Review Article
IASR Journal of Medical and Pharmaceutical Science
Website: https://iasrpublication.com/ijmps
ISSN(*online*): 2582-9343

A Review Article On Solubility Enhancement Techniques

Rajesh Kumar[1]; Harendra Prasad[2]; Navneet Kumar Verma*[3]
[1]Associate Professor, Shri Babu Singh College of Pharmacy Sanyara Meethepur Kaushambi, UP, India
[2]Assistant Professor, Rajiv Gandhi College of Pharmacy, Nautanwa, Maharajganj, UP, India
[3]Associate Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209

A B S T R A C T
This review's objective is to investigate several factors that could enhance the solubility and bioavailability of medications that aren't very water soluble. Due to the ease of consumption for many medications, the oral route of administration is the most popular and widely accepted method of delivery. When taken orally, medications with slow dissolution rates exhibit partial absorption that results in limited bioavailability. The solubility of drugs that are poorly soluble in water has been improved using a variety of techniques, including particle size reduction, micronization, cosolvency, hydrotropy, pH adjustment, sonocrystallization, supercritical antisolvent technique, solid dispersion, inclusion complexation, micro emulsion, and liquid solid methods. The writers of this review covered a number of methods for improving drug absorption and bioavailability as well as a number of solubility improvement patents.

Keywords*: Solubility, Solubility enhancement, Bioavailability, Novel methods.*

Corresponding Author
Navneet Kumar Verma
Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209

INTRODUCTION
The maximum amount of solute that may dissolve in a specific amount of solvent is referred to as "solubility." Both a quantitative and a qualitative definition are possible. It is described quantitatively as the solute concentration in a saturated solution at a particular temperature. The spontaneous interaction of two or more substances to create a homogeneous molecular dispersion is a qualitative definition of solubility. When the solute and solvent are in balance, a solution is said to be saturated. Different concentration expressions, including parts, percentages, molarity, molality, volume fractions, and mole fractions, are used to represent a drug's solubility [1, 2, 3]. It is possible to increase the solubility of hydrophobic medications using a variety of methods. If substances may pass through the epithelium orally, the fraction of orally absorbed medicine may increase because the solubility of the poorly soluble drug is increased as compared to water alone. To further improve the poorly soluble drug's solubility, pH modification is usually paired with co-solvents. Due to a larger concentration gradient and increased surface area for dissolution, bioavailability can be increased if the precipitate after dilution is fine or amorphous. The bioavailability of the medicine may not be sufficiently boosted when it precipitates into poorly soluble particles that need to be dissolved and do so slowly. Due to its universality and relative simplicity, this method is commonly used in surveys to evaluate the effectiveness of medications that are poorly soluble. However, the interpretation of the data may be incorrect if the poorly soluble medication precipitates uncontrolled after coming into touch with a pH level (oral or parenteral) where the drug is significantly less soluble. The following are some conventional and cutting-edge methods to increase solubility:

IMPORTANCE OF SOLUBILITY
Due to its ease of administration, high patient compliance, cost effectiveness, lack of sterility restrictions, and flexibility in the creation of dosage forms, oral consumption is the most practical and frequently used mode of drug delivery. Because of this, many generic medication manufacturers are more likely to create bioequivalent oral drug formulations [4]. The poor bioavailability of oral dose forms, however, presents the biggest design problem. Aqueous solubility, drug permeability, dissolving rate, first-pass metabolism, presystemic metabolism, and sensitivity to efflux mechanisms are some of the variables that affect oral bioavailability. Poor solubility and inadequate permeability are the two most common causes of low oral bioavailability. Other dosage forms, such as parenteral formulations, also heavily rely on solubility [5]. One of the crucial factors in attaining the needed drug concentration in the systemic circulation for the desired pharmacological reaction is solubility [6]. After oral administration, poorly water-soluble medications may need high dosages to attain therapeutic plasma concentrations. The main issue in developing formulations for new chemical entities as well as generics is low water solubility. Any medicine that is to be absorbed must be present at the absorption site in the form of an aqueous solution. The preferred solvent for liquid medicinal compositions is water. Most medications have poor aqueous solubility and are either weakly basic or mildly acidic. Over 40% of the NCEs (new chemical entities) created by the pharmaceutical sector are essentially water insoluble. These poorly water-soluble

medications' sluggish drug absorption causes insufficient and unpredictable bioavailability as well as damage to the gastrointestinal mucosa. The most crucial rate limiting factor for medications taken orally is solubility, which allows for the achievement of the desired concentration of the drug in the systemic circulation for pharmacological response. For formulation scientists, the solubility problem presents a significant issue [7]. One of the most difficult areas of drug development, particularly for oral-drug delivery systems, continues to be the enhancement of drug solubility and, consequently, its oral bioavailability. There are several methods to improve the solubility of weakly water-soluble substances that have been documented in the literature. The methods are chosen based on a number of factors, including the qualities of the medicine under consideration, the kind of excipients to be chosen, and the kind of dosage form intended. Insufficient bioavailability is frequently caused by the poor solubility and slow rate of dissolution of poorly water-soluble medications in aqueous gastrointestinal fluids. Increases in the drug's solubility and rate of dissolution in gastrointestinal fluids, particularly for class II (low solubility and high permeability) compounds, may improve bioavailability. Since solubility in stomach fluid and drug release from the dosage form are the rate-limiting steps for BCS class II medications rather than absorption, boosting solubility also increases the bioavailability of BCS class II pharmaceuticals [4, 7, 8].

TECHNIQUE FOR IMPROVING SOLUBILITY

Formulation methods are necessary early in the drug discovery process when the solubility of compounds in aqueous media is low, and they continue to be crucial for the choice of the lead substance and the creation of commercial drug products [16]. Poorly water-soluble medications have been made to dissolve and dissolve more quickly using a variety of ways, including the following:

1) Particle Size Reduction
2) Micronization
3) Cosolvency
4) Hydrotropy
5) pH Adjustment
6) Sonocrystallization
7) Supercritical Antisolvent technique
8) Solid Dispersion
9) Inclusion Complexation
10) Micro Emulsion
11) Liquisolid Methods

1.PARTICLE SIZE REDUCTION

The drug's solubility is frequently inversely correlated with the size of the drug particle because as a particle gets smaller, its surface area to volume ratio rises. Greater contact with the solvent is made possible by the larger surface area, increasing solubility [9]. The active ingredient is disaggregated by mechanical stress in conventional particle size reduction techniques including comminution and spray drying. The industry is well-aware of the crucial comminutional parameters, making it possible to reduce particle size in an effective, repeatable, and cost-effective manner.However, the physical stress that is frequently applied to the therapeutic product during comminution processes like milling and grinding could lead to degradation. When processing thermosensitive or unstable active chemicals, the thermal stress that may occur during comminution and spray drying is also a concern. Additionally, these conventional techniques frequently fail to reduce the particle size of medicines that are practically insoluble (0.1 mg/mL) [10,11,12].

2.MICRONIZATION

Another common method for reducing particle size is micronization. Drug surface area is enhanced by micronization, which speeds up drug dissolution but does not increase equilibrium solubility [13]. Their rate of dissolution is improved by reducing the size of these medications' particles, which results in an increase in surface area. Drugs are micronized utilising milling processes, such as jet mills, rotor stator colloid mills, etc. Because micronization does not alter the drug's saturation solubility, it is not appropriate for medications with high dosage numbers. These procedures were used with fenofibrate, diosmin, progesterone, spironolactone, and griseofulvin. Each medicine was micronized to increase its gastrointestinal absorption, which in turn increased its bioavailability and therapeutic effectiveness. [14,15].

3.COSOLVENCY

Co-solvency/Solvent Blending: This technique lowers the interfacial tension between the aqueous solution and the hydrophobic solute, improving the solubility of a medication that is poorly soluble in water. Pharmaceuticals are always sold in liquid form. A co-solvent strategy may be appropriate for poorly soluble chemicals that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. Due to the low toxicity of many co-solvents and the relative better capacity of co-solvents to solubilize nonpolar pharmaceuticals, it has found its primary employment in parenteral

dosage forms. Cosolvents that are frequently employed include glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol. [16, 17].

4.HYDROTROPHY

In the solubilization process known as hydrotropy, another solvent is employed to increase the mixtures' solubility. The presence of a lot of additives can improve an additive's solubility in water. Although the process being used in the works is in non-micelle-forming materials, whichever solids or solids, whether inorganic or organic, are capable of solubilizing insoluble compounds, its mechanism is solubility because it related to the Complexation which involved in the weak interaction between the hydrotropic agents [9]. The hydrotropy is divided into three categories in the approach that follows: aromatic catatonics, aromatic anionics, and linear anionics. Sodium acetate, sodium alginate, and other hydrotropy agents are examples. The advantages of this process is it suggest to superior solubilizing method and the solvent is independent through the PH also have wide range of compound have been report exhibit hydrotropic conditions [18, 19].

5. pH- ADJUSTMENT

More easily solubilized ionic drugs need PH in order to be soluble. The primary factor affecting a drug's solubility and pharmacological reaction is its pH. For the purpose of administering drugs, PH is necessary. Because blood has an acidic composition that affects the blood, a medicine with low solubility can precipitate in blood rather than being soluble in it. For the absorption of the medicine, the appropriate PH should be needed. The degree of solubility is what allows substances to pass into the body. The PH of the stomach is 1–2 and the duodenum is 5–6. This technique is frequently used in pre-clinical examinations for pH correction. It is a brand-new technique for determining how well low-soluble medicines work. Advantage of this method is simple to formulate the formulation and uses of small quantity for the evaluation [20].

6.SONOCRYSTALLIZATION

In order to promote the solubility and dissolution of hydrophobic medications and to investigate its impact on the crystal characteristics of the drug, sonocrystallization is a new particle engineering technology. Ultrasound-assisted recrystallization of insoluble materials utilising antisolvents and liquid solvents has also been used successfully to reduce particle size. Sonocrystallization uses ultrasonic energy with a 20–100 kHz frequency range to cause crystallisation. The majority of applications use ultrasound between 20 kHz and 5 MHz. To find porous, amorphous materials with great stability, melt sonocrystallization (MSC) is a promising sonocrystallization process. [21].

7.SUPERCRITICAL ANTISOLVENT TECHNIQUE

The late 1980s saw the introduction of this technique. Numerous methods have been created and patented in the field of supercritical fluid-assisted particle design since Hannoy et alinitial .'s experiments in 1879. Carbon dioxide is employed in the supercritical fluid antisolvent method as an antisolvent for the solute but as an organic solvent's solvent. Due to its low critical temperature and pressure, supercritical carbon dioxide is helpful for processing medications that are heat-labile. When the process is finished, it is also non-toxic, non-flammable, cheap, and much simpler to remove from the polymeric materials. Even though a little quantity of carbon dioxide is still trapped inside the polymer, there is no risk to the customer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds [22].

8.SOLID DISPERSION

Sekiguchi and Obi, who studied the production and efficacy of eutectic melts of a sulfonamide medication and a water-soluble carrier in the early 1960s, were the ones who first put up the idea of solid dispersions. 8 Solid dispersions are a practical pharmaceutical approach for enhancing the absorption, therapeutic efficacy, and dissolution of medications in dosage forms. A collection of solid products with at least two separate components, often a hydrophilic matrix and a hydrophobic medication, are referred to as solid dispersion. The hydrophilic carriers Plasdone-S630, Polyvinylpyrrolidone, and Polyethylene Glycols are most frequently utilised for solid dispersions. Surfactants are frequently used in the creation of solid dispersion. Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate are examples of surfactants. The solubility of celecoxib9, halofantrine [23], ritonavir [24] can be improved by solid dispersion using suitable hydrophilic carriers.

9.INCLUSION COMPLEXATION

The inclusion complex creation technique has been used more accurately than any other solubility enhancement method to increase the aqueous solubility, dissolution rate, and bioavailability of medicines that are weakly water-soluble. The nonpolar molecule or nonpolar area of one molecule (referred to as the guest) is inserted into the cavity of another molecule or group of molecules to produce inclusion complexes (known as host). The main structural prerequisite for inclusion complexation is that the guest must fit tightly inside the host molecule's cavity. In order to reduce the overall contact between water and the nonpolar portions of the host and the guest, the cavity of the host must

be both large enough to hold the guest and tiny enough to drain away water. Various techniques are used to prepare for making inclusion complexes of poor soluble drugs with an aim to improve their aqueous solubility are listed here: [25]

10.MICRO-EMULSION

The procedure known as micro-emulsion can be used to dissolve drugs with limited solubility. Along with the injection of a protein mixture to the body, it can function to increase the solubility of certain medications that are nearly insoluble in the aqueous form. A hydrophilic surfactant, mixture of oil and a hydrophilic solvent, and a pure pre-concentrate are all components of a micro-emulsion, which can readily dissolve a medicine that is soluble in it [26]. The preparations easily dissolve when they come into contact with water, creating a transparent emulsion of tiny, homogeneous oil droplets that contains the medicine that has been solubilized. This technique is isotropic, thermodynamically stable, and uses pure systems of water, oil, and surfactant. It is frequently used in conjunction with a co-surfactant, and its droplet size range is (20–200 nm). All low viscosity fluids can be prepared in homogenous systems with a wide range of surfactant concentration in both water and oil. Micro-emulsions' main flaw is that they have higher co-surfactant/surfactant concentrations, rendering them unsuitable for intravenous administration. The drug precipitates when its micelle concentration falls below a certain level and microemulsions of the surfactants are diluted; nonetheless, because of the precipitate's tiny particle size, absorption is still improved. The benefit of micro-emulsions is that they are simple to make and have a soluble medication with the best bioavailability. [27, 28].

11.LIQUISOLID METHODS

Both absorption and adsorption occur when the drug dissolved in the liquid vehicle is introduced into a carrier material that has a porous surface and fibres in its interior, such as cellulose. Specifically, the liquid is initially absorbed in the interior of the particles and is captured by its internal structure, and after this process has reached saturation, the liquid is adsorbing onto the internal and external surfaces of the porous carrier particles. The coating material then imparts the desired flow characteristics to the liquid-solid combination by having high adsorptive qualities and a large specific surface area. Silica and cellulose powders, both crystalline and amorphous, can be employed as coating materials. [29].

CONCLUSION

The success of a medicine depends on the phenomena of solubility, which is the dissolution of a solid in a liquid phase to produce a uniform molecular dispersion. However, the majority of the active medicinal components are hydrophobic and poorly soluble in water. The drug's solubility becomes one of the most difficult formulation development challenges. Important substances are unable to reach the final medications due to poor water solubility, which prevents them from reaching their full medicinal potential. Therefore, despite their potential pharmacokinetic action, many novel medicines' poor water solubility is a key barrier to their successful market introduction.If a molecule's bioavailability is restricted by its solubility in water, it would not be possible to produce molecules that would have a highly favourable effect on their physiological target. The drug's aqueous solubility also affects the drug's physical and chemical properties, dosage, stability in the gastrointestinal tract, the rate of solid dissolution, the rate and extent of absorption, and the achievement of the desired concentration of the drug in the systemic circulation for the desired (anticipated) pharmacological response. As a result, solubility is a crucial notion that plays a vital role in the creation of medications.

REFERENCE

1. Martin, A., Bustamanate, P., & Chun, A. (1994). H, C,"Physical Pharmacy" BI Wavely Pvt. Ltd, New Delhi, 4, 223.
2. Osol, A(1990). (Eds.) in: "Remington's Pharmaceutical sciences" Mack Publishing Company, Eastern Pennsylvania, 18, 203.
3. Neuberg, C. (1989). Hydrotrophy: A promising tool for solubility. Biochem J Pharm, 75(7), 577.
4. Krishnaiah, Y. S. (2010). Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequiv Availab, 2(2), 28-36..
5. Di, L., & Kerns, E. (2015). Drug-like properties: concepts, structure design and methods from ADME to toxicity optimization. Academic press.
6. V. R. Vemula, V. Lagishetty, and S. Lingala(2010), "Solubility enhancement techniques," International Journal of Pharmaeutical Sciences Review and Research, vol. 5, no. 1, pp. 41–51.
7. Sharma, D., Soni, M., Kumar, S., & Gupta, G. D. (2009). Solubility enhancement—eminent role in poorly soluble drugs. Research Journal of Pharmacy and Technology, 2(2), 220-224..
8. Kumar, A., Sahoo, S. K., Padhee, K., Kochar, P. S., Sathapathy, A., & Pathak, N. (2011). Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale, 3(3), 001-007.
9. Vemula, V. R., Lagishetty, V., & Lingala, S. (2010). Solubility enhancement techniques. International journal of pharmaceutical sciences review and research, 5(1), 41-51.
10. Rinaki, E., Valsami, G., & Macheras, P. (2003). Quantitative biopharmaceutics classification system: the central role of dose/solubility ratio. Pharmaceutical research, 20(12), 1917-1925.

11. Persky, A. M., & Hughes, J. A. (2012). Solutions and solubility. Referred in the website http://www. cop. ufl. edu/safezone/prokai/pa5100/pha5110. htm. Accessed on, 2(2).
12. Blagden, N., de Matas, M., Gavan, P. T., & York, P. (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews, 59(7), 617-630.
13. Aulton, M. E., & Taylor, K. (2002). Pharmaceutics-The Science of Dosage Form Design. Churchill Livingstone. London, England, 340, 348
14. Dubey, R. (2006). Impact of nanosuspension technology on drug discovery and development. Name: Drug Deliv Technol, 6(6).
15. Chaumeil, J. C. (1998). Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods and findings in experimental and clinical pharmacology, 20(3), 211-216.
16. Chaudhary, A., Nagaich, U., Gulati, N., Sharma, V. K., Khosa, R. L., & Partapur, M. U. (2012). Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res, 2(1), 32-67.
17. Vemula, V. R., Lagishetty, V., Lingala, S.(2010). Int. J Pharm Sci Rev Res. 2010, 5 (1), 41-51.
18. Chaudhari, P. D., & Uttekar, P. S. (2009). Melt-sonocrystallization: a novel particle engineering technique for solubility enhancement. Int J Pharm Tech Res, 1(1), 111-120.
19. Hecq, J., Deleers, M., Fanara, D., Vranckx, H., & Amighi, K. (2005). Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. International journal of pharmaceutics, 299(1-2), 167-177.
20. Jatwani, S., Rana, A. C., Singh, G., & Aggarwal, G. (2012). An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical Sciences and Research, 3(4), 942.
21. Ahmad, Z. and M.N. Khan, (2011). Solubility enhancement of poorly water soluble drugs. International Journal of Pharmacy and Technology, 3(1): 811.
22. Dohrn, R., Bertakis, E., Behrend, O., Voutsas, E., & Tassios, D. (2007). Melting point depression by using supercritical CO2 for a novel melt dispersion micronization process. Journal of Molecular Liquids, 131, 53-59.
23. Vogt, M., Kunath, K., & Dressman, J. B. (2008). Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. European Journal of Pharmaceutics and Biopharmaceutics, 68(2), 283-288.
24. Sekiguchi K, Obi N(1961). Studies on absorption of eutectic mixtures. I.A. comparison of the behaviour of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man, Chem. Pharm. Bull, 9:866-872.
25. Devi, N. K. D., Rani, A. P., Javed, M., Kumar, K. S., Kaushik, J., & Sowjanya, V. (2010). Cyclodextrins in pharmacy-an overview. Pharmacophore, 1(3), 155-165.
26. Singh, M. C., Sayyad, A. B., & Sawant, S. D. (2010). Review on various techniques of solubility enhancement of poorly soluble drugs with special emphasis on solid dispersion. J Pharm Res, 3(10), 249-250.
27. Jain, S., Patel, N., & Lin, S. (2015). Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug development and industrial pharmacy, 41(6), 875-887.
28. A. P. Gowardhane, N. V. Kadam, and S. Dutta(2014). "Review on enhancement of solubilization process," American Journal of Drug Discovery and Development, vol. 4, no. 2, pp. 134-152.
29. Pardhi, D., Shivhare, U., Suruse, P., & Chabra, G. (2010). Lquisolid Technique For Solubility Enhancement of Poorly Water Soluble Drugs. Research Journal Pharmaceutical Dosage Forms and Technology, 2(5), 314-322.