INNOVATIVE APPROACHES TO ENHANCE SOLUBILITY FOR OPTIMAL DRUG DELIVERY

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Abstract

This article provides a thorough examination of recent developments in solubility enhancement techniques for poorly water-soluble drugs. With the increasing number of drug candidates exhibiting low aqueous solubility, the need for effective solubility enhancement strategies has become paramount in pharmaceutical research. The review encompasses a wide range of approaches, including particle size reduction, solid dispersion, lipid-based formulations, and cyclodextrin complexation. Additionally,the article discusses the role of nanotechnology, co-solvents, and surfactants in improving drug solubility. Critical insights into the mechanisms underlying each method, along with their advantages and limitations, are presented. This comprehensive overview aims to guide researchers and pharmaceutical scientists in the selection of optimal solubility enhancement strategies for enhancing drug bioavailability and therapeutic efficacy. The review also addresses recent advancements, challenges, and potential future directions in the field. By synthesizing a wealth of information, this article aims to serve as a valuable resource for researchers, pharmaceutical scientists, and industry professionals engaged in the pursuit of effective solubility enhancement strategies for improved drug formulation and bioavailability.

Keywords: Biopharmaceutical classification system, Co-solvents, Molarity, Solid dispersion, Solvent evaporation.

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DOI: 10.53555/ecb/2022.11.12.298

Introduction

In the process of developing new drugs, solubility is the most important factor. The challenge of resolving solubility-related problems has been taken up by scientists and researchers. It is estimated that solubility issues affect around 40% of the novel drugs or pharmaceuticals that are undergoing clinical trials. A successful drug delivery system must consider the solubility of the drug at the absorption site, which is a crucial characteristic.[1] For the researchers involved in the formulation design and development process, the oral route presents a difficult challenge due to its poor solubility, permeability, and substantial first pass impact. [2] Biopharmaceutics classification system (BCS) class II medications, such as phenytoin, danazol, and nifedipine, and BCS class IV pharmaceuticals, such as furosemide, domperidone, and hydrochlorothiazide, are examples of drugs with poor solubility.[3] Before a drug maybe absorbed when taken orally in a solid dosage form—such as a tablet, capsule, or suspension—it must dissolve in the gastrointestinal fluids and be freed from the dosage form. Many weakly water-soluble drugs have restricted bioavailability due to their dissolution rates, which are regulated by the surface area available for dissolution. The oral absorption of drugs from solid dosage forms may be divided into two distinct processes:

1. First drug's in vivo dissolution into a solution,
2. Second the drug's transportation across the gastrointestinal barrier.

There is a rate constant that may be used to describe any process. In the event where the drug dissolves more slowly than it absorb, the drug's dissolution becomes the rate-limiting stage in the absorption process. [4]

Particle size reduction, supercritical fluid technology, salt formation, micellization, amorphization, complexation or encapsulation, solid dispersion, and micro- and nano-crystal technologies are just a few of the techniques and technologies that have been used to boost the concentration of poorly water- soluble active pharmaceutical substances. For the enhancement of solubility polymers like cyclodextrins are used with forms the complex with the drug results in increasing the solubility. [5]

Expressions of solubility

- **g/ml:** Most used method for expressing solubility. It is the number of grams of solute that dissolvesin 1 ml of the solvent.
- **Molarity:** It is the number of moles (gram molecular weight) of the solute in 1 liter of the solvent.
- **Normality:** It is the gram equivalent weight of the solute in 1 liter of the solution.
- **% w/w:** It is the weight in grams of the solute dissolved in 100 gm of the solution
- **% w/v:** It is the weight in grams of solute dissolved in 100 gm of the solution.
- **%v/v**: It is the volume of the solute ml dissolved in 1 solution.[6]

Table 1: Solubility aspect of parameters

S. No.	Descriptive terms	Approximate volume of milliliters per gram of solute
1	Very soluble	Less than 1
2	Freely soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly soluble	From 30 to 100
5	Slightly soluble	From 100 to 1000
6	Very slightly soluble	From 10000 to 10,000
7	Insoluble	More than 10,000

Based on the drug substance's solubility, permeability, and drug product's dissolution, the Biopharmaceutics Classification System (BCS) is a well-established scientific framework that ensures in vivo bioequivalence (BE) through comprehensive comparative in vitro assessments. [7]

Predicting a drug's in-vivo performance from in vitro measurements is the aim of BCS. Class I medications have thehighest absorption rate, Class II drugs have restricted solubility, Class III drugs have limited permeability, and Class IV pharmaceuticals have low absorption rates. [8]

By understanding the solubility of a compound in biorelevant media and its permeability across biological membranes, the rate limiting factors determining the rate and extent of oral drug absorptioncan be identified. This information can be invaluable for predicting the potential influence of formulation and physiological variables on oral drug bioavailability. [9]

The greatest dosage strength in an Immediate Release product serves as the basis for a drug's solubilitycategorization in the BCS. When a drug substance dissolves at its peak intensity in 250 milli-liters or less of aqueous medium within the pH range of 1.0 to 7.5, it is considered highly soluble; if not, it is considered poorly soluble.

The basic idea underlying BCS is that two drug products will provide the same plasma profile following oral delivery if they produce the same concentration profile along the gastrointestinal (GI) tract.[10]

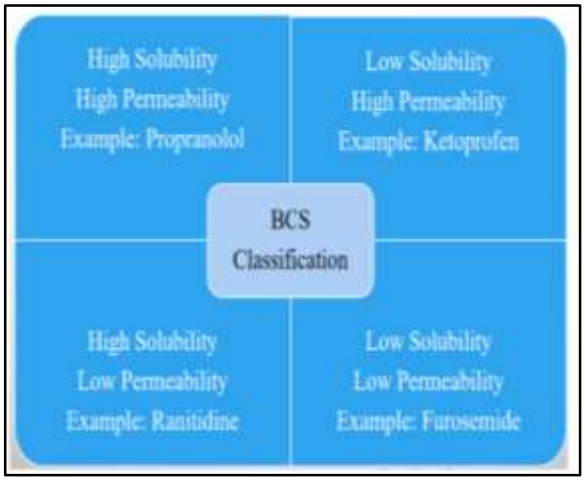

Fig. 1: Biopharmaceutical classification system

It assisted the pharmaceutical industry in submitting NDAs (new drug applications) and ANDAs (abbreviated new drug applications) more easily by merging information on the solubility of drugs in water with information on drug release from in vitro dissolution. [11]

Methods for solubility enhancement

1. Solid dispersion

A solid dispersion is one of the most effective methods for improving solubility. Solid dispersion designates a group of solid items made up of at least generally consist of two different parts, a hydrophilic matrix and a medication that is hydrophobic. The matrix might be amorphous or crystalline, and the drugs can be distributed in any way. [12]

Manufacturing methods of solid dispersion

• **Solvent evaporation method:** One of the most popular techniques for creating drug-loaded polymeric systems, or polymeric nanoparticles, for use in pharmaceutical formulations is the solvent evaporation approach.[13] The drugand carrier are dissolved in a single solvent in the solvent evaporation process, and the solvent is subsequently evaporated under vacuum to provide a stable resolution. After a high degree of homogenization, the final solution is added to the aqueous phase containing surfactant to create an emulsion. Following the creation of a stable emulsion, the organic solvent is removed by either swirling continuously to cause nanodroplets to disperse or by raising the temperature while applying less pressure. [14]

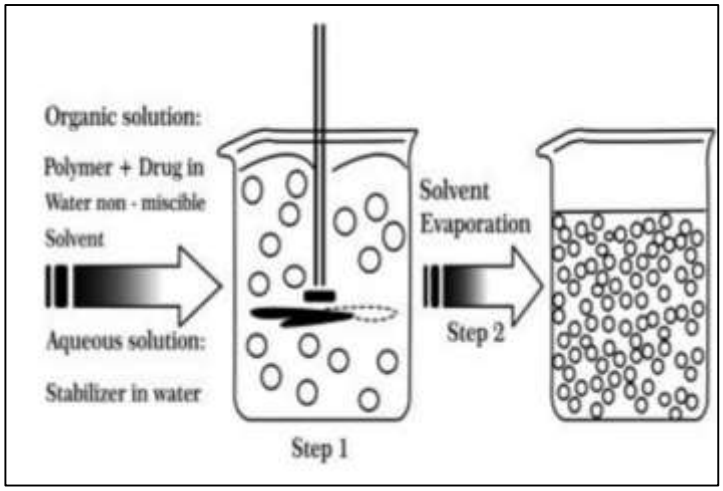

Fig. 2: Solubility enhancement by solvent evaporation

- **Holt melt extrusion:** An extruder is used in this procedure to combine the components very thoroughly. The barrel, hopper, heating jacket, kneading screw, and die are the parts of the extruder. The drug and carrier are typically physically mixed, inserted into the hopper, passed via a screw, and then extruded out the die. [15]

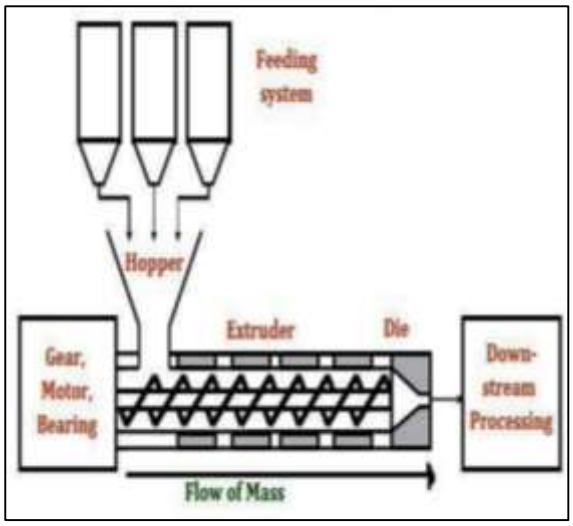

Fig. 3: Hot melt extruder

- **Super critical fluid method:** Compared to conventional procedures, the solid dispersion developed with supercritical fluid technology demonstrated superior flow characteristics, tiny particle size, and lack of the residual organic solvent.[16]

Using super critical fluid, solid dispersion may be created that improves solubility in a number of ways, including by precipitating the medication in a nano-size or amorphous form. The supercritical fluid system consists of a CO2 pump, a sample-containing pressure vessel, a pressure holding device to sustain the pressure between the pump and the pressure vessel, and a collection vessel to gather sample particles. [17]

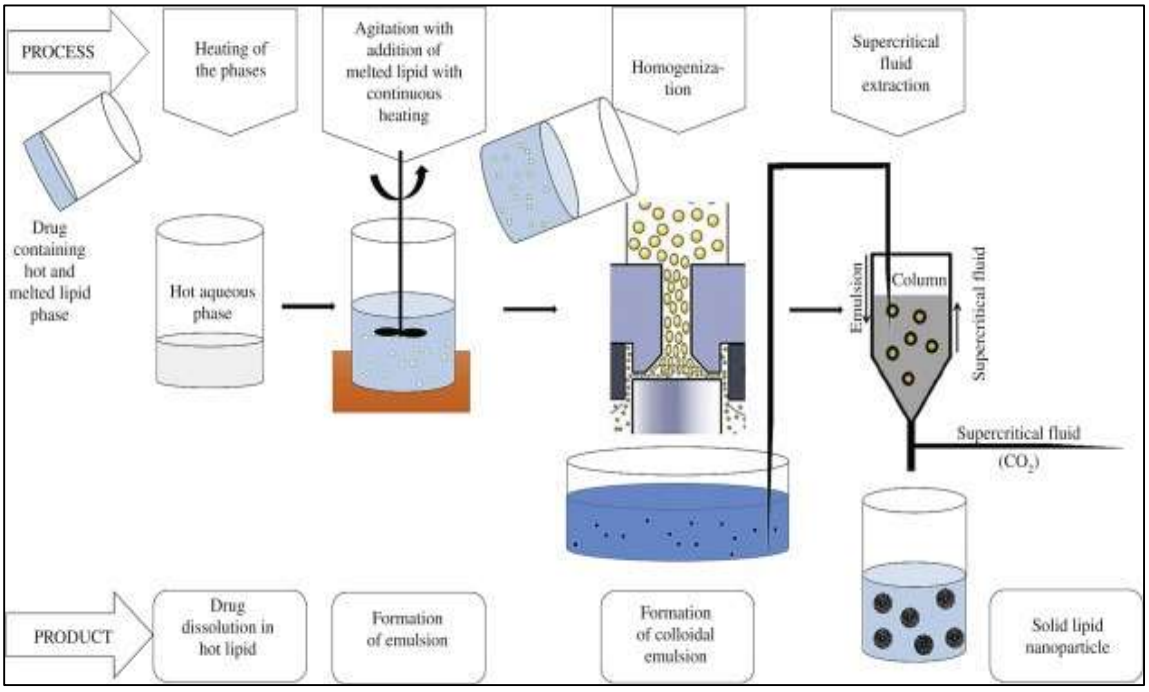

Fig. 4: Supercritical fluid process

- **Spray drying method**

Spray drying is a one-step procedure that produces dry particles from a liquid feedstock (solution, suspension, or emulsion). The equipment setup and the spray drying method have a significant impact on the qualities of the particles that are spray dried. The three primary parts of the spray dryer are the atomizer, drying chamber, and collector. [18]

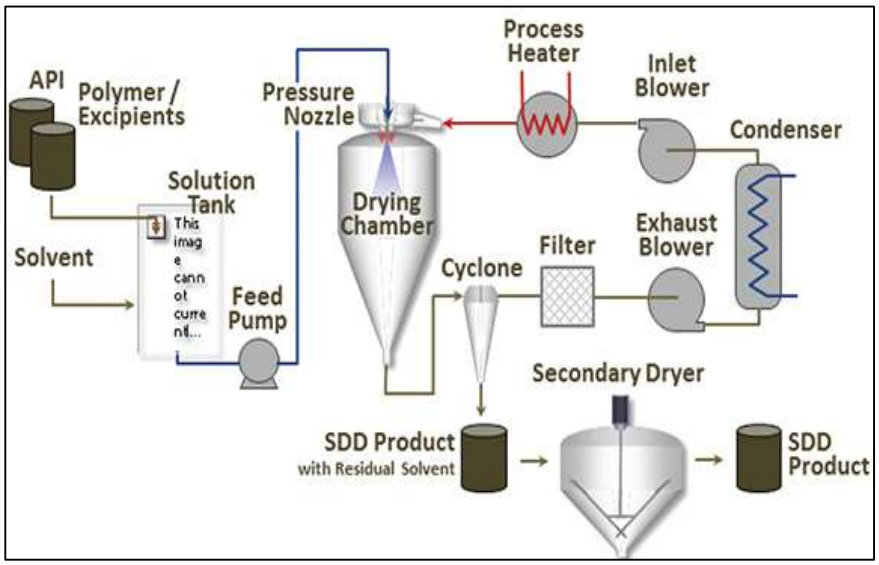

Fig. 5: Spray drying process

- **Liquisolid technique:** Liquisolid technique involves reworking a liquid into a free-flowing, instantly compressible, and seemingly dry powder by simple physical mixing with certain excipients known as the carrier and coating material. The liquid component is mixed with the carrier material. It can be a liquid drug, a drug suspension, or a drug solution in appropriate non-volatile liquid vehicles.[19]

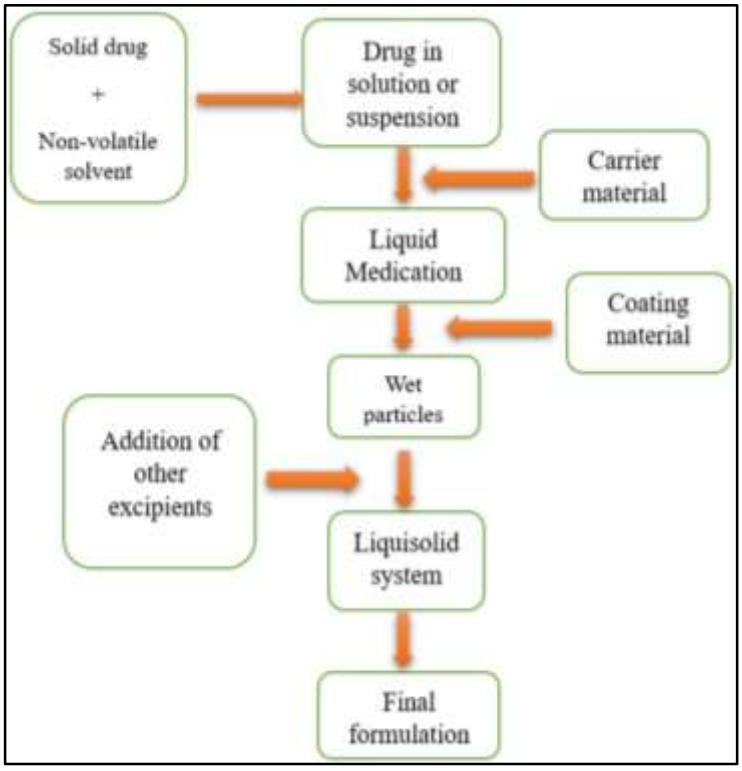

Fig. 6: Flow liquisolid technique

2. Sono crystallization Technique

Sono crystallization is the use of ultrasonic energy to alter the crystallization process's nucleation. Ultrasound energy creates successive expansion and compression. Following several cycles, a bubble appears and expands crumbles.

Energy from the bubble burst helps to accelerate the nucleation process. As a result, the crystallization process becomes extremely predictable and reproducible. When Ultrasound is used to induce crystallization, it causes nucleation at the lowest level of supersaturation in the crystal-forming region defeats the compound's propensity to re-dissolve inside the mixture. [20]

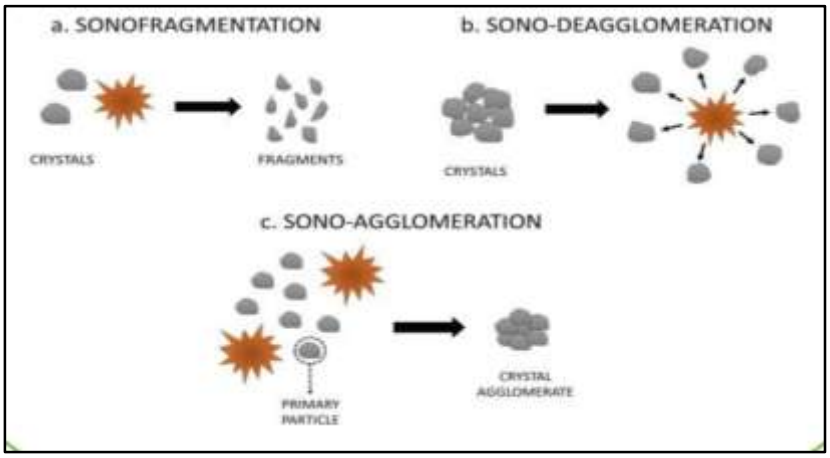

Fig.7: Process of sonocrystallization

3. Nano-suspension technique

Submicron colloidal dispersions of drug particles that are nanosized and stabilized by surfactants are called nanosuspensions. The weakly water-soluble medication is suspended in a dispersion with no matrix material in nanosuspensions. These can be applied to improve the solubility of medications that have low solubility in lipid and water environments. Increased solubility causes the active ingredient to flood at a quicker pace, reaching the maximum plasma level more quickly. This method works well for compounds that are difficult for formulators to work with because they have poor permeability, poor solubility, or both. Because of the smaller particle size, poorly soluble medications can be administered intravenously without obstructing blood vessels. [21]

4. Co-solvency method

Cosolvents are mixes of miscible solvents that are frequently added to water to drastically alter the solubility of medications that are not very soluble in water. Poor water solubility is a common characteristic of nonpolar compounds and weakly electrolytes. The addition of a water miscible solvent,in which the medicine has strong solubility, frequently increases their solubility. The solvents employed to improve solubility are referred to as cosolvents, and this process is known as cosolvency. Reducing the interfacial tension between the hydrophobic solute and aqueous solution is how the cosolvent system functions.

Another term for it that is frequently used is solvent blending. In addition to tiny hydrocarbon areas, the majority of cosolvents include donor and/or acceptor groups for hydrogen bonds. Their hydrophobichydrocarbon regions interfere with the water's hydrogen bonding network, lowering the water's total intermolecular attraction, while their hydrophilic hydrogen-bonding groups guarantee water miscibility Cosolvents increase solubility by reducing the capacity of fluids to squeeze out nonpolar, hydrophobic molecules by interfering with their self-association.

Enhancing drug solubility in a liquid-based formulation through cosolvent technology has several benefits: it is convenient to not need to mix the solvent before administration; it's safe to avoid contamination during the dispensing process; and it's affordable because it eliminates the need for costly pharmaceutical technology for dosage form formulation. For parenteral application, propylene glycol, ethanol, glycerin, polyethylene glycol (PEG), dimethyl sulfoxide (DMSO), and dimethylacetamide (DMA) are the most often used low-toxicity cosolvents. [22]

Conclusion

In conclusion, the ever-expanding landscape of solubility enhancement strategies presents a dynamic and promising field within pharmaceutical research. This comprehensive review has shed light on the diverse methodologies employed to tackle the challenge of poor aqueous solubility in drug candidates. From traditional approaches like particle size reduction to cutting-edge techniques involving nanotechnology, the arsenal available to researchers is vast and

continually evolving. While each solubility enhancement strategy has its unique advantages and limitations, the overarching goal remains consistent—to enhance the bioavailability and therapeutic effectiveness of poorly water-soluble drugs.As we move forward, the integration of these strategies into a tailored, multifaceted approach may hold the key to overcoming the complexities associated with solubility challenges. The synergy between academia and industry, coupled with advancements in analytical techniques, will play a pivotal role inunravelling the intricate interplay of factors influencing drug solubility. As researchers delve deeper into understanding the physicochemical properties of drug molecules, personalized solubility enhancement approaches may emerge, revolutionizing the landscape of drug formulation.

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