Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 5 (2023)

A Review on Solubility Enhancement Techniques

[1]Naresh Kumar Dhinwa, [2]Yuvraj Singh Sarangdevot, [3]Bhupendra Vyas
Research Scholar, Faculty of Pharmacy
Bhupal Nobles' University, Udaipur (Rajasthan), india-313001
E-Mail: [1] nareshkumardhinwa@gmail.com; [2] yuv_cog@rediffmail.com; [3] vyashdt8@yahoo.com

Abstract
The solubility of drugs plays a crucial role in pharmaceutical formulation. It is particularlyimportant for the drug to reach its intended site of action in order to achieve success. Additionally, the bioavailability and solubility of the drug are significant factors in determining the pharmacological effect of any formulation, especially in the case of oral dosage forms. However, formulating poorly water-soluble drugs can often be quite challenging. The poorsolubility of the drug can lead to decreased absorption and dissolution rates, making it necessary to improve solubility through various methods such as salt formulation, solid dispersion, co-solvency, and the addition of solubilizing agents. These approaches are commonly employed to enhance the dissolution rate of the drug. Nevertheless, it is important to note that achieving thedesired bioavailability enhancement through these techniques may not always be possible. In this review, we will explore several techniques used to increase the solubility of poorly soluble drugs, including reducing particle size, adjusting pH, solid dispersion, and hydrotrophy, among others.
Keywords: Solubility Enhancement, bioavailability, hydrotrophy, solid dispersion.

Introduction

The formulation of drugs with low solubility for oral drug delivery is currently a significant challenge for formulation scientists in the pharmaceutical industry. In formulations containing poorly soluble drugs, the rate of dissolution is the limiting factor in the absorption process. Various solubilization techniques are available, but to date, there is no universal excipient or technique that can effectively solubilize a wide range of drug molecules. During the development stage, many potential candidates may be excluded due to their poor solubility and bioavailability. Solubility refers to the extent to which a solute-dissolves when excess solid is brought into contact with a liquid, resulting in a saturated solution at the experimental temperature [1].

Expressing the solubility of a drug can be done in various ways such as parts, percentage, molarity, molality, volume fraction, and mole fraction. This is why enhancing solubility is a crucial factor in the development of orally administered drugs with poor aqueous solubility.

Solubility refers to the physical property of a substance, the solute, to dissolve in a solvent. Sincemore than 90% of drugs are orally administered, the solubility of a compound in an aqueous medium greatly affects drug absorption, bioavailability, and pharmacokinetic profile. Unfortunately, more than 90% of drugs approved since 1995 have poor solubility, and about 40% of new chemical entities identified in screening programs are poorly water-soluble. This poses a major challenge in the oral delivery of new drug substances, especially for drugs on the Model list of Essential Medicines of the WHO, which are assigned BCS classifications based on publicly available data. Out of the 130 orally administered drugs on the list, only 61 could be classified with certainty [2].

Enhancing solubility is a crucial factor to consider in the development of orally administered drugs with poor aqueous solubility. Solvents are the primary components of a solution that can dissolve other substances to create a uniformly dispersed mixture at the molecular level. Solute, on the other hand, is a substance that dissolves in a solvent in small quantities. The maximum amount of solute that can dissolve in a specific amount of solvent or solution at a given temperature is referred to as solubility. In simpler terms, solubility refers to the ability of one substance to form a solution with another substance [3].

IUPAC defines solubility as the analytical composition of a saturated solution, which is the proportion of a specified solute in a specified solvent. Various units such as concentration, molality, mole fraction, mole ratio, and others can be used to quantify solubility.

The solubility should be ideally at two temperatures

□ 4^0 C - To ensure physical and chemical stability. The maximum density of water occurs at40C and this leads to minimum aqueous solubility.

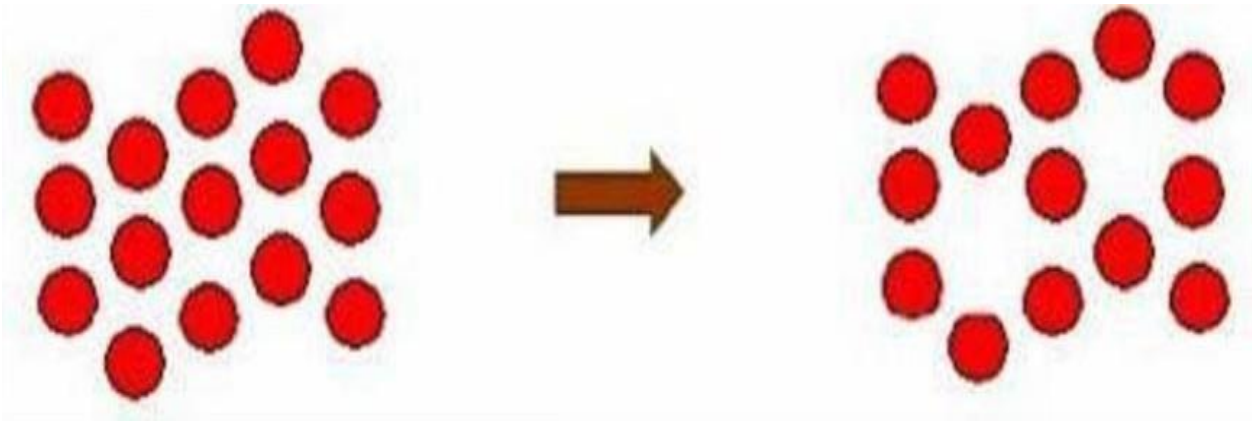
□ 37^0 C- To support Biopharmaceutical evaluation. [4]

S. no.	Descriptive terms	Parts of solvent required to dissolve one part of solute
1.	Very soluble	Less than 1
2.	Freely soluble	More than 1 but less than 10
3.	Soluble	More than 10 but less than 30
4.	Sparingly soluble	More than 30 but less than 100
5.	Slightly soluble	More than 100 but less than 1000
6.	Very slightly soluble	More than 1000 but less than 10,000
7.	Very very slightly soluble or practically Insoluble	More than 10,000

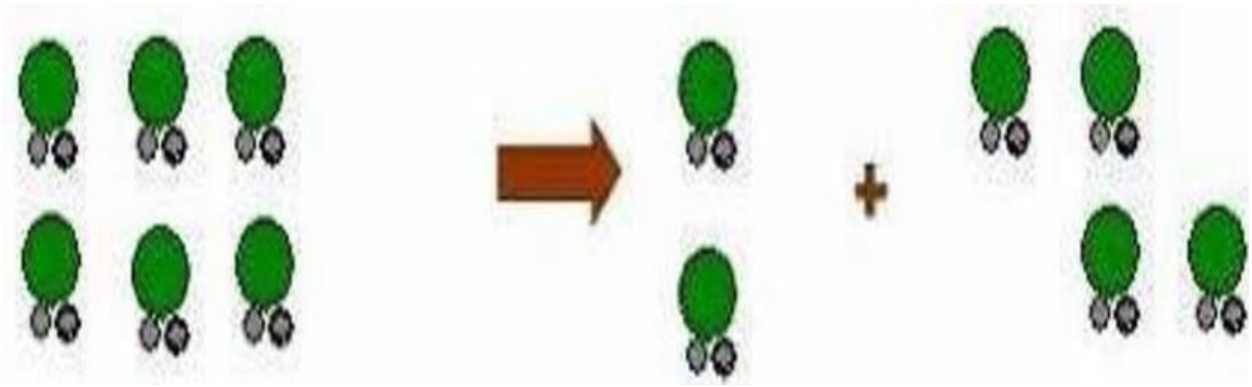
Solubilization

Solubilization is a chemical process that entails the disruption of inter-ionic or intermolecular bonds within the solute. This allows for the separation of solvent molecules, creating room forthe solute to dissolve. Additionally, solubilization involves the interaction between the solvent and the solute molecule or ion [5].

Step 1: Holes opens in the solvent



Step 2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

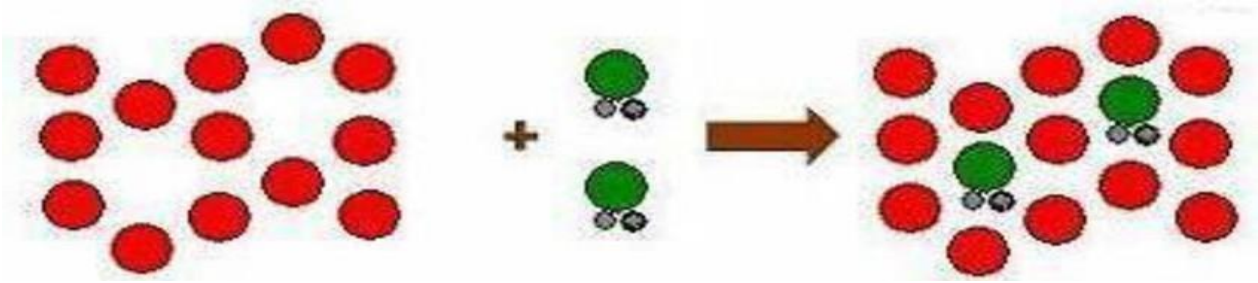


Figure 1: Steps of solubilization process

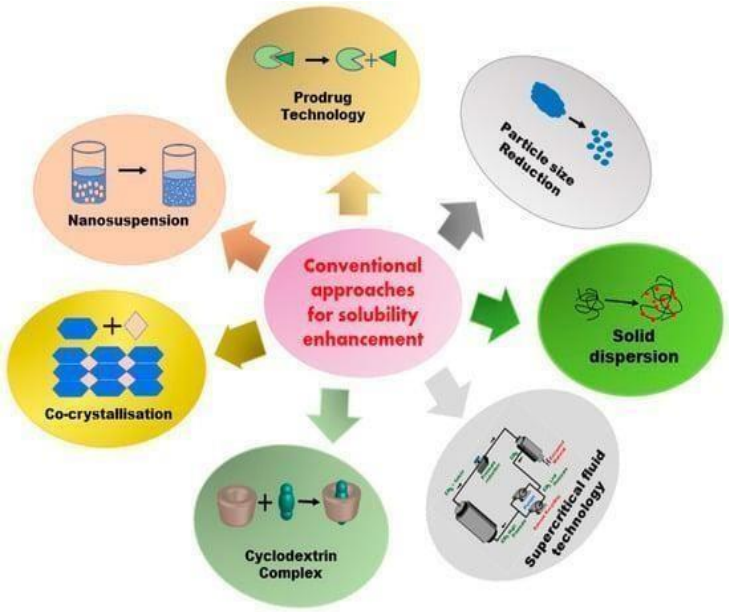
Solubility affecting factors

1. **"Nature of solute and solvent"**: The characteristics of the solvent and solute are reliant on the solute's composition, which is exclusive to the solvent at a given temperature. As an example, at room temperature, water can only dissolve 1gm of lead, whereas 200gm of zinc chloride can be dissolved.
2. **"Size of particles"**: The solubility of a substance can be altered by the size of its particles. As the particle size decreases, the ratio of surface area to volume increases, leading to greater interaction with the solvent and increased solubility.
3. **"Molecular size":** The solubility of a substance can also be impacted by the size of its molecules. As the molecular weight and size increase, the solubility tends to decrease.
4. **"Temperature":** The solubility of drugs can be impacted by various factors, including the solution process and temperature. When the solution process absorbs energy, the solubility tends to increase as the temperature rises. Conversely, if the solution process releases energy, the solubility tends to decrease as the temperature increases.
5. **"Pressure":** The solubility of liquids and solid solutes remains unaffected by changes in pressure, whereas for gaseous solutes, solubility increases with an increase in pressure and decreases with a decrease in pressure [6].

"Importance of Solubility"

Oral ingestion is the preferred and practical method of drug delivery due to its affordability, simple administration, minimal sterility requirements, patient compliance, and flexibility indosage formulation.

Solubility is a crucial factor in various dosage forms, including parenteral formulations. Achieving optimal blood circulation and desired therapeutic responses heavily rely on solubility. Even water-insoluble drugs require appropriate doses to attain therapeutic plasma concentration after oral administration. For effective absorption, a drug must be present at the absorption site in the form of an aqueous solution. Water is commonly chosen as the primary solvent for liquidpharmaceutical formulations [7,8].



***F*igure 2:** Conventional methods for solubility enhancement.

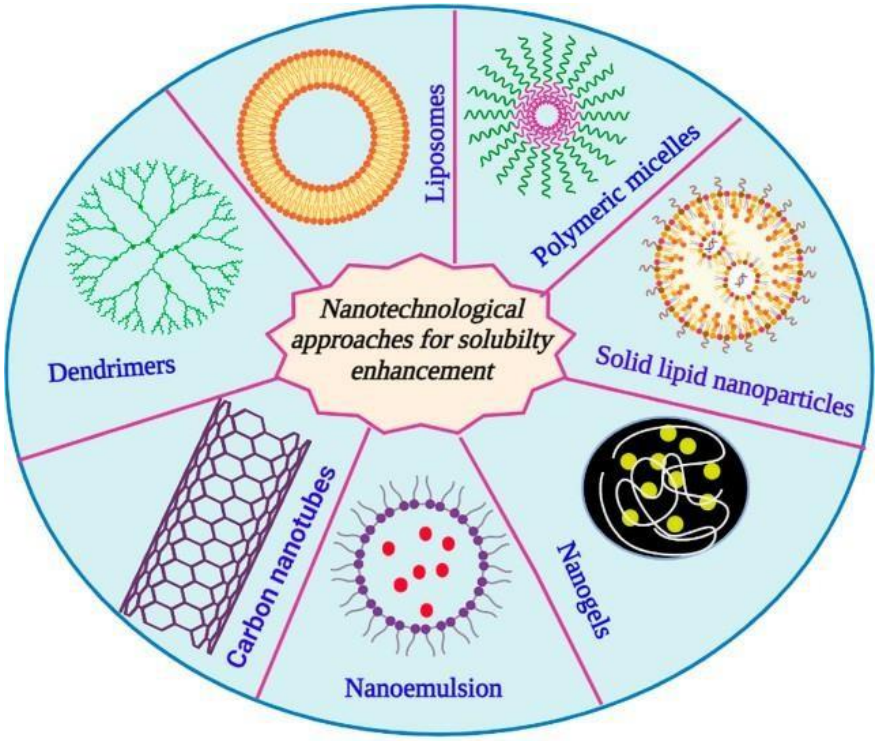


Figure 3: Nanocarrier-mediated solubility enhancement techniques.

1. **Physical Modification**

a. Particle size reduction

a) Micronization
b) Nanosuspension

b. Modification of crystal habit

a) Polymorphs
b) Pseudopolymorphs

c. Drug dispersion in carriers

a) Solid solutions
b) Solid dispersion

d. Solubilization by surfactants

a) Microemulsion
b) Self-micro emulsifying drug delivery system

e. complexation

2. Chemical modification

a. Hydrotrophy

a) Co-solvency
b) Salt formation

3. PH adjustment

4. Supercritical fluid process

5. Liquisolid methods

1. Physical Modification

a. Particle size reduction

The solubility of a drug is influenced by the size of its particles. When the particle size is reduced, the surface area increases, leading to improved dissolution properties of the drug. The particle size of a drug is often associated with the bioavailability of poorly soluble drugs. Techniques such as milling using colloid mills and jet mills are employed to reduce particle size. It is important to note that while particle size reduction enhances dissolution, it does not alter the saturation solubility of the drug. However, this method may not be suitable for drugs with high dosage requirements [9].

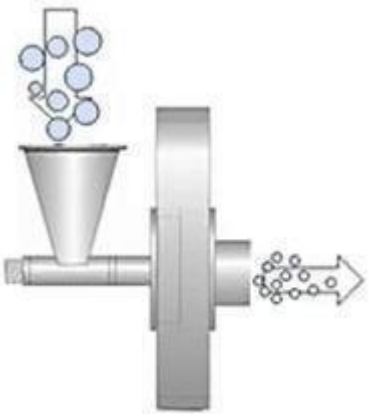


Figure 4: Particle size reduction

ADVANTAGES

- Liquid forms can be rapidly developed for early-Stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Typically, low excipients to drug ratios are required.
- Formulations are generally well tolerated Provided that strong surfactants are not required for stabilization. Generally, crystal forms are chemically and physically more stable than amorphous particles.
- A method to consider for stubborn compounds that defeat previous attempts to increase Solubility.

DISADVANTAGES

- The presence of a significant surface charge on individual small particles often leads to a pronounced inclination for particle agglomeration.
- Creating a solid dosage form with a substantial payload while minimizing the occurrence of agglomeration can pose technical difficulties.
- The technical complexities involved in developing sterile intravenous formulations are evenmore demanding.

Nanosuspension:

Prompt: Paraphrase the following text: "This technology is used to poorly soluble drugs that are insoluble in Water & oils."

This method is utilized for drugs that have low solubility and cannot dissolve in water or oils. It involves creating a biphasic system consisting of nano-sized particles in an aqueous medium. The surfactant stabilizes the drug particles, which can be administered through parenteral and

pulmonary routes or orally and topically. The particle size distribution of solid particles in the nanosuspension is typically less than one micron, with an average particle size range of 200 to 600nm. This technique has been applied to several drugs, including tarazepide, atovaquone, amphotericin, paclitaxel, and buparvaquone. Different methods for preparing nanosuspensions include Nanocrystals, DissoCubes, Nanopore, and Nano edge [10].

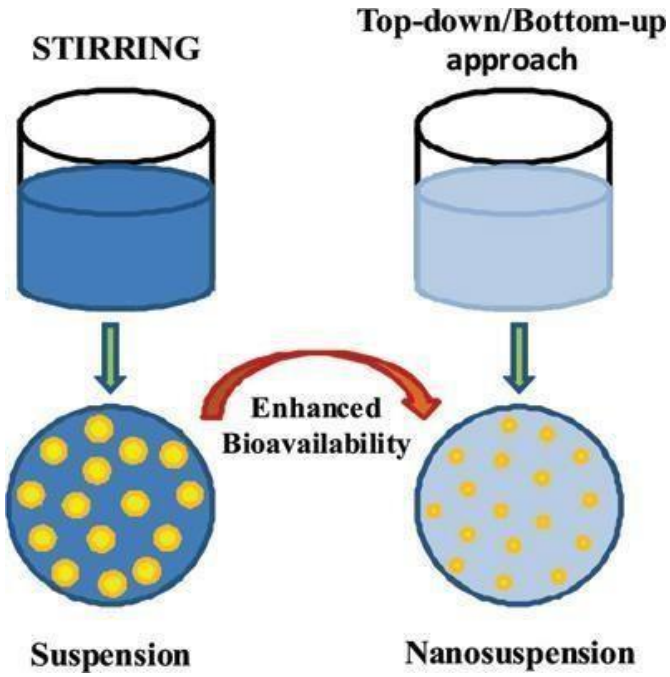


Figure 4: Nanosuspension

ADVANTAGES:

- The reduction in drug particle size in nanosuspensions leads to an increase in surfacearea, which in turn enhances dissolution, solubility, and bioavailability.
- Nanosuspensions improve drug permeability.
- The duration of action of residence is increased with nanosuspensions.
- Nanosuspensions enhance the bioadhesion of drugs.
- High drug loading is achievable with nanosuspensions.

- Organic solvents can be avoided with nanosuspensions.

DISADVANTAGES:

- The main challenge faced by nanosuspensions is instability caused by crystal growth,agglomeration, and Ostwald ripening.

MODIFICATION OF CRYSTAL HABBIT:

Polymorphs:

Polymorphism refers to the capacity of a substance to crystallize in multiple crystalline forms. An agent with this ability is known as a polymorph. It is conceivable for a solid to crystallize in various forms or polymorphs. These polymorphs can exhibit variations in their melting points.As the melting point of a solid is connected to its solubility, it follows that polymorphs will display different solubilities [11].

Pseudo polymorphs:

Polymorphism is the ability of solid material to exist in 2 or more different crystalline Formswith different arrangements in crystal lattice. Polymorphs are different crystalline Forms. Crystalline forms of drugs are chemically same but they have different.

The physiochemical characteristics that are taken into consideration include melting point, texture, density, solubility, and stability. In comparison, the amorphous state of a drug is preferred over its crystalline form due to its higher surface area and associated energy. The order of solid forms of drugs is as follows: amorphous > metastable polymorphs > stable polymorphs [12,13].

DRUG DISPERSION IN CARRIER:

Solid solutions:

A new crystalline solid is formed by blending two crystalline solids together in a homogenous, single-phase system. This mixed crystal has a significantly higher dissolution rate compared to a simple enteric system [14].

Solid dispersion:

Sekiguchi & Obi introduced the idea of solid dispersion, which is a valuable pharmaceutical method for improving the speed of dissolution, absorption, and therapeutic effectiveness of medications. Solid dispersion refers to a collection of solid products that typically contain a hydrophilic matrix and a hydrophobic drug. Polyethylene glycols, polyvinyl pyrrolidone, and plasdone-S630 are commonly used hydrophilic carriers. Surfactants are frequently employed in the creation of solid dispersion [15,16].

ADVANTAGES:

- Preventing the thermal decomposition of drugs and carrier materials is achievable.

DISADVANTAGES:

- Costly
- Challenging to eliminate a liquid solvent entirely
- Challenging to identify a widely available solvent

(d). Solubilization by surfactantsMicroemulsion:

A microemulsion is a translucent system that is optically clear, thermodynamically stable, and isotropic. It contains a mixture of oil, surfactant, and hydrophilic solvent that dissolves poorly aqueous soluble drugs. The selection of a surfactant is based on parameters such as HLB and non-toxicity. Upon contact with water, the formulations self-emulsify, resulting in a highly clear emulsion of small, homogeneous oil droplets that carry the solubilized weakly soluble medication [17,18].

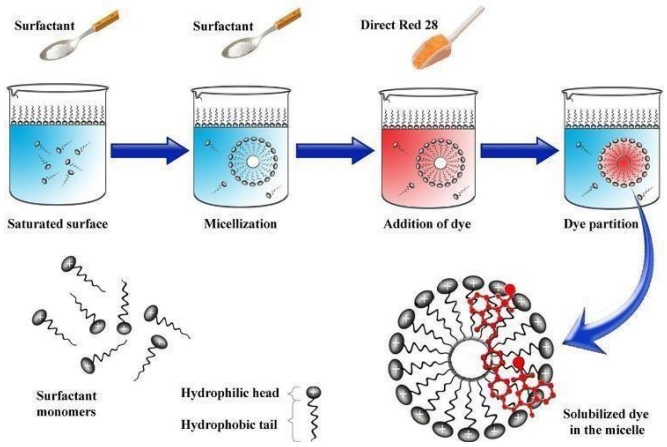


Figure 5: Microemulsion

A microemulsion is a translucent system that is optically clear, thermodynamically stable, and isotropic. It is composed of a mixture of oil, surfactant, and hydrophilic solvent, which can dissolve poorly aqueous soluble drugs. The selection of a surfactant is based on parameters such as HLB and non-toxicity. Upon contact with water, the formulations self-emulsify, resulting in a highly clear emulsion of small, homogeneous oil droplets carrying the solubilized weakly solublemedication. Microemulsions have been utilized to enhance the solubility of various medications that are nearly insoluble in water, as well as to incorporate proteins for oral, parenteral, and intravenous administration. The most suitable formulation is an oil-in-water (o/w) microemulsion, which dissolves molecules with low water solubility into the oil phase solubility [19-21].

ADVANTAGES:

- The liberation of drugs from fully-formed microemulsion pre-concentrates is typically not influenced by digestion. Therefore, one can anticipate optimal bioavailability and consistency without the requirement for simultaneous meal intake.

DISADVANTAGES:

- Validation becomes more challenging when dealing with formulations that contain multiple components.
- Self-emulsifying drug delivery system: This system consists of a mixture of oil, surfactant, co-surfactant, and one or more hydrophilic solvents. Unlike traditional formulations, it does not require an external phase (such as water) and instead forms a clear isotropic solution with the help of a cosolvent. This self-emulsifying solution is capable of emulsifying itself, and some researchers have referred to it as a"microemulsion pre-concentrate." When administered orally, these innovative colloidal compositions exhibit behavior similar to oil-in-water microemulsions.

COMPLEXATION

Drugs have been combined with cyclodextrins in order to enhance their water solubility and stability. In the field of pharmaceutical formulations, the most commonly utilized derivatives of β-cyclodextrin, which exhibit improved water solubility, are employed. Due to their large molecular weights exceeding 1000 Da, cyclodextrins are not easily able to penetrate the skin. However, it has been observed that the complexation of cyclodextrins can both increase and decrease skin penetration. In addition to their role in enhancing solubility, cyclodextrins can also serve as membrane permeability enhancers and stabilizing agents. Their presence has been found to improve permeability across biological membranes. Furthermore, in pulmonary drug delivery systems, cyclodextrins can be utilized as permeability enhancers[22-25].

CHEMICAL MODIFICATIONS:HYDROTROPHY:

Hydrotrophy refers to a process where a significant quantity of a second solute is introduced to enhance the aqueous solubility of a third solute. The mechanism through which it enhances solubility is primarily associated with complexation. This involves a weak interaction between hydrotropic agents like sodium alginate, sodium acetate, sodium benzoate, urea, and poorly soluble drugs. The phenomenon of "salting in" of non-electrolytes, also known as "hydrotropic salts," is caused by numerous salts with large anions or cations that are highly soluble in water. This process is referred to as "hydrotropism." Hydrotropic solutions are not colloidal and exhibit a weak interaction between the hydrotropic agent and the solute [26-28].

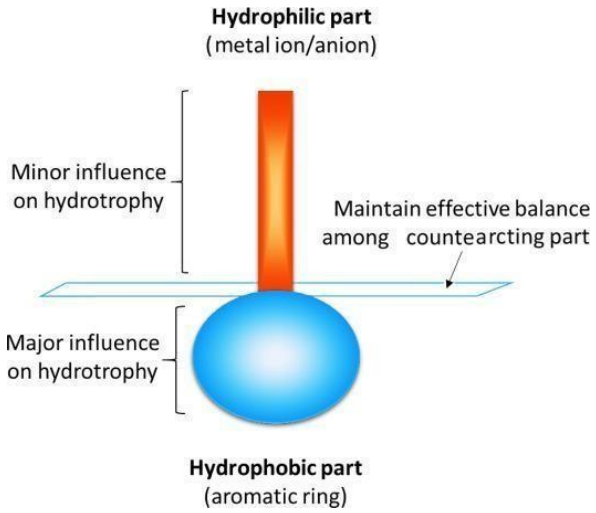


Figure 5: Hydrotrophy (aromatic ring)

ADVANTAGES:

- Hydro trophy exhibits excellent selectivity without the need for emulsification, and itssolvent properties remain unaffected by pH changes.
- There is no requirement for the utilization of organic solvents or the creation of anemulsion system.

DISADVANTAGES

- Collect individually in a mixture
- For instance: ketoprofen, aceclofenac, salicylic acid, cefixime, tinidazole, frosemide, Amoxicillin.

Co-solvency

Co-solvency refers to the combination of one or more compatible liquids that are used toenhance the solubility of drugs. By adding a co-solvent solution, the solubility and miscibility of

the drug solution can be improved, as well as its dissolution. In comparison to simple drugs, the addition of a co-solvent significantly enhances the solubility of poorly soluble drugs by a factor of nearly a thousand. This technique is particularly suitable for drugs that have low solubility, are lipophilic, or have a highly crystalline structure, but exhibit high solubility in the solvent mixture. Co-solvents, due to their low toxicity and ability to solubilize nonpolar pharmaceuticals, are primarily used in parenteral dosage forms. In order to reduce the amount of solvent in the formulation prior to administration, the addition of water or a dilution step using an aqueous medium may be necessary [29-31].

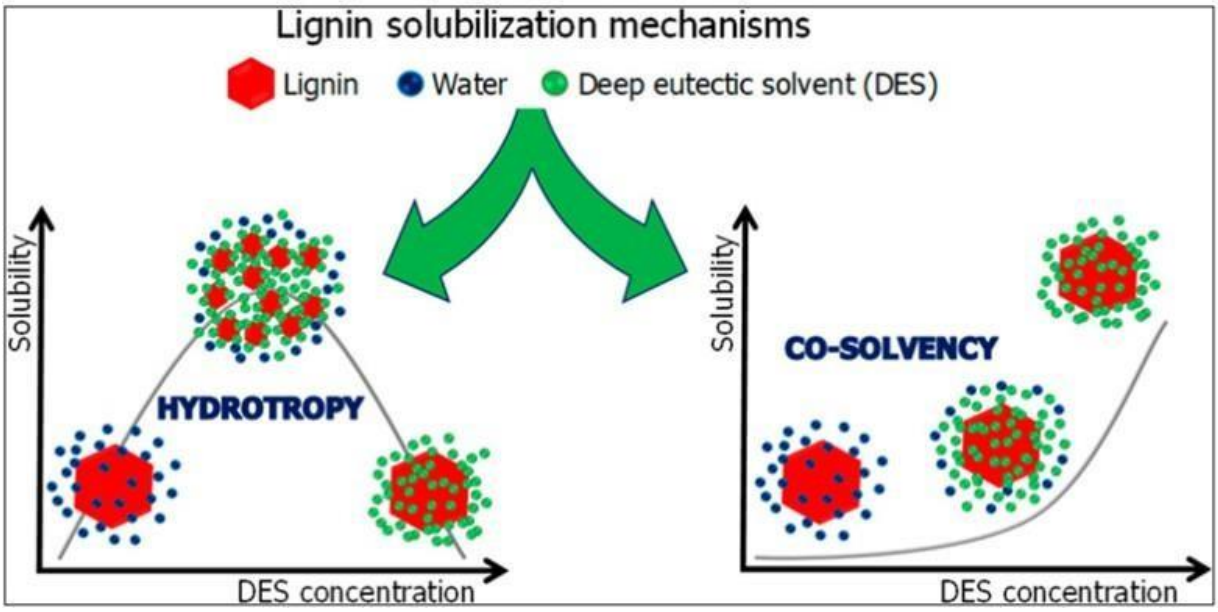


Figure 6: co-solvency

Co-solvents can also be combined with various solubilization techniques and pH adjustments to enhance the solubility of weakly soluble substances. The use of co-solvents to improve the solubility of poorly soluble pharmaceuticals is a highly effective strategy. Commonly used low-toxicity co-solvents in parenteral administration include propylene glycol, ethanol, glycerin, and polyethylene glycol. Dimethyl sulfoxide (DMSO) and dimethylacetoamide (DMA) are also widely employed as co-solvents due to their significant solubilization capacity for poorly solubledrugs and relatively low toxicity [32-34].

ADVANTAGES:

- The formulation, production, and evaluation processes are made simple and efficient.
- Additionally, it can be utilized in conjunction with other solubilization methods and pH adjustment to enhance the solubility of compounds that are poorly soluble.

DISADVANTAGES:

- The toxicity and tolerability associated with the level of solvent administered must betaken into account, just like with any other excipients.
- When mixed with water, uncontrolled precipitation can take place, resulting in theformation of either amorphous or crystalline precipitates that can differ in size.
- Phares encounters numerous insoluble compounds that are not suitable for co-solventsalone, especially when it comes to intravenous administration.
- This occurs due to the drugs' high insolubility in water and their limited ability todissolve again after being precipitated from the cosolvent mixture.
- These circumstances carry a potential risk of Embolism and negative local outcomes atthe site of Injection.
- The chemical stability of an insoluble drug is comparatively lower than that of acrystalline state, as is the case with all solubilized forms.

Salt Formation

The utilization of salt formation techniques is aimed at enhancing the solubility and dissolution of drugs. This method is employed to observe any chemical reaction or variation in different drugs. Salt is formed when the drug undergoes ionization. The process involves various methods such as physiochemical properties

that affect the stability, bioavailability, purification, and manufacturability of the drug. Salt formation has been a preferred approach for a considerable period to improve the solubility of low soluble drug candidates [35-37].

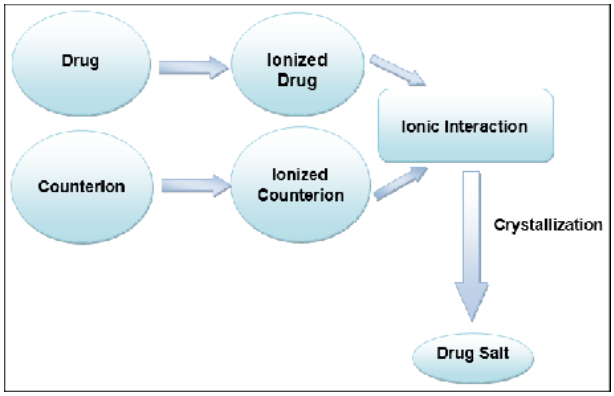


Figure 7: Salt Formulation

PH ADJUSTMENT

The solubility of a drug is dependent on the pH level, with more ionic drugs being more easily solubilized. Maintaining the appropriate pH level is crucial for the drug's solubility and for achieving the desired pharmacological response. Additionally, pH is necessary for the administration of the drug, as drugs with low solubility can precipitate in the blood and cannot dissolve due to the acidic nature of blood. The absorption of the drug also requires a suitable pH level, with the stomach having a pH of 1-2 and the duodenum having a pH of 5-6. The degree of solubility is responsible for the drug's ability to pass through the body. This method is regularly used for pre-clinical pH adjustment and is a new way to measure the efficiency of low soluble drugs. The advantage of this method is its simplicity in formulating the drug and using small quantities for evaluation [38-41].

ADVANTAGES

- Simple to formulate and assess.
- Involves small amounts of compound, allowing for convenient high throughput evaluations.

DISADVANTAGES:

- There is a potential risk of precipitation when the compound is diluted with aqueous media that has a lower solubility pH. This can result in emboli when administered intravenously and variability when taken orally. It is important to take into account the tolerability and toxicity, both locally and systemically, associated with the use of non-physiological and extreme pH levels.
- When a drug is dissolved in an aqueous environment, it tends to be less chemically stable than formulations in crystalline solid form, just like any other solubilized and dissolved systems. The pH level chosen can either speed up hydrolysis or catalyze other degradation mechanisms.

SUPER CRITICAL FLUID PROCESS:

Supercritical fluids (SCFs) possess the ability to dissolve nonvolatile solvents, specifically carbon dioxide at its critical point. SCFs are known for being safe, environmentally friendly, and cost-effective. Above its critical temperature and pressure, a SCF exists as a single phase. These fluids exhibit properties that are advantageous for product processing, as they lie between those

of pure liquid and gas. Additionally, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) of SCFs vary significantly with slight changes in operating temperature, pressure, or both around the critical points. The unique processing capabilities of SCFs, which have long been utilized in the food industry, have recently found applications in the pharmaceutical field. Commonly employed supercritical solvents include carbon dioxide, nitrous oxide,

ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Various methods of SCF processing have been developed to address specific limitations, such as the precipitation with compressed antisolvents process (PCA), rapid expansion of supercritical solutions, gas antisolvent recrystallization, precipitation with impregnation or infusion of polymers with bioactive materials, compressed fluid antisolvent, solution enhanced dispersion by supercritical fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES), and supercritical antisolvents processes (SAS) [42-46].

ADVANTAGES:

- SCFs are becoming increasingly popular in pharmaceutical research due to their low operating conditions, including temperature and pressure. By solubilizing drug particles within SCFs, they can be recrystallized at significantly smaller particle sizes. Recent advancements in SCF processes have shown the ability to produce nanosuspensions of particles ranging from 5-2,000nm in diameter.
- The SCF processes provide a high level of flexibility and accuracy, enabling the micronization of drug particles with precise control over particle size, often achieving sub-micron levels.

LIQUID SOLID METHODS:

When the drug dissolves in the liquid vehicle and is introduced into a carrier material with a porous surface and fibers in its interior, such as cellulose, both absorption and adsorption occur. Initially, the liquid is absorbed into the interior of the particles and captured by the internal structure. Once saturation is reached, the liquid is adsorbed onto the internal and externalsurfaces of the porous carrier particles. As a result, the coating material, which has high adsorptive properties and a large specific surface area, creates a liquisolid system with desirable flow characteristics. Coating materials such as microcrystalline and amorphous cellulose, as well as silica powders, can be used for this purpose [47].

CONCLUSION:

The dissolution of a drug plays a crucial role in determining the rate of oral absorption for poorlywater-soluble drugs. This, in turn, can have an impact on the drug's absorption in vivo. Due tothe solubility issues faced by many drugs, their bioavailability is often affected, making solubility enhancement necessary. The primary objective of all currently available technologies involved in solubility and dissolution enhancement is to maximize bioavailability and therapeuticefficacy. Various solubility enhancement methods have been developed to overcome the solubility problem, and these methods are applicable in industrial settings. By utilizing the discussed newer techniques, it is possible to improve the solubility of poorly water-soluble drugs.

REFERENCES:

[1] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.
[2] Batrisyia RN, Janakiraman AK, Ming LC, Uddin AH, Sarker ZI, Bin LK. A review onthe solubility enhancement technique for pharmaceutical formulations. Nveo-Natural Volatiles & Essential Oils Journal| NVEO. 2021 Nov 9:3976-89.
[3] Yon JA, Lee SK, Keng JW, Chow SC, Liew KB, Teo SS, Shaik Mossadeq WM, Marriott PJ, Akowuah GA, Ming LC, Goh BH. Cassia alata (Linnaeus) roxburgh for skin: Natural remedies for atopic dermatitis in Asia and their pharmacological activities. Cosmetics. 2022 Dec 26;10(1):5.
[4] Liew KB, Ming LC, Goh BH, Peh KK. Fast Melt Cocoa Butter Tablet: Effect of Waxes, Starch, and PEG 6000 on Physical Properties of the Preparation. Molecules. 2022 May 13;27(10):3128.
[5] Janakiraman AK, Islam T, Liew KB, Elumalai M, Hanish Singh JC. Improved oral bioavailability of poorly water-soluble vorinostat by self-microemulsifying drug delivery system. Beni-Suef University Journal of Basic and Applied Sciences. 2022 Dec;11(1):1-3.
[6] Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov;5(1):41-51.
[7] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques.

International Scholarly Research Notices. 2012;2012.

[8] Kumar S, Singh P. Various techniques for solubility enhancement: An overview. The Pharma Innovation. 2016;5(1, Part A):23.

[9] Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Partapur MU. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res. 2012;2(1):32-67.

[10] Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotrophy. International Journal of Pharma Professional's Research (IJPPR). 2010;1(1):34-45.

[11] Singh J, Walia M, Harikumar SL. Solubility enhancement by solid dispersion method: a review. Journal of drug delivery and Therapeutics. 2013 Sep 14;3(5):148-55.

[12] Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale. 2011;3(3):001-7.

[13] Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. International journal of pharmaceutical sciences and research. 2011 Oct 1;2(10):2501.

[14] Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation. 2012 Jan;2(1):12.

[15] Vimalson DC. Techniques to enhance solubility of hydrophobic drugs: an overview. Asian Journal of Pharmaceutics (AJP). 2016 Jun 27;10(2).

[16] Sharma DK. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: a review. Asian Journal of Pharmaceutics (AJP). 2007;1(1).

[17] Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. Journal of Applied Pharmaceutical Science. 2012 Oct 28;2(10):170-5.

[18] Kalia A, Poddar M. Solid dispersions: an approach towards enhancing dissolution rate. Int j pharm pharm sci. 2011;3(4):9-19.

[19] Sharma A, Jain CP. Solid dispersion: A promising technique to enhance solubility of poorly water soluble drug. International Journal of Drug Delivery. 2011 Apr 1;3(2):149.

[20] Sridhar I, Doshi A, Joshi B, Wankhede V, Doshi J. Solid dispersions: an approach to enhance solubility of poorly water soluble drug. J Sci Innov Res. 2013;2(3):685-94.

[21] Dehghan MH, Saifee M, Hanwate RM. Comparative dissolution study of glipizide by solid dispersion technique. Journal of Pharmaceutical Science and Technology. 2010;2(9):293-7.

[22] Sharma DK. Solubility enhancement strategies for poorly water-soluble drugs in solid dispersions: a review. Asian Journal of Pharmaceutics (AJP). 2007;1(1).

[23] Singh G, Kaur L, Gupta GD, Sharma S. Enhancement of the Solubility of Poorly Water Soluble Drugs through Solid Dispersion: A Comprehensive Review. Indian Journal of Pharmaceutical Sciences. 2017 Sep 1;79(5).

[24] Argade PS, Magar DD, Saudagar RB. Solid dispersion: solubility enhancement technique for poorly water soluble drugs. Journal of Advanced Pharmacy Education & Research. 2013 Oct;3(4).

[25] Singh J, Walia M, Harikumar SL. Solubility enhancement by solid dispersion method: a review. Journal of drug delivery and Therapeutics. 2013 Sep 14;3(5):148-55.

[26] Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation. 2012 Jan;2(1):12.

[27] Aggarwal S, Gupta GD, Chaudhary S. Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs. International journal of pharmaceutical sciences and research. 2010;1(8):1-3.

[28] Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique–A review. J. Pharm. Res. 2010 Sep;3(9):2314-21.

[29] Kumar P, Singh C. A study on solubility enhancement methods for poorly water soluble drugs. American Journal of Pharmacological Sciences. 2013;1(4):67-73.

[30] Das SK, Roy S, Kalimuthu Y, Khanam J, Nanda A. Solid dispersions: an approach to enhance the bioavailability of poorly water-soluble drugs. International journal of pharmacology and pharmaceutical

technology. 2012;1(1):37-46.
[31] Babu VR, Areefulla SH, Mallikarjun V. Solubility and dissolution enhancement: an overview. J Pharm Res. 2010 Jan;3(1):141-5.
[32] Sridhar I, Doshi A, Joshi B, Wankhede V, Doshi J. Solid dispersions: an approach to enhance solubility of poorly water soluble drug. J Sci Innov Res. 2013;2(3):685-94.
[33] Ainurofiq A, Putro DS, Ramadhani DA, Putra GM, Santo LD. A review on solubility enhancement methods for poorly water-soluble drugs. Journal of Reports in Pharmaceutical Sciences. 2021 Jan 1;10(1):137-47.
[34] Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility enhancement techniques for poorly water-soluble drugs. Int. J. Pharm. Sci. Nanotechnol. 2017 May 31;10(8).
[35] Tiwari R, Tiwari G, Srivastava B, Rai AK. Solid dispersions: an overview to modify bioavailability of poorly water soluble drugs. International Journal of PharmTech Research. 2009 Oct 1;1(4):1338-49.
[36] Sharma A, Jain CP. Solid dispersion: A promising technique to enhance solubility of poorly water-soluble drug. International Journal of Drug Delivery. 2011 Apr 1;3(2):149.
[37] Chokshi RJ, Zia H, Sandhu HK, Shah NH, Malick WA. Improving the dissolution rate of poorly water-soluble drug by solid dispersion and solid solution—pros and cons. Drug delivery. 2007 Jan 1;14(1):33-45.
[38] Singh S, Baghel RS, Yadav L. A review on solid dispersion. International journal of pharmacy & life sciences. 2011 Sep 1;2(9).
[39] Gupta AK, Sehrawat SK. Bioavailability enhancement of poorly water-soluble drugs. IJRLS. 2011 Mar;2(3):640-50.
[40] Kadam SV, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. IJPBS. 2013;3(3):462-75.
[41] Chawla G, Bansal AK. A comparative assessment of solubility advantage from glassy and crystalline forms of a water-insoluble drug. European journal of pharmaceutical sciences. 2007 Sep 1;32(1):45-57.
[42] Yadav K, Sachan AK, Kumar S, Dubey A. Techniques for increasing solubility: A reviewof conventional and new strategies. Asian Journal of Pharmaceutical Research and Development. 2022 May 16;10(2):144-53.
[43] Nikghalb LA, Singh G, Singh G, Kahkeshan KF. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs. Journal of Applied Pharmaceutical Science. 2012 Oct 28;2(10):170-5.
[44] Wahab A, Khan A, Khan GM. Preparation and evaluation of solid dispersions of ibuprofen using glucosamine HCl as a carrier. British Journal of Pharmaceutical Research. 2013 Oct 1;3(4):722-33.
[45] Saharan V, Kukkar V, Kataria M, Gera M, Choudhury PK. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. International Journal of Health Research.2009;2(2).
[46] Sajid MA, Choudhary V. Solubility enhancement methods with importance of hydrotropy. Journal of Drug Delivery & Therapeutics. 2012;2(6):96-101.
[47] Dholakiya A, Shah AK, Jakasania P, Patel J, Garala K. A review on solid self emulsifyingdrug delivery systems and dosage forms.