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Prasad Subhash Shelke
UG Scholar of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Waghmare. SU
Assistant Professor of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Suryawanshi RK
Assistant Professor of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Tushar B Pawar
UG Scholar of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Harshal R Bhinagre
UG Scholar of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Priyanka A Narode
UG Scholar of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

Corresponding Author:
Prasad Subhash Shelke
UG Scholar of Rashtriya College of Pharmacy Hatnoor, Tq. Kannad, Chhatrapati, Sambhajinagar, Maharashtra, India

A review on solubility enhancement technique

Prasad Subhash Shelke, Waghmare. SU, Suryawanshi RK, Tushar B Pawar, harshal R Bhinagre and Priyanka A Narode

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Abstract
One of the key factors in achieving the appropriate drug concentration in the systemic circulation for the intended pharmacological response is solubility, which is the phenomenon of a solute dissolving in a solvent under particular conditions to produce a homogeneous system. Because BCS Class-II medications have a low solubility and dissolution rate, the main goal of this review was to increase their solubility. Pharmaceutically active molecules with low solubility transmit a larger risk of failure for drug research and development; so, improving the solubility of practically insoluble drugs was the most demanding part of drug development. Their solubility has a huge impact on pharmacokinetics, pharmacodynamics, and a few other characteristics like drug absorption, drug distribution, protein binding, etc. Oral dosage forms, out of all medicinal dosage forms, include more than50%, and the medication's molecule needs to dissolve in water. Solubility and bioavailability are key components in ensuring the drug molecule has good therapeutic action at the target site. Therefore, as chemical science advances, pharmaceutical technology must also advance to increase patient adherence to medicine. In order to achieve effective absorption and increased bioavailability, this article aims to describe various solubility enhancement techniques. These techniques include both traditional and novel approaches, such as pH adjustment, micronization, homogenization, salt formation, lyophilization, hot melt extrusion, solvent evaporation, melt-son crystallization, prodrug approach, etc [1].

Keywords: Solubility enhancement, dissolution, bioavailability, solid dispersion, BCS classification, lipophilicity

Introduction
Oral route is most desirable route of administering the dosage form. The major problem faced during the oral delivery of active agent is the bioavailability. The solubility is defined as a maximum amount of solute that, at a given temperature, may dissolve in a given amount of solution or solvent. As the solubility increase bioavailability increases**.** Invalid source specified [2].

Solubility defines as

Table 1: USP and BP Expression for Approximate solubility [1].

Defining Words	Milliliters of the approximate solvent volume for each gram 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 1000-10000
Insoluble	Greater than 10000

The drug is classified by the Biopharmaceutics Classification System (BCS) in NSAIDs from the newer generation, such as Zaltoprofen, Aceclofenac, and Flurbiprofen; their older congeners, such as Indomethacin, Ibuprofen, Ketoprofen, and Diclofenac; and anti-diabetics, such as Gliclazide and Glipizide, face solubility challenges in the Class II and Class IV of the BCS system identifies cases where dissolution becomes the crucial factor limiting the absorption of the drug newer calcium channel blockers such as Nimodipine and Felodipine.

The biopharmaceutics Classification System (BCS) was initially developed in 1995 by Amidon *et al*.

Table 2: BCS Classification of Drug.

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol.
II	High	Low	Neteglinide.
III	Low	High	Cimetidin.
IV	Low	Low	Hydrochlorothiazide

Medications with poor solubility are often a challenge in front of pharmaceutical industry. Increasing a medication's solubility and, consequently, its oral bioavailability is still this process is considered one of the most challenging aspects of drug development, especially for oral drug delivery systems. To solve the solubility problem we discuss the various traditional as well as a more recent technique for improving solubility [2].

The significance of solubility

Solubility also has a significant impact on other dosage forms, such as parenteral formulations. One of the soluble materials is most significant aspects of achieving the required medication concentration within the bloodstream and the required pharmacological response. After oral administration poorly water-soluble medications sometimes require considerable quantities needed to reach therapeutic plasma levels. The primary issue with creating new chemical entities and creating genetic material. For the best solvent for liquid pharmaceutical formulations is water. This is due to the fact that it allows any substance that has to be absorbed at the absorption site to be present in the form of an aqueous solution. answer. The majority of drugs have subpar aqueous solubility and are either weakly basic or mildly acidic [3].

Because of their low bioavailability, oral dose forms present a significant design issue. Oral bioavailability is influenced by characteristics such as aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms. Low permeability and poor solubility are predominant factors contributing to low oral bioavailability. Solubility is a critical factor for alternative dosage forms like parenteral formulations. It plays a key role in determining the appropriate drug concentration in the systemic circulation to achieve the required pharmacological response. Poorly soluble drugs taken orally may require higher doses to reach therapeutic plasma levels. Low water solubility is a major challenge in formulating novel chemical entities and manufacturing generic drugs. For absorption to occur, medications need to be in an aqueous solution at the site of absorption. Water is typically the preferred solvent for liquid medicinal formulations. Most drugs have limited aqueous solubility and tend to be weakly basic or mildly acidic [4].

Factors affecting solubility

Particle size: Particle size affects solubility. As particle size decreases, the ratio of surface area to volume rises. As the surface area of the particle increases, it leads to a more significant interaction with the solvent.

Temperature: Solubility affected by temperature. If the solution process absorbs energy then the solubility will rise as the temperature rises. The soluble will decrease as the temperature rises if the solution process releases energy [4].

Molecular size: Higher molecular weight and size molecules reduce the substance's soluble nature since it is harder for larger molecules to surround with solvent molecules and solvate the substance.

Nature of solute and solvent: The nature of solute and solvent depends on The solute's concentration in a specific amount of solvent at a specific temperature.

Example: Only 1 At room temperature, one grame of lead chloride can dissolve in one hundred grames of water whereas 200 grams of zinc chloride can [5].

Pressure: For gaseous solutes, a rise in pressure increases solubility, and a reduction in a pressure lessen the solubility. Solubility is unaffected by pressure variations for both liquid and solid solutes.

Polarity: The solubility is affected by the solvent's polarity and solute molecules. In general, molecules of polar solutes will dissolve in polar solvents, while molecules of non-polar solutes will dissolve in non-polar solvents.

Polymorphs: Polymorphism is the capacity of a material to crystallize in several crystalline forms. An agent with polymorphism is one that can crystallize in multiple different forms. It is conceivable. that solid can crystallize in different forms or polymorphs. Polymorphs can vary in the point of melting. Since solubility and the solid's melting point are related, the solubility of polymorphs will vary [6].

Methods for Solubility enhancement

Solid dispersion

In 1961, Sekiguchi and Obi first introduce the solid dispersions in order to accelerate the breakdown and oral ingestion of inadequate water-soluble drugs. [In solid dispersion a highly soluble solid hydrophilic matrix is used to disperse a poorly soluble drug. This improves the drug's solubility and allows for the production of either solid solution (molecular level mixing) or eutectic (non-molecular level mixing) products.

Classification of solid dispersion

1. Solid dispersion classified in 3 groups

First generation solid dispersions

The creation of eutectic mixes or molecular dispersions enhanced the rate of drug release in first generation solid dispersion, which in turn improves the bioavailability of poorly water soluble drugs. Disadvantage related formulation of crystalline solid does not release drug quickly.

Examples of crystalline carriers include organic acids, sugars, and urea.

Second generation solid dispersion

To enhance drug release in the second generation, we employ amorphous carriers, such as povidone (PVP), which are entirely synthetic polymers. polyethylene glycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by derivatives of cellulose, such ashydroxypropyl methylcellulose (HPMC),ethylcellulose or

hydroxypropyl cellulose or starchderivates, like cyclodextrins.

Third generation solid dispersion

We employ carriers with surface activity and self-emulsifying capabilities in the third generation. Surfactants lessen the recrystallization of drug and thus improve the solubility of drug.

Example: The following are surface-active self-emulsifying carriers: Gelucire 44/14, Tween 80, and Poloxamer 408. [2].

2. Particle Size Reduction

The solubility of drugs and particle size are frequently inversely correlated; as a particle gets smaller, the area of the surface to volume ratio rises. Increased solubility results from increased contact between the surface area and the solvent. The active component is broken down by mechanical stress in conventional particle size reduction techniques like commination and spray drying Solubility augmentation is thus made achievable by a scalable, economical, and efficient technique of reducing particle size. Nonetheless, the medication product frequently experiences high levels of physical stress due to the mechanical forces involved in combination, such as milling and grinding, which could lead to deterioration. The possibility of heat stress during commination and spray drying is particularly concerning when handling thermo sensitive or unstable active substances.It might not be possible to increase the solubility of almost insoluble medications to the required degree by using conventional methods. Another common method for reducing particle size is micronization. Micronization does not improve equilibrium solubility; rather, it improves the rate at which pharmaceuticals dissolve by increasing their surface area. These medications dissolve more quickly when their particle sizes are reduced because they have more surface area. Pharmaceuticals are micronized using milling techniques such as jet mills, rotor stator colloid mills, and so on. However, because Micronization is not suitable for medications with high dosage numbers, even though it does not change the medication's saturation solubility. These approaches were applied to progesterone, spironolactone diosmin, griseofulvin, and fenofibrate. Micronization increased the absorption of each medication from the digestive system, which increased its bioavailability and therapeutic effectiveness.In 30 minutes, micronized fenofibrate showed a dissolution increase of more than ten times (1.3% to 20%) in biorelevant medium [4].

3. Nanoionisation

It's a process whereby the drug powder is converted to Nano crystals of size 200-600nm, e.g. Amphotericin B.

The main production technologies currently in use to produce drug Nano crystals yield as a product a medication dispersion Nano crystals in a liquid, typically water (called Nano suspension).

There are three basic technologies currently in employ using nanoparticles

1. Pearl milling.
2. Homogenization in water (colloid milling done this way).
3. Homogenization in non-aqueous in water or in the media with water-miscible liquids. Prepared, megestrol acetate (MA) nanoparticles through the use of liquid precipitation. While the raw MA had a mean particle size of roughly 3.02 μm, the as-prepared MA particles had a mean size of 208 nm and 90% of the particles were dispersed in the range of 100−300 nm. ranging widely from 0.2 μm to 30 μm. The results of the contact angle measurement showed that the freeze-dried MA nanoparticles had better wettability, indicating that a hydrophilic layer had covered the particles.In dissolution rate tests, the While the raw MA did not entirely dissolve after 120 minutes, the nanoparticles achieved 100% drug solubility in 5 minutes, indicating that the dissolution property of MA nano particles was significantly enhanced [7].

4. Supercritical Fluid (SCF) Processes

Particle size reduction by supercritical fluid (SCF) operations is another innovative nanosizing and solubilization technique whose use has grown in the last several years. Super-critical fluids can take on the characteristics of both a liquid and a gas because their temperature and pressure are higher than their critical temperature (Tc) and critical pressure (Tp). Due to their considerable compressibility at near-critical temperatures, SCFs can significantly modify their solvent power through modest pressure changes that affect the fluid's mass transport and density properties. The drug particles may recrystallize at significantly smaller particle sizes after becoming dissolved in the SCF, which is typically carbon dioxide. The SCF techniques provide flexibility and accuracy that allow drug particles to be micronized down to submicron sizes, frequently within very small particle size ranges. Current SCF techniques can be used to generate particles in nanoparticulate suspensions with diameters ranging from 5 to 2,000 nm. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, specialise in particle engineering using SCF technologies for the purposes of particle size reduction and solubility augmentation. Several methods of processing SCF have been devised to tackle different facets of these deficiencies. Supercritical antisolvent processes (SAS), gas antisolvent recrystallization.

(GAS), aerosol supercritical extraction system (ASES), rapid expansion of supercritical solutions (RESS), solution enhanced dispersion by SCF (SEDS), and precipitation with compressed antisolvent process (PCA) are some of these techniques [4].

5. pH Adjustment

By altering the pH, poorly soluble medications that contain segments of the molecule that can be either basic or acidic may dissolve in water. In theory, pH correction can be utilized for both oral and intravenous infusion. Because blood has a strong pH of 7.2-7.4, it may precipitate the poorly soluble medication when administered intravenously. The buffer capacity and tolerability of the chosen pH are crucial factors to take into account when evaluating the approach's suitability. Because the pH of the duodenum is between 5 and 7.5 and that of the stomach is between 1 and 2, oral medication administration may also have an impact on the drug's degree of solubility as it goes through the intestines. The ideal ionizable chemicals are those that

remain stable and soluble even after pH correction. The sorts of compounds could be zwitterionic, bases, or acids. It can also be used with poorly soluble lipophilic and crystalline substances. The solubility of a drug is increased by soluble excipients that raise the pH of the surrounding environment within a dosage form, like a tablet or capsule, to a range higher than the pKa of weakly acidic pharmaceuticals. Similarly, soluble excipients that function as alkalizing agents may increase the solubility of weakly basic drugs [6].

6. Liquisolid methods

When a medicine that has been dissolved in a liquid medium is added to a carrier material like cellulose that has fibers within and a porous surface, both adsorption and absorption take place. To be more precise, the liquid first enters the particles' interiors and is caught by their internal structure; once this system reaches saturation, the liquid is adsorbed onto the internal and external surfaces of the porous carrier particles. A liquid drug can be converted into a free-flowing, dry, non-adherent, compressible powder by blending it with specific powder excipients, like the carrier and coating material. Microcrystalline and amorphous cellulose, additionally silica powders, are used as coating materials [8].

7. Sonocrystallisation

Recrystallization of Liquid solvents and antisolvents have also been effectively used to minimize particle size in poorly soluble compounds. The innovative method for reducing particle size based on crystallization by using ultrasound is Sonocrystallisation. To induce crystallization, sonocrystallization uses ultrasonic power with a frequency range of 20–100 kHz. Most applications use ultrasound within the range kHz-5 MHz [9].

8. Micellar Solubilization

One of the main techniques for enhancing the effectiveness of weakly soluble medication dissolution is the use of surfactants. It is a helpful instrument for controlling the size distribution and size reduction components of the active medicinal substance and enhances the nucleation rate. Surfactants are added to drug solutions to stabilize them and, by reducing surface tension, improve lipophilic drug solubility. Drugs become trapped in micelles when the concentration of the surfactant exceeds its critical micelle concentration (CMC). Micellization is the process of forming micelles, which increases the solubility of weakly soluble medicines [10].

9. Co-crystallization

Most frequently, co-crystallization is used as a technique to increase solubility. As a result, co- crystals usually increase the drug's solubility, which isn't achievable when using a different molecule. For instance, telmisartan is a medication from the II class that is not feasible in this situation due to a different molecule. One medication from the II class with poor solubility is telmisartan. The effectiveness of medication therapy is directly influenced by the drug's solubility, which is strongly dependent on the drug's concentration in blood. The most crucial elements in a drug's pharmacological impact that demonstrates a pharmacological response are its solubility and dissolution. A medication with improved solubility characteristics will also have better absorption, which will increase its bioavailability. Nevertheless, the drug's water solubility is poor in about 40% of cases. Due to its limited solubility, the medication enters the body slowly and accumulates at low levels. Since over 70% of candidate medications have solubility issues, it is very risky in the pharmaceutical industry to design dosage forms and drug procedures that demonstrate the drug's good solubility and dissolution rate, particularly for oral preparations. Within the pharmaceutical sector, one percent of the most prominent cases on the market are related to the shortcomings of biologic drugs, such as medication failure [11].

10. Lyophilization Technique

Freeze-drying involves moving mass to and from the product preparation area as well as a change in temperature. This plan developed into an opportunity strategy for solvent evaporation. In order to create a lyophilized molecular dispersion, the medication and service must first dissolve in a common solvent, freeze, and then sublimate. One of the main benefits of freeze drying is that the medicine is exposed to the lowest possible temperature pressure while the stable dispersion is developing. Furthermore, section separation is reduced as soon as the solution turns syrupy this is freeze drying's most significant benefit. The remover is sprayed into bloodless dry air or liquid nitrogen, and the resulting frozen droplets are lyophilized.

It is a phenomenon where mass and heat are transferred from the product to itself [1].

11. Hot melt extrusion [HME]

HME can be simply defined as the procedure for forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder.

Advantage of HME

1. Boost the bioavailability and solubility of poorly soluble substances.
2. Processing in the absence of solvents and water.
3. Economical method that operates continuously, has fewer processing stages, and shortens manufacturing times.
4. Uniform dispersion of fine particle occurs.
5. Good stability at varying pH and moisture levels.
6. Because they are water insoluble and non-swellable, they can be used safely on humans. Negative aspects:
7. Not suitable for materials that are heat sensitive.
8. restricted quantity of polymers available.
9. This approach needs a lot of energy. [2].

12. Polymorph

There are two types of polymorphs: stable forms, which have poor solubility in water, and metastable forms, which have great solubility. For example, riboflavin's polymorphic form III is 20 times more water soluble than its form I.

13. Pseudopolymorphs

In addition to polymorphism, which is the study of solid crystalline materials with two or more molecules or atoms in the same crystal lattice, pseudopolymorphs, or co-crystals, are also researched. In general, co-crystals are also described as hydrates (molecules trapped in a solvent), solvates (solvent present), and clathrates (solvent present). Friedrich Wöhle's co- crystals of quinone and hydroquinone, which were discovered in 1844, were the first to be documented. The solubility and bioavailability of solid-state characteristics are directly impacted by co-crystals. Because of the co-crystal phenomenon, numerous medicinal products, like tropomyosin and troponin, have already been designed. Co-crystals are often used in pharmaceutical formulations [12].

Conclusion

Solubility and its significance, categories of solubility-enhancing techniques, physical modification, chemical modification, various methods, solid dispersion, particle size reduction, hot melt method, nano suspension, media milling, high pressure homogenization, ultrarapid freezing, inclusion complex formation-based technique, and crystal engineering are just a few of the many techniques and methods available. Solubility, however, is a crucial factor in determining a drug's therapeutic impact [8].

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