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Solubility Enhancement of Poorly Water-Soluble Drugs

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Abstract: *This article provides an overview of nanocrystals as a potentially valuable technology for enhancing the solubility of water-insoluble pharmaceuticals. Nanocrystals increase surface area by reducing particle size, hence improving bioavailability and solubility. The authors describe the preparation processes, benefits, and difficulties of employing nanocrystal formulations to overcome the solubility limitations of poorly soluble drugs. The authors examine formulation techniques that help with solubility problems, such as liposomes and self-emulsifying drug delivery systems. These lipid formulations are a useful technique in drug development because they further investigate how they affect drug absorption and bioavailability.*

Keywords: Increase in solubility, bioavailability, and BCS class II medications

I. INTRODUCTION

Solubility refers to a solid's capacity to dissolve into liquids and form a homogeneous solution. The optimal medication concentration in systemic circulation for the greatest pharmacological response is strongly reliant on solubility. To achieve therapeutic plasma concentrations, substantial dosages of poorly water-soluble medicines are frequently administered orally. Poor water solubility is a significant challenge when developing new chemical compositions(1). More than 40% of newly discovered chemical entities have limited bioavailability and solubility. These medications are classified as BCS class II, indicating high permeability and poor solubility. Increasing the solubility of drugs can significantly improve their bioavailability and efficacy(2).

Achieving the necessary medication concentration in the systemic circulation for the best pharmacological response depends on solubility. The solubility of poor aqueous lipophilic drugs makes them challenging to produce and administer. Various methods have been explored to make lipophilic medicines more soluble in water. Many methods are used to increase the solubility and bioavailability of drugs that are poorly soluble(3). Techniques typically There are several methods for solubilizing medications, including hydrotropic, solid dispersion, complexation, co-solvency, micellar solubility, micronization, chemical modification, and pH modulation. Solubilizing poorly soluble medications is a common difficulty in screening novel chemicals and designing formulations(4).

Objectives:

The goal of solubility augmentation techniques for medications that are not very water soluble is to improve the drugs' rate of dissolution, bioavailability, and therapeutic efficacy. By overcoming solubility restrictions, ensuring consistent therapeutic effects, and reducing pharmacokinetic variability, these strategies aim to increase pharmaceutical absorption. Physical, chemical, and formulation alterations are used to improve drug solubility without sacrificing stability or safety, allowing for the efficient delivery of difficult pharmaceutical substancesutilizing methods derived from advanced physics, chemistry, and nanotechnology(5). The objective is to improve drug bioavailability and therapeutic efficacy by tackling solubility limits, a critical problem in pharmaceutical development. Many techniques, such as solid dispersions, particle size reduction, salt generation, co-solvent use, and nano formulations, are highlighted in this work along with their uses, advantages, and disadvantages (6).

Methods and Techniques:

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BCS Classification:

Class I-High Solubility, High Permeability:

Class I drugs show a high absorption number and a high dissolution number. Since the dissolving rate of Class I compounds designed as immediate release products typically surpasses stomach emptying, approximately 100% absorption can be predicted if at least, In vitro dissolution testing over a range of pH values requires at least 85% of a product to dissolve after 30 minutes; therefore, in vivo bioequivalence data are not required to ensure product comparability [(7)].

e.g.: Metoprolol, propranolol, verapamil, and diltiazem.

Class II -Low Solubility, High Permeability:

Class II drugs have a high absorption number but a low dissolution number. Aside from a very large dose numbers, in vivo drug dissolution is a rate-limiting step for absorption. Since these medications' bioavailability is most likely dissolution-rate limited, there may be a relationship between their in vitro dissolving rate and in vivo bioavailability. e.g.: nifedipine, ketoconazole, mefenamic acid, danazol, and phenytoin.

Class III – High Solubility, Low Permeability:

In this class for drug absorption permeability is rate limiting step. The amount and pace of drug absorption varies greatly for these medications. It has been suggested that, as long as the test and reference formulations do not contain agents that potentially alter drug permeability or GI transit, dissolution will probably happen extremely quickly but absorption is permeability-rate limited[(8)].

Time, it might be reasonable to use waiver criteria akin to those for Class I compounds. e.g.: Cimetidine, Acyclovir, Neomycin B and Captopril

Class IV- Low Solubility, Low Permeability:

These substances typically have a low bioavailability due to poor absorption across the intestinal mucosa, and a considerable degree of variability is anticipated with extremely low oral bioavailability. In addition to being challenging to dissolve, these substances frequently exhibit partial permeability across the GI mucosa after dissolution[(10)]. These medications can have very significant side effects and are sometimes quite difficult to create. Variations across and within subjects.

Methods of solubility enhancement:

1. Particle Size Reduction

Drug dissolvability is frequently correlated with molecule size, with smaller molecules being more insoluble. To increase dissolvability, techniques like comminution and shower drying employ mechanical force [(9)]. However, damage can result from mechanical forces like crushing and processing. For chemicals that are unstable or thermosensitive, warm stretching during comminution and shower drying is also an issue.

2. Nanonization:

To improve the bioavailability and disintegration rates of medications that are ineffective in water, nanonization techniques are being employed. These methods increase drug solubility and lessen systemic side effects by employing materials and structures at a nanoscale level of 100 nm or less. Because micronization tends to agglomerate, it is insufficient for underutilized chemicals with limited dissolvability. Instead, nanonization is utilized [(10)]. For nanonization, a variety of techniques are employed, such as shower drying, emulsification-solvent dissipation, pears, homogenization, and damp processing.

3. Co-solvency

When medications are mixed with a water-soluble solvent, like cosolvent, they dissolve in water through a process known as co-solvency. This lowers the pressure between the hydrophobic solute and the watery structure. By extending a natural co-solvent into water, cosolvents—also referred to as dissolvable mixing—alter the dissolvability of drugs. While hydrophilic hydrogen bonds guarantee water insolvency, cosolvents feature hydrogen acceptor or giver groups with a tiny hydrocarbon position, which reduces the intermolecular attraction of water.

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4. Hydrotropy:

A solubilization method called hydrotropy makes hydrophobic substances more soluble in liquids. A large amount of a water-soluble material known as a hydro trope is employed to form a complex with the hydrophobic molecule. Agrochemicals, cosmetics, and pharmaceuticals are just a few of the industries that use hydro tropes, which are tiny atoms with hydrophilic and hydrophobic groups, to make hydrophobic compounds more soluble and bioavailable[(11)].

5. Sono crystallization:

A novel method called Sono crystallization reduces molecular estimations by using ultrasound crystallization. It improves nucleation rate and regulates medication dispersion by using ultrasound control with a repetition range of 20-100 kHz, usually employed between 20 kHz and 5 MHz.

6. Solid Dispersion

In order to improve drug disintegration, assimilation, and useful viability in dose shapes, Sekiguchi and Obi introduced the idea of strong scatterings in the 1960s. PVP, PEGs, Plasdone-S630, and surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate are examples of common hydrophilic carriers [(12)].

7. PH Adjustment

Lack of water Applying a pH change may cause dissolvable medication to degrade in water. In order to improve drug disintegration, assimilation, and useful viability in dose shapes, Sekiguchi and Obi introduced the idea of strong scatterings in the 1960s. PVP, PEGs, Plasdone-S630, and surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate are examples of common hydrophilic carriers.

8. Inclusion complexation

A solubilization method called incorporation complexation makes medications more soluble by forming a complex between the drug and a particle, usually a cyclic atom. Van der Waals forces, hydrophobic forces, and hydrogen holding are examples of non-covalent processes that create this complex. Particles including zeolites, cucurbiturils, calixarenes, and cyclodextrins are frequently utilized. This procedure can be carried out via kneading, freeze-drying, or co-precipitation. It is a method that is both economical and environmentally beneficial [(13)].

9. Self-emulsifying:

Ineffectively dissolvable medications can be broken down and transported using self-emulsifying sedate conveyance systems (SEDDS), which are stable, uniform, and viable. When combined with water or gastrointestinal fluids, their components—an oil stage, surfactant, co-surfactant, and sedate—form oil-in-water emulsions. SEDDS increase the assimilation and solvency of drugs, increasing their effectiveness and usability. They can be tailored to fit particular sedative qualities and the mode of administration, and they can be taken orally as pills or capsules.

10. Technology for Supercritical Fluids (SCF)

The ability of supercritical liquids (SCFs) to break down non-volatile solvents like carbon dioxide has made them more valuable in medical applications. SCFs have qualities that make them appropriate for handling products, and they are safe and environmentally beneficial. They are thicker than liquids, compressible like gases, and have a higher diffusivity than fluids. SCFs are useful for fine-tuning particular features for particular uses [(14)]. Carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, and water are examples of common SCF solvents. SCFs are appropriate for nano suspensions because they can micronize particles down to molecular levels. Nektar Therapeutics and Lavi pharm are two pharmaceutical businesses that specialize in leveraging SCF breakthroughs to increase dissolving and reduce molecules.

11. Liquisolid Technology

One technique that turns fluid sedate into a compressible powder is called liquidsolid innovation. The liquid sedate is combined with a carrier fabric to form a semi-solid mass, which is further ground into a powder. By acting as a barrier, the coated fabric enhances powder flowability and stops fluid spills. Compared to conventional forms like pills and capsules, liquidsolid frameworks have advantages including a more accurate dosage schedule and enhanced sedate dissolvability and disintegration rate. Liquisolid frameworks can be planned using three different techniques: co-precipitation, solvent dissipation, and the traditional way [(15)].

12. Micellar and Liposomal Systems:

These are colloidal systems that improve solubility and stability by incorporating the medicine into lipid bilayers (liposomes) or surfactant molecules (micelles). This technique works especially well for medications that are lipophilic.

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Particularly, hydrophobic medications can be encapsulated in liposomes to improve drug delivery to target tissues and increase their water solubility.

13. Prodrug Approach

A prodrug is a parent drug that has undergone chemical modification to increase its solubility. Through metabolic processes, the body transforms the prodrug back into its active form. This technique can improve the drug's absorption and solubility[16]. Ester prodrugs, for instance, are used to make medications that are not very soluble in their parent form more soluble in water.

14. Drying by Spraying

Using this technique, a drug and carrier solution (such a polymer) are sprayed into a heated chamber, where the solvent evaporates and a solid powder is left behind. Amorphous solid dispersions that have been spray-dried can significantly improve the solubility of medications that are not very soluble. This method might also increase the drug's bioavailability and rate of dissolution[17].

15. Enhancers of Bioavailability (Permeation Enhancers)

Enhancers of bioavailability improve drug absorption even while solubility is still restricted. Increased systemic drug exposure can arise from these enhancers' potential to improve drug permeability across biological membranes, including the gut wall. Common enhancers include bile salts, surfactants, and chemicals that disrupt the gut barrier to increase medication absorption.

16. Host–Guest Systems

Host-Guest Complexes: In this system, a poorly soluble drug (the "guest") and a "host" molecule (often cyclodextrin) combine to produce a complex that increases the drug's solubility by keeping it dissolved. The medication's therapeutic efficacy can be increased by releasing it in response to a particular environment (such a pH shift)[18]. Additionally, by shielding the medication from oxidation and degradation, these systems increase its solubility and stability**.**

17. Cocrystals

Cocrystals are crystalline solids composed of two or more molecules with a particular stoichiometric ratio, typically a conformer and a medication. The conformer, which is frequently a small molecule, can increase the drug's solubility without compromising its therapeutic effectiveness. In addition to offering advantages including enhanced stability and the ability to adjust dissolving settings, cocrystals can boost the solubility of medications that are poorly soluble.

18. Gel-Forming System

In Situ Gelation: When the formulation comes into contact with body fluids, it forms a gel from a drug solution and a gelling agent. These systems can be utilized to improve medication solubility by allowing for regulated release and a longer residence period in the body[19]. Gel-based formulations are effective for local drug administration (e.g., topical or ophthalmic formulations) and increasing bioavailability by prolonged release.

LATEST TECHNOLOGIES IN THE FIELD OF SOLUBILITY ENHANCEMENT:

1. Nanoemulsions:

Beads smaller than 100 nm in width make up nano-emulsions, which have a few advantages over traditional emulsions. In addition to making significant progress in sedation and toxicity reduction, nano-emulsions can increase the bioavailability and solubility of medications that are ineffectively solvent.

2. Co-crystals:

Co-crystals can improve the solubility and disintegration rate of pharmaceuticals that are ineffective solvents because they are formed by the interaction of two or more atoms. Co-crystals can be designed to enhance sedative solidity and reduce toxic quality. They can also be specially created to fit the specific physicochemical characteristics of the medication[20].

3. Nebulous strong scatterings:

A drug that is ineffectively soluble is scattered throughout a polymer lattice to create undefinable strong scatterings. While the polymer lattice provides stability and prevents medication recrystallization, the medicates shapeless form enhances its dissolvability and disintegration rate.

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4. Cyclodextrin complexes:

Drugs that are ineffectively soluble can form incorporation complexes with cyclic oligosaccharides called cyclodextrins[21]. In addition to improving medication solubility and bioavailability, cyclodextrin complexes can be tailored to the specific physicochemical characteristics of the drug.

5. Supercritical liquid innovation:

One use of supercritical liquid innovation is the dissolution and extraction of dynamic pharmaceutical fixes using supercritical liquids, such carbon dioxide. Tall dissolvability and natural affect are two of the innovation's main features.

Mechanisms of Solubility Enhancement:

The maximum amount of solute that may dissolve in a specific amount of solvent is referred to as "solubility." Both quantitative and qualitative definitions are also possible. It is defined quantitatively as the solute concentration in a saturated solution at a particular temperature. The spontaneous interaction of two or more substances to produce a homogenous molecular dispersion is a qualitative definition of solubility [22]. When the solute and solvent are in balance, the solution is said to be saturated.

Solubility Enhancement Techniques:

Physical modifications:

Techniques that change the drug's physicochemical characteristics to increase its solubility fall under this category. Milling, spray-drying, and particle size reduction are a few examples of physical alterations.

Chemical modifications:

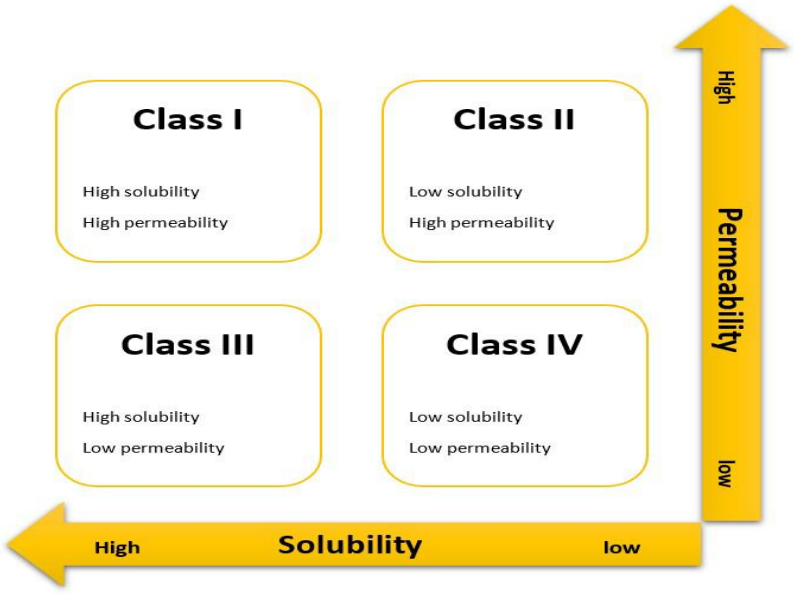
Techniques that alter the medication chemically to increase its solubility fall under this category. Esterification, prodrug synthesis, and salt production are a few instances of chemical changes[23].

Co-solvents:

Co-solvents are water-miscible solvents that can be employed to increase a drug's solubility. Propylene glycol, polyethylene glycol, and ethanol are a few examples of co-solvents.

Surfactants:

Surfactants are substances that can improve solubility by lowering the interfacial tension between the medicine and the dissolving liquid[24]. Tween 80, Pluronic, and sodium lauryl sulphate are a few examples of surfactants.



Complexation:

To increase solubility, complexation entails the medication and a carrier molecule forming a complex. Polymers, polyvinylpyrrolidone, and cyclodextrins are a few examples of carriers.

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Solid dispersion:
To increase the drug's solubility, solid dispersion entails dispersing it in a hydrophilic matrix. Polyethylene glycol, polyvinylpyrrolidone, and hydroxypropyl methylcellulose are a few examples of matrices [25].
Nanoparticles:
By increasing the drug's surface area, nanoparticles can improve its solubility. Liposomes, solid lipid nanoparticles, and polymeric nanoparticles are a few types of nanoparticles.

Solid Dispersion:
The dispersion of one or more active substances in an inert carrier or matrix at a solid state created by melting (fusion) is referred to as solid dispersion. "Solvent or the method of melting-solvent.
" This category excludes the dispersion of a medication or pharmaceuticals in solid diluents or diluents by conventional mechanical mixing. Another name for the solid dispersion is solid state dispersion [26].
There are five main types into which solid dispersions have been categorized:
Basic eutectic compounds
Amorphous drug precipitations in a crystalline carrier
compound or complex forms between the drug and the carrie
solid solutions
glass solutions of suspension [27].
Drug Overview: Itraconazole
Therapeutic Use: Treatment of fungal infections (e.g., aspergillosis and histoplasmosis).
Issue: The water solubility is extremely low (<1 µg/mL), limiting its bioavailability.
Biopharmaceutical Classification System (BCS): Class II (poor solubility and high permeability).
Strategies for Solubility Enhancement:
Solid Dispersion:
Mechanism: The drug is distributed in a hydrophilic polymer matrix.
Example: Itraconazole solid dispersions containing Hydroxypropyl Methylcellulose (HPMC) or Polyvinylpyrrolidone (PVP) improve dissolving by lowering drug crystallinity and enhancing wettability.
Outcome: Improved solubility and oral bioavailability.
Nanoformulations:
Mechanism: The reduction of particle size to the nanoscale improves surface area and dissolving rate.
Example: Nanocrystal versions of itraconazole with stabilizers such as Poloxamer.
Outcome: Increased bioavailability due to greater solubility and quicker absorption [28].
Cyclodextrin Complexation:
Mechanism: Increased bioavailability due to higher solubility and faster absorption.
Example: Sporanox® is a commercial formulation that contains itraconazole and cyclodextrin.
Outcome: Enhanced solubility and bioavailability for oral and parenteral administration.
Lipid-Based Formulations:
Mechanism: Itraconazole can be incorporated into lipid vehicles such as self-emulsifying drug delivery systems (SEDDS) or liposomes [29].
Example: Itraconazole-loaded SEDDS containing oils and surfactants.
Outcome: Increased solubilization in the gastrointestinal system.
pH Modifiers:
Mechanism: Itraconazole is more soluble at low pH, hence an acidic microenvironment can be used to improve solubility.
Example: Adding organic acids like citric acid to formulations.
Outcome: Enhanced solubility in gastrointestinal circumstances.
Mechanism of Drug Itraconazole

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Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophilic outer surface and hydrophobic inside. They can form inclusion complexes with poorly soluble medications such as itraconazole by enclosing the hydrophobic portion of the drug molecule within their cavity, while the hydrophilic outside interacts with water [30].

Result:

- Enhanced medication solubility.
- Improved stability.
- Improved bioavailability without compromising the drug's fundamental characteristics.

Itraconazole, a lipophilic chemical, easily fits into the cavity of β-cyclodextrin and its derivatives, including hydroxypropyl-β-cyclodextrin (HP-β-CD)[31].

II. CONCLUSION

Improving the solubility of medications that are not very soluble in water is essential for increasing their bioavailability and therapeutic efficacy. Numerous methods, including complexation, solid dispersions, particle size reduction, and lipid-based formulations, provide creative answers to this problem. The qualities of the medication and the intended release profile determine which approach is best, allowing for the creation of more accessible and efficient pharmaceutical formulations for difficult-to-treat therapeutic candidates. For weakly water-soluble medications to have an effective therapeutic effect, their solubility must be improved. The target formulation, the intended release profile, and the drug's type all influence the technique selection. Novel approaches to enhancing the bioavailability of these medications are still being offered by developments in formulation science, solid-state chemistry, and nanotechnology. Cyclodextrin complexation is a highly successful approach for increasing itraconazole solubility, which leads to better therapeutic efficacy and patient compliance.

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