2 to 7.4, acts as a strong buffer, which may cause insoluble medicine to separate when delivered via IV. A pH about the duodenum exists between 5 -7.5 and the stomach's 1 to 2, therefore when a medicine is taken orally, its solubility will probably also change as it moves through the intestines. There are three possible types of compounds: zwitterionic, bases, and acids. It is also applicable to poorly soluble lipophilic and crystalline substances. [13,14,15,16]

Particle size reduction

For medications that are poorly soluble, drug particle size and bioavailability are often closely correlated. Expanded wider region may improve a medication efficacy until disintegrates by reducing the size of the particles, allowing for a wider range of formulation and administration strategies.[17] Increased solubility is caused by a higher contact between the surface area and the solvent.[18]

These days, Micronizing & Nanosuspension can be used until minimize particles. Various equipment is used in each process until compress particle. To reduce granule extent each technique makes use of a unique collection of equipment. Medication dissolvability during micronizing is frequently reciprocally correlated with granulometry. The particle's reduced size due to its enlargement outer region enhance a drug's solubility features. Micronizing does not exist suitable to megadose drugs considering that doesn't change dissolution. Another method exists nano-suspension, where the nanodispersion, surfactant-stabilized clean particle forms. Narazepide, Antiprotozoal, Antifungal, Antineoplastic, are amongst those medications for which the nano-suspension method has been used. The procedures utilised into make nanosuspensions occur homogenization and wet milling. [19,20]

Co-solvency

A medication that dissolves poorly in water can frequently become more soluble by adding cosolvents, or A hydrophilic solvent where the medication exhibits strong dissolvability.[21] Additive solvent are mixtures composed of water and at least one hydrophilic solvent that enhance the dissolvability of chemicals that are poorly soluble. Co-solvency has been applied to both liquid and solid formulations. Ethanol, 1,2-Propanediol, and Carbowax 300 are examples of agents used in solvent mixtures. Oral and parenteral administration are both possible with solvent mixture of low solubility medications. It could be necessary for parenteral formulations to dilute the solvent concentration before administration by adding water or using an aqueous medium. Co-solvents, when used with current dissolution method & acid-base balance correction, can continued growth the dissolvability of weakly Dissolvable substances. Utilising compatibility solvent is extremely

beneficial strategy to improve the dissolution of poorly soluble medication.[22,23,24] Ethanol, glycerin, propylene glycol, & PEG are the typically utilized biocompatible dissolving agent for injectable administration.[25,26] Dimethylsulfone & N,N-Dimethyl-2-oxopropanamide are often utilized in the form of solvation agents due to them exceptional capability to solubilise medications that are difficult to dissolve & their(s) low hazard potential.[27]

Hydrotropy[28]

When a considerable amount of a second solute is introduced, it becomes more water soluble, a process known as hydrotrophy takes place. The solute is made up of sodium and potassium salts of various carboxylic acid. Hydrotropic agents represent ionic organic salts. This term "salt in" indicates additives either salt as increase a Dissolved substance solubility within a certain dissolving medium whereas the term "salt out" indicates solutes which become slightly dissolvable. The "salting in" from neutral compound called "hydrotropic salts," or "hydrotropism," exists contributed via a number of electrolytes including big electron donor either electron acceptor which exist also highly water- dissolvable.

Use of novel solubilizer

Using a variety of solubilizing agents can also help medications that are poorly soluble become more soluble. Hydrophobic API becomes more soluble when it is dissolved in conventional solubilizers such as polysorbates, PEG 400 Sepitrap, Soluplus, Povacoat, and dendrimers.

Sepitrap: An Innovative Solubilizer

Sepitrap M, a microencapsulated solubilizer for solid dose application, desorbs 80% of its solubilizers in less than five minutes, making the medication component soluble. The drug to spectrum ratio of 2:1 can be effectively utilized to accelerate the rate of dissolution without compromising the tablet's characteristics and without imposing any limitations on formulation.[29]

Nanotechnology

Generally, describe study & implementation about substances & nanostructured design dimension about fewer than one hundred nanometers. Nanosizing was the next stage since, regarding numerous novel molecular species including extremely limited dissolvability, gastrointestinal absorption improves through particle size reduction exist insufficient due to the micronized product's relatively limited effective surface area for dissolving. There are several preparation techniques that can be used, including vacuum deposition, high-temperature evaporation, high-pressure homogenisation, and grinding.[30]

Ball milled products

Through the process of ball milling, drug particles are mechanically decreased in size. This high-energy impact method may also alter the drug's crystalline structure. Hard balls (usually made of steel or ceramic) are placed within a revolving chamber to perform the procedure. The drug particles are broken into tiny pieces by the balls' collisions with them while the chamber rotates.[31]

Microemulsions

Proteins have been added to microemulsions for oral, parenteral, and transdermal administration, as well as enhance a solubility comprising certain medicine which exist essentially hydrophobic. Water, oil, and surfactants (with or without a cosurfactant) combined in an isotropic mixture to form microemulsions that are clear or translucent and thermodynamically stable. Hydrophobic drug molecules can form micelles around themselves or lipophilic medicines may exist integrated in their oil phase to increase the solubility of pharmaceuticals. Since the small droplet size increases the surface area and allows more drug to come into touch with the biological medium, absorption is improved. It also speeds up the process of drug dissolving. [32,33]

Micellar Solubilization

Surfactants have also utilized enhance dissolvability capabilities containing pharmaceutical compound insoluble. Surfactants have the ability to decrease interfacial energy & enhance solubility containing hydrophobic medicines within hydrous solutions. [34,35,36] Colloid production happens when at the level of emulsifier presence surpasses its threshold concentration for micellization. That typically within the interval of 0.05-0.10% for Most surface-active agents. This entraps medicines inside of colloid.[37] Micellar solubilisation has become a common alternative for dissolving poorly soluble medicines. [38]

Supercritical fluid process (SCF)

Nonvolatile solvents, such as carbon dioxide, can be dissolved by supercritical fluids (SCFs). It is affordable, safe, and eco-friendly. Over of it crucial pressure and temperature, an (SCFs) maintain a homogeneous state. (SCFs) become an intermediary among true liquid & gas, which gives those features beneficial in medication processing. Recently, pharmacies have embraced the unique processing abilities of SCFs, which have been acknowledged and utilized in the food sector for a long time. The present state of SCF techniques has demonstrated capability for generate nanostructured suspensions particulate with diameters ranging from 5 to 2,000 nanometers. Different SCF processing techniques are formulated into tackle specific limitations.[39]

Solid dispersions [40]

Enhancing the solubility, adherence & medicinal effectiveness about medications within formulations be accomplished by means of the use about solid amorphous distribution a valuable pharma technology.

By dispersing a weakly soluble medicine in a solid hydrophilic matrix with high solubility., this approach improves an drug's solubility. The results produced by solid dispersion methods can be either solid solution or eutectic.

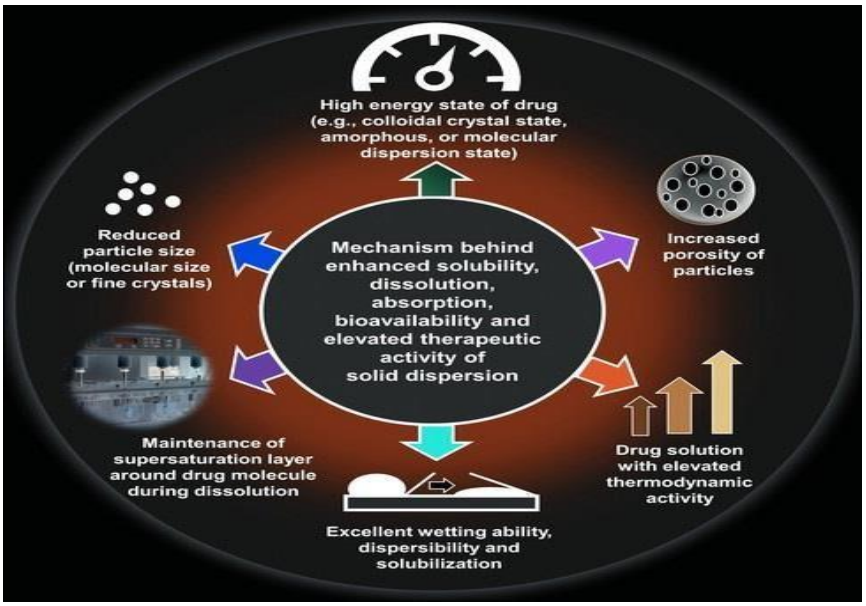


Figure 5*: *Mechanism of Solid dispersion Polymers Used in Solid Dispersions

Povidon
Macrogol
Hypromellose
Eudragit
Sugars (e.g., mannitol, sorbitol)

The selection of polymer is based on the drug's physicochemical properties and targeted release characteristics. Here are various methods for creating solid dispersions of hydrophobic drugs to enhance their water dissolvability.

Fusion Method (Melting Method)

In order to create a solid mass that is subsequently pulverised into a powder, the drug and carrier are heated until they melt together and are then quickly cooled.

Solvent Evaporation

A typical solvent is utilized to disintegrate the drug & the carrier, after which the solvent is evaporated, resulting in a solid dispersion.

Spray Drying

In order to quickly evaporate the solvent and generate fine particles of solid dispersion, the pharmaceutical and excipient are either mixed in suspension or dissolved within it before being sprayed into a chamber.

Hot-Melt Extrusion

After carefully regulated mixing and melting of the medication and carrier, the mixture is extruded into a solid shape.

Cyclodextrin

Cyclodextrin(s) are cyclic oligosaccharides made up of glucose units that can improve the solubility of drugs with low water solubility. Their hydrophilic exterior and hydrophobic central cavity enable them to create inclusion complexes with drug molecules. This encapsulation enhances the solubility, stability, and bioavailability of the drug by promoting its dissolution in water. Cyclodextrin(s) are commonly utilized in pharmaceutical formulations to boost the efficacy of different medications.[41]

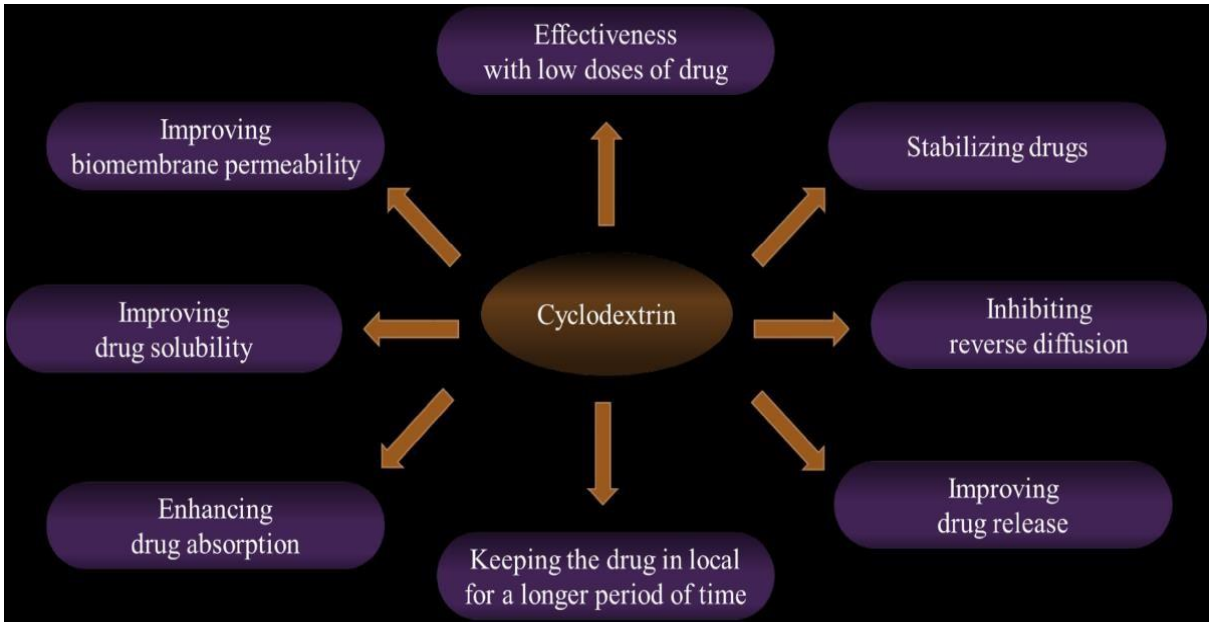


Figure 6: *Cyclodextrin Applications*

Cryogenic techniques

Cryogenic techniques improve drug solubility by generating amorphous, nanostructured, and highly porous drug particles at very low temperatures. These processes utilize a range of injection devices and cryogenic liquids to form fine drug particles that dissolve more easily in solvents. Afterward, various drying methods, including spray freeze drying and lyophilization, can be used to produce dry powders. This approach leads to enhanced dissolution rates and bioavailability for drugs with low solubility. [42]

Spray Freezing

Droplets of liquid medication formulations are sprayed into a cryogenic medium, rapidly freezing to produce tiny particles.[43]

Freeze Drying

This process involves freezing a medication solution to create a porous solid, followed by vacuum removal of the solvent to enhance solubility.[44]

Cryogenic Milling

In order to produce small particle sizes while avoiding thermal deterioration, this process includes grinding medicinal ingredients at cryogenic temperatures.[45]

CONCLUSION

One of the most important steps towards resolving the issues with poorly soluble drug formulation and bioavailability is improving drug solubility. This review has looked at a wide range of traditional and novel techniques for boosting solubility, including reducing particle size, solid dispersion, adjusting pH, and using creative co-solvents and solubilizers. Innovative technologies that have the potential to completely change medication formulation techniques include nanotechnology and amorphous solid dispersions. Which approach is ideal be based on several elements, involving a specific drug's physicochemical properties, intended use, and therapeutic goals. Even though there has been a lot of progress, more study on solubility enhancement is necessary to improve medication administration methods & increase therapeutic capability of novel drug candidates. Pharmaceutical development will become more effective and patient-centred with the integration of various methodologies and developing technology.

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