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A review article on solubility enhancement

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Abstract
A key concern in both formulation research and screening studies of new chemical entities has been the solubility of poorly soluble medications. Poor water solubility can limit medication efficacy, and certain pharmaceuticals can exhibit negative effects as a result of their poor solubility. There are various methods used to increase a substance's solubility in water. Therefore, the ability to increase water solubility can be a valuable aid in boosting effectiveness or lowering negative effects for some medications. For solutions delivered topically, orally, or by a parent, this is literal. It is a difficult challenge for pharmaceutical researchers to use the solubility attribute in bioavailability, pharmacology action, and solubility augmentation of various poorly soluble substances. One method for increasing solubility is hydrotropy or hydrotropic solubilization.

Keywords: Solubility enhancement, determination of solubility, techniques, advantages, application

Introduction
In terms of quantity, solubility is defined as the amount of the solute present in a saturated solution at a particular temperature. In terms of quality, solubility is the spontaneous interaction of two or more substances to create a homogenous molecular dispersion. When the solute and solvent are in balance, a solution is said to be saturated. Parts, percentages, molarity, molality, volume fraction, and mole fraction are all acceptable ways to express a drug's solubility. The maximum amount of a drug's solute that can be dissolved in a solvent under a given set of temperature, pH, and pressure conditions is known as the drug's solubility. Drug dissolution rate is a dynamic feature that is more closely related to bioavailability than drug solubility in saturated solution, which is a static property.

Table 1: Definitions of Solubility [1]

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Insoluble	More than 10,000

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water-soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid and not the absorption, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs. BCS Classification System with examples of different drug is discussed in Table-2.

Table:2 Biopharmaceutical Classification System

BCS Class I	High Solubility High Permeability	B-blockers propranolol, Metoprolol
BCS Class II	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carbazepine
BCS Class III	High Solubility Low Permeability	B blockers Atenolol,H2 antagonist Ranitidine
BCS Class IV	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, frusemide

BE studies are currently being conducted for New Drug Applications (NDAs) of new compounds, in supplementary NDAs for new medical indications and product line extensions, in Abbreviated New Drug Applications (ANDAs) of generic products, and in applications for scale-up and post-approval changes. NDA BE studies could be needed, for instance, when critical clinical trials and products destined for the market compare various formulations. Numerous dose strengths may be used during the development process, which frequently increases study complexity and quantity. The comparison of blinded and original comparator products in clinical studies may also require BE documentation. As a result, a typical NDA includes a document.

A scientific method for categorizing medicinal compounds based on solubility as it relates to dose and intestinal permeability, as well as the dissolution characteristics of the oral immediate-release dosage, has been created, and it is known as the Biopharmaceutics Classification System (BCS). form The BCS aims to provide a regulatory tool for accurate in-vitro dissolution tests to replace some BE studies. This will undoubtedly cut down on direct and indirect expenses and time spent on medication development as well as unnecessary drug exposure in healthy people, who often make up the sample population in BE studies. Currently, only oral immediate-release medications that are absorbed throughout the intestinal system are covered by the BCS. This is a result of the most popular delivery method being oral.

The BCS was primarily created for purposes in regulation. However, it also has a number of other effects on the preclinical and clinical drug development processes and is well known in the research-based sector. Since the 1960s, it has been widely recognised that the oral absorption process depends on drug dissolution in the gastrointestinal tract and permeability across the gut wall barrier. However, the research done to create the BCS has produced new quantitative data that is crucial for contemporary drug development, particularly in the area of drug permeability. The BCS's ability to provide extremely simple, straightforward principles for identifying the ratelimiting element in the process of gastrointestinal medication absorption is another advantage in a development environment. Consequently, the BCS framework has effects.

2. Determination of solubility

The significance of thermodynamic solubility in biopharmaceutical chemical or medication characterization as well as the value of having procedures that precisely demonstrate it have been extensively explored. However, determining it precisely is still difficult to do. More so when there are numerous compounds to assess and little of each compound is readily available, both of which are necessary for compound characterization during the drug development process. It is currently impossible to state that another appropriate model that is frequently used to estimate thermodynamic solubility is being employed, with the exception of the shake-flask method, which is still regarded as the "gold standard" in getting thermodynamic data. Consequently, this review provides a summary of the many experimental strategies.

In pharmaceutical research, determining a drug candidate's solubility is crucial for both the discovery phase and the development phase. Solubility is used to screen potential drugs in the early phases of drug discovery, along with other physicochemical factors like lipophilicity, ionisation, and permeability. To enable formulation development, including salt choice and product optimization, this data is required. Solubility considerations are helpful in anticipating for difficulties that could arise when addressing formulation adjustments and the related bioequivalence issues during the later stages of product development.

In recent years, there has been an increase in interest in the formulation of solid dispersions for purposes such as solubility enhancement, sustained drug release, and taste masking. The main issue with these dispersions is drug-carrier (in) solubility. In this section, we will look at solubility parameters as a tool for predicting a drug's solubility in various carriers. Solubility parameters were determined in two ways: solely through calculation methods and through experimental approaches. Six different calculation methods were used to determine the solubility parameters of ibuprofen and several excipients. However, we were unable to do so in the case of ibuprofen lysinate because salt calculation models have yet to be defined. As a result, the extended Hansen's method and inverse gas chromatography (IGC) were used.

3. Techniques

To meet the challenge posed by insoluble compounds, various technologies have emerged, and these technologies have made a difference. The following techniques for overcoming poor drug solubility are discussed:

3.1. Chemical modification

- pH adjustment
- Salt formation

- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agents
- Nanotechnology

3.2. Physical modifications

1. Particle size reduction:
a. Micronization
b. Nanosuspension
2. Modification of the crystal habit:
a. Polymorphs
b. Pseudopolymorphs
3. Complexation:
a. Use of complexing agents
4. Solubilization by surfactants:
a. Microemulsions
b. Self microemulsifying drug delivery system
5. Drug dispersion in carriers:
a. Solid solution
b. Solid dispersion

1. Chemical Modification

• pH Adjustment: Poorly water-soluble drugs with molecule parts that can be protonated (base) or deprotonated (acid) may be dissolved in water by changing the pH. In theory, pH adjustment can be used for both oral and parental administration. Best suited are ionizable compounds that are stable and soluble after pH adjustment. The compounds can be acids, bases, or zwitterionic. It can also be used to treat crystalline and lipophilic poorly soluble compounds.

• Salt Formation: A neutralising reaction between acids and bases results in the creation of salt. For medications that can be ionised, salt production is employed to boost solubility. Protons are transferred from acids to bases to create salt. If the pKa difference between acids and bases is more than 3, ionic bonding from salts can form and are stable. A counter ion, stoichiometric molar ratio, and an appropriate solvent are required for salt production through this reaction. As salt selection might affect the pre-formulation assessment of pharmaceuticals, it is important to choose the right salt structure for active medicinal components. The production of salt compounds must take into account a variety of elements, including the drug administration route, biological factors, pKa, biopharmaceutical factors, and ionic factors.

A different approach for improving medication solubility is salt formation. It is thought to be a low-cost, highly efficient way to improve the drug's solid-state characteristics. Active pharmacological components must protonate from an ionizable functional group structure in order to create salt. Isoniazid is one medication that can be altered by salt production (INH). According to a study, the medication INH was tested using a number of acids (maleic acid, oxalate, and methane sulfonic acid). These salts were created in order to provide a new solid form that is more thermally stable and soluble than the original INH, which can lessen INH degradation. The salt's crystalline structure revealed that it had layers that were mostly stabilised by the C-H... OH.

Acetazolamide (ACL), a BCS class IV medication, is another illustration. In this case, it has been changed to take the solid forms of ACL-PPZ-H2O salt and ACL-THP cocrystal. The creation of cocrystals and salts boosts a material's permeability and solubility, according to *in vitro* permeation comparison tests and powder dissolution experiments utilising various techniques. When compared to ACL-THP cocrystals, ACL-PPZ-H2O has greater ACL solubility, while the cocrystalline form has superior permeability. This knowledge is crucial for comprehending the structure of drug-related activities since it demonstrates the relationship between the creation of salt and the concurrent rise in ACL permeability and solubility.

The advantages of salt formation include increased drug solubility; increased stability against thermolysis, photolysis, or hydrolysis; good organoleptic properties; and increased tabletability. The salt formation method for active drug compounds also has some weaknesses. The salt that forms can transform into its nonionic state from hydrolysis reaction or disproportionation. Disproportionation can change the physicochemical aspect of active drug compounds. The result is decreased solubility of drugs that have been modified by salt formation.

• Co-Crystallisation: This is also known as molecular complexes. Co-crystal occurs when the solvent is an integral part of the network structure and forms at least two component crystals. A co-crystal is a crystalline material made up of two or more molecular (and electrically neutral) species that are held together by non-covalent forces. Only three of the co-crystallizing agents have been classified and are widely accepted as safe. It contains saccharin, nicotinamide, and acetic acid, which limits its pharmaceutical application. Co-crystallisation of two active pharmaceutical ingredients, such as aspirin or acetaminophen, has also been reported. To date, at least 20 polymorphic co-crystals of caffeine and glutaric acid have been reported. Co-crystals can be formed through evaporation of a heteromeric solution, sublimation, or growth from the solution.

• Co-solvency: The solubility of a poorly water-soluble drug can frequently be increased by adding a water miscible solvent in which the drug is well soluble, known as cosolvents. Cosolvents are water and/or more water miscible solvent mixtures used to create a solution with enhanced solubility for poorly soluble compounds, such as PEG 300, propylene glycol, or ethanol. Dimethyl sulfoxide (DMSO) and dimethyl acetonamide (DMA) have been widely used as cosolvents due to their large solubilization capacity of poorly soluble drugs and their relatively low toxicity.

• Hydrotropic: Hydrotropy is a solubilization process in which another solvent is used to increase the soluble of the mixtures. Because of the presence of a large amount of additive, it can improve water solubility. Its mechanism is solubility because it is related to Complexation, which involves in the weak interaction between the hydrotropic agents; however, the process used in the works is in non-micelle-forming materials, whichever solids or solids, inorganic or sorganic, capable of solubilizing insoluble compounds. Hydrotropy is classified in three ways in the following method: aromatic catatonics, aromatic anionics, and linear anionics. Sodium acetate, sodium alginate, and other Hydrotropy agents are examples.

• Solubilizing agents: Solvents are used in this method to improve drug solubility and dissolution in the body, as well as to improve therapeutic effects. Solubilizing agents such as super-disintegrates such as cross-carmellose sodium and sodium starch glycolate are used as solubilizing compounds in various types of preparations to increase drug solubility

and dissolve. Improved gum Arabic or gum karaya, an established material, was estimated as a dissolution carrier and improved the low soluble of drugs such as nimtop. The addition of caffeine and niacinamid increased the water solubility of halofantrine hydrochloride drug antimalarial agent tablet.

• Nanotechnology: The study and application of materials and structures at the nanoscale level of 100 nanometres (nm) or less. Oral bioavailability enhancement by micronization is insufficient for many new chemical entities with very low solubility because micronized product has very low effective surface area for dissolution, so the next step was nanonization. Milling, high-pressure homogenization, vacuum deposition, and high temperature evaporation are examples of preparation methods.

2. Physical modifications

1. Particle size reduction:

•Micronization is a high energy particle size reduction technique that can reduce coarse particles to less than 5 mm in diameter. Micronization produces a uniform and narrow particle size distribution, which is required for the development of a uniform dosage form. Surface area increases with decreasing particle size and solubility increases as micronization occurs. The type of micronization technique used influences the properties of the micronized drug substance, such as particle size, size distribution, shape, surface properties, agglomeration behaviour, and powder flow. The most commonly used techniques for producing micronized drug particles are mechanical communication, spray drying, and supercritical fluid (SCF) technology. The administration of a drug in micron size, according to the Noyes-Whitney postulations, is a prominent method to improve the bioavailability of poorly bioavailable drugs.

Techniques for Micronization:

a) Jet milling /fluid energy mill or micronizer
b) Rotor stator colloids mills
c) Microprecipitation & microcrystallization
d) Controlled crystallization
e) Supercritical fluid technology
f) Spray freezing in to liquid

•Nanosuspension: This technology is used for drugs that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system composed of nano-sized drug particles suspended in an aqueous vehicle stabilised by surfactants and intended for either oral and topical administration or parenteral and pulmonary administration. Solid particles in nanosuspensions typically have a particle size distribution less than one micron, with an average particle size ranging between 200 and 600 nm. Bottom-up and top-down technologies are used to create nanosuspension. Top-down technology includes a variety of techniques such as nano edege, nanojet technology, and milling technology (Nanocrystals).

2. Modification of the crystal habit

•Polymorphism: Is the ability of a solid material to exist in two or more different crystalline forms with different crystal lattice arrangements. Polymorphs are various crystalline forms. Although crystalline forms of drugs are chemically identical, they differ in physiochemical properties such as melting point, texture, density, solubility, and stability. Similarly, amorphous forms of drugs are preferable to crystalline forms. Because of the increased surface area and associated energy. order of various solid forms of drugs.

Amorphous > Metastable polymorphs > Stable polymorphs.

3. Complexation: To improve water solubility and drug stability, drugs have been complexed with cyclodextrins. The most commonly used -cyclodextrin derivatives with improved water solubility are used in pharmaceutical formulations. Cyclodextrins are large molecules with molecular weights greater than 1000 Da and are unlikely to easily penetrate the skin. The complexation of cyclodextrin has been shown to increase and decrease skin penetration. In addition to increasing solubility, CDs can be used as membrane permeability enhancers and stabilising agents. Cyclodextrins increase permeability through biological membranes. CDs can also be used as a permeability enhancer in pulmonary drug delivery systems.

4. Solubilization by surfactants

•Microemulsions: Microemulsions are thermodynamically stable isotopically clear dispersions of two immiscible liquids, such as oil and water, that are stabilised by an interfacial film of surfactants and co-surfactants. Microemulsions outperform both colloidal systems under investigation and traditional emulsions, suspensions, and micellar solutions. Alternative drug carriers are microemulsions. Microemulsions have the advantages of spontaneous formation, ease of manufacturing and scaling-up, thermodynamic stability, improved hydrophobic drug solubilization, and bioavailability. Microemulsions are classified into three types based on their composition:

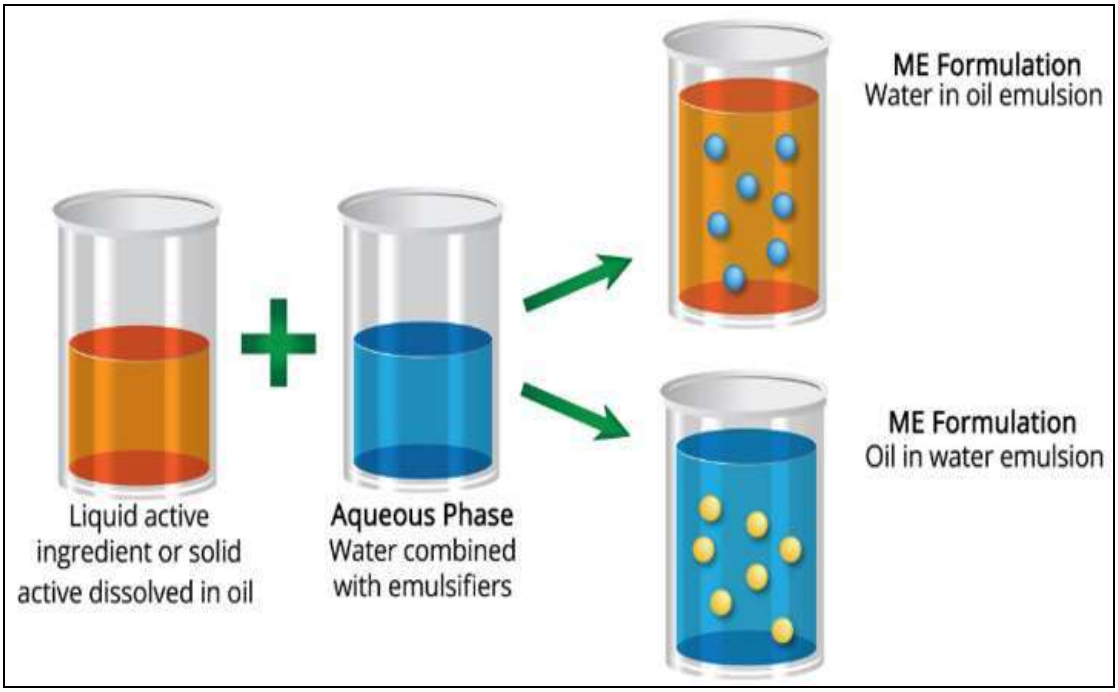

Fig 1.

- Microemulsions of oil in water in which oil droplets are dispersed in a continuous aqueous phase.
- Water-in-oil microemulsions, in which water droplets are dispersed throughout the continuous oil phase.
- Bi-continuous microemulsions, in which oil and water microdomains are interspersed within the system.

The interface of all three types of microemulsions is stabilised by an appropriate combination of surfactants and/or co-surfactants.

Self microemulsifying drug delivery system (SMEDDS): SMEDDS are isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants with the unique ability to form fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. 1. SMEDDS spread easily through the GI tract, and the digestive motility of the stomach and intestine provides the necessary agitation for selfemulsification. The primary distinction between self-emulsifying drug delivery systems (SEDDS), also known as self-emulsifying oil formulation (SEOF), and SMEDDS is that SEDDS typically produce opaque emulsions with droplet sizes ranging from 100 to 300 nm, whereas SMEDDS form transparent micro emulsions with droplet sizes ranging from 100 to 300 nm.

5. Drug dispersion in carriers:

•Solid dispersion: A useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms is solid dispersion. A solid dispersion is a type of solid product that consists of at least two different components, typically a hydrophilic matrix and a hydrophobic drug. Polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and Plasdone-S630 are the most commonly used hydrophilic carriers for solid dispersions. Surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) play a role in solid dispersion formulation. Solid dispersion of celecoxib, halofantrine, and ritonavir using suitable hydrophilic carriers such as celecoxib with povidone (PVP) and ritonavir with gelucire can improve solubility.

• Hot-Melt Method (Fusion Method): The main benefits of this direct melting method are its simplicity and cost-effectiveness. The physical mixture of a drug and a water-soluble carrier is heated directly until the two melts in this method. The melted mixture is then rapidly cooled and solidified in an ice bath while being vigorously stirred. The final solid mass is crushed, pulverised, and sieved before being compressed into tablets using tableting agents. The melting point of a binary system is determined by its composition, specifically the carrier chosen and the weight fraction of the drug in the system. The miscibility of the drug and the carrier in the hot-melt method is an important requirement for the formation of solid dispersion. Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent, then evaporate the solvent under vacuum to produce a solid solution. They were able to create a solid solution of the highly lipophilic -carotene in the highly water-soluble carrier povidone as a result of this. The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be avoided due to the low temperature required for organic solvent evaporation. However, the disadvantages of this method include the higher preparation cost, the difficulty in completely removing the organic solvent (from a regulatory standpoint), and the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the product.

Hot-Melt Extrusion: Hot-melt extrusion is essentially the same as fusion, except that the extruder induces intense mixing of the components. Miscibility of the drug and the matrix, as in the traditional fusion process, could be an issue. High shear forces in the extruder cause a high local temperature, which is a problem for heat sensitive materials. However, when compared to the traditional fusion method,

this technique allows for continuous production, making it suitable for large-scale production.

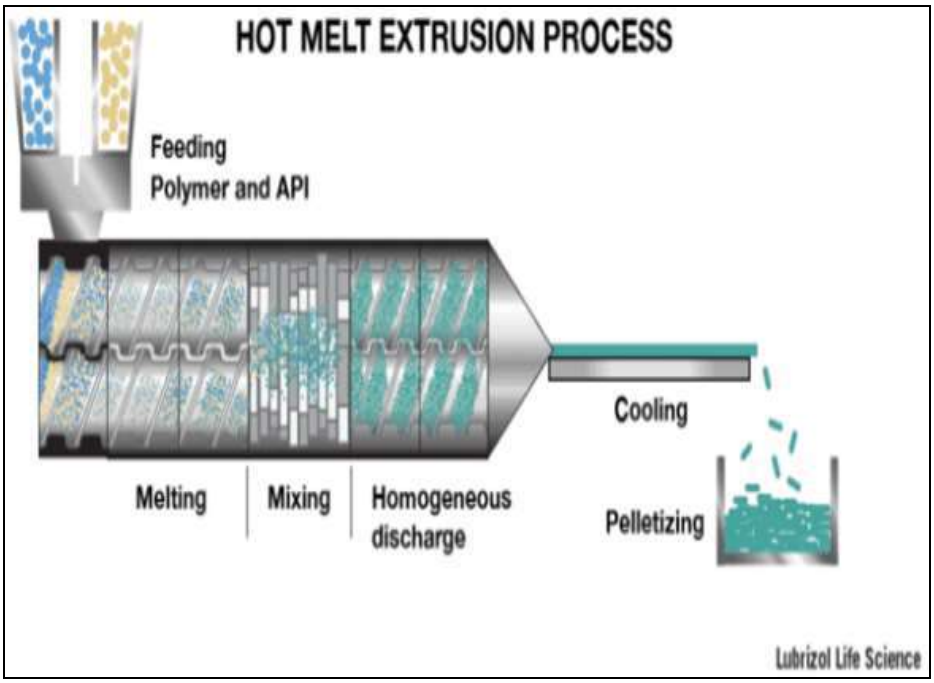

Fig 2.

4. Advantages

1. When compared to conventional tablets, enhanced bioavailability can be obtained.
2. A larger portion of the drug's surface area is exposed to the dissolution medium.
3. The cost of production is low when compared to soft gelatin capsules.
4. These liquisolid systems can be formed into immediate release, sustained release, or controlled release dosage forms.
5. This principle governs or administers the mechanism of drug delivery from liquisolid systems of powdered drug solutions, and it is primarily responsible for this preparation's improved dissolution profiles.

5. Applications

1. Ultimate role in improving the solubility of poorly water-soluble drugs.
2. Increased absorption and bioavailability.
3. It is important in improving the solubility of volatile constituents used to impart a desirable flavour and odour to the product, in addition to increasing solubility.
4. Considerations for solubility in dosage form design.

6. Conclusion: The solubility of any molecule is crucial and plays a significant role in formulation and medication development, we conclude from this review paper. The solubility of the molecule or any poorly soluble medications can be improved or enhanced by using any of the aforementioned procedures or strategies alone or in combination with others. By increasing, solubility also improves patient compliance and raises the bioavailability of less soluble drugs. The choice of a method to increase solubility depends on the type and properties of the drug, such as its chemical and physical makeup and its pharmacokinetic behaviour.

7. References

1. Sandeep Kumar, Pritam Singh. Various techniques for solubility enhancement, The Pharma Innovation Journal. 2016;5(1):23-28.
2. Hans Lennerna¨s, Bertil Abrahamsson. The use of biopharmaceutic classification of drugs in drug discovery and development, Journal of Pharmacy and Pharmacology. 2004;57:273-285.
3. Veseli A, Kristal A. A review of methods for solubility determination in biopharmaceutical drug characterization, Drug Dev Ind Pharm. 2019;11:1717-1724.
4. Mike Apley, Bryan Crist G, *et al*. Determination of Thermodynamic Solubility of Active Pharmaceutical Ingredients for Veterinary Species, Dissolution Technologies. 2017;24:36-39.
5. Kitak T, Dumičić A, *et al*. Determination of Solubility Parameters of Ibuprofen and Ibuprofen Lysinate, Molecules. 2015;20:21549-21568.
6. Jatwani S, *et al*. An Overview On Solubility Enhancement Techniques For Poorly Soluble Drugs And Solid Dispersion As An Eminent Strategic Approach, IJPSR. 2012;3:942-956.
7. Ahmad Ainurofiq, David Sarono Putro, *et al*. A review on solubility enhancement methods for poorly water-soluble drugs, review article. 2021;10:137-147.
8. Gupta Shilpa Kumari, Gupta RK. *Et al*. Solubility Enhancement Techniques, International Journal of Research and Analytical Reviews. 2018;5:69-84.
9. Jagtap Sneha, Magdum Chandrakant, *et al*. Solubility Enhancement Technique, J. Pharm. Sci. & Res., 2018;(10)9;2205-2211.
10. Khatri Himanshi, Md. Sadique Hussain, *et al*. Solubility enhancement techniques. World Journal Of Pharmaceutical Research. 2022;11:468-482.
11. Sujatha B, Himabindu E, *et al*. Microemulsions, Internationale Pharmaceutica Sciencia. 2020;10:1-06.

12. Uma Maheswara Reddy P, Ramesh Babu P, *et al*. Self Microemulsifying Drug Delivery SYSTEMS, International Journal of Research in Pharmaceutical and Nano Sciences. 2013;2(3):317-331.
13. Gupta J, Anjana Devi. Solubility Enhancement Techniques for Poorly Soluble Pharmaceuticals, Indian Journal of Pharmaceutical and Biological Research 2019;7:9-16..
14. DR. Zulcief Ahmad, https://www.slideshare.net/Drzulcaifahmad/solubility-method-for-determination-of-solubility.
15. Madhuri Gite, https://www.slideshare.net/shaikhazaroddin/solubility-enhancement-and-cosolvency-by-madhavi.