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Solubility Enhancement Technique: A Review

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ABSTRACT

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous molecular dispersion which is essential to drug's success. The solubility, property of the drugs becomes one of the most challenging aspects in formulation development. Aqueous solubility of drug also affects physical, chemical properties of the drug, dose, stability in gastrointestinal track, severs as standard for test of purity, the rate of dissolution of solid, rate and extent of absorption, achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. The usable pharmaceuticals with poor solubility must be answered well by solubilization techniques such as chemical modification which involve use of solubilizer such as soluplus, povacoat, dendrimers, and physical modification, complexation, use of surfactant which are becoming more and more important to the pharmaceutical sector by opening up pathway to prepare effective and marketable drugs are discussed in present review article.

Key Words: ***Solubility, Solubility enhancement, Bioavailability, Novel methods, Dissolution.***

INTRODUCTION

A substance's solubility in a specific solvent is one of its properties. It is the concentration of dissolved solute in a saturated solution at a particular temperature, to put it quantitatively. It refers to clear homogeneous molecular dispersion, which is the continuous interaction of two or more compounds to produce one phase. The maximum amount of solute dissolved in a solvent at equilibrium is used to measure it. A saturated solution is the name given to the resulting liquid. A list of ions and their ability to form precipitates or remain aqueous when combined with other ionsare shown in a solubility chart.1,2.

When a chemical substance in the solid state demonstrates chemical equilibrium with a solution of that molecule, a solubility equilibrium, a dynamic equilibrium, results. Pharmaceuticals depend on solubility equilibria. Drugs with poor aqueous solubility—class II or even class IV BCS compounds—present absorption-related dissolving issues. In pharmaceutical sciences, solubility can be described as parts, molarity, normalcy, formality, mole fraction percent solution, volume fraction, and molality when quantitative data are available.

Solubility Expression

Definition	Parts of solvent required for one part ofsolute
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 – 10,000
Insoluble	Greater than 10,000

Potential Reasons for Poor Oral Absorption [4] Any medication is deemed to be poorly soluble when:1.Aqueous solubility <100µg/ml.

2.Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min, 3.High molecular weight: (>500), Self association and aggregation.4.High crystal energy.

Solubilization Process [5]
Step 1: Breaking of inter-ionic or intermolecular bonds in the solute, separating of solvent molecules to make roomfor the solute, and contact of the solvent with the solute molecule or ion are all steps in the solubilization process. Step 2: A solid molecule different from the bulk.

Step 3 involves integrating the feed of a solid molecule into the hole in the solvent.

Biopharmaceutics classification system (BCS) was developed by the US Food and Drug Administration (FDA) and divides drugs into four types based on solubility and permeability. Due to low solubility, Class II and Class IV of the system experience solubility obstruction, with dissolution acting as the rate-limiting step for drug absorption.

BCS Classification of Drug. [6]

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Factors Affecting Solubility [1, 5]
Particle size: Solubility is affected by particle size. The surface area to volume ratio rises as article size decreases. Increased particle surface area results in increased solvent interaction.

Temperature: Temperature affects solubility. The solubility will rise with rising temperature if the solution process takes in energy. The solubility will decrease with rising temperature if the solution process releases energy. [8]

Molecular size: Higher molecular weight and larger molecules reduce a substance's solubility since it is more challenging to surround larger molecules with solvent molecules in order to dissolve them**.**

Nature of solute and solvent The nature of the solute and solvent relies on the solute's concentration in a given amount of solvent at a certain temperature. As an illustration, at room temperature, 200 grammes of zinc chloride may dissolve in 100 grammes of water, whereas only 1 gramme of lead (II) chloride can. [4].

Pressure: The solubility of gaseous solutes changes with pressure, increasing when pressure increases and decreasing when pressure decreases. Variations in pressure have no impact on the solubility of solid or liquid solutes.

Polarity: The solubility is influenced by the polarity of both the solute and solvent molecules. In general, polar solvents dissolve polar solute molecules and non-polar solvents dissolve non-polar solute molecules.

Polymorphs: Polymorphism is the capacity of a substance to crystallise in more than one crystalline form. A substance that can crystallise in more than one crystalline form is said to be polymorph. A solid may crystallise in a variety of shapes called polymorphs. Melting points can differ amongst polymorphs. Since a solid's solubility and melting pointare connected, various polymorphs will have varied solubilities. [4]

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 [9]. The low bioavailability of oral dose forms, however, presents the largest design complication. 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 dose forms, such as parenteral formulations, are significantly influenced by solubility as well. [10].

One of the key factors in reaching the desired drug concentration in the systemic circulation and the necessary pharmacological response is solubility [11]. When taken orally, 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 construction 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 inconsistent bioavailability as well as harmful effects on 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 is a significant obstacle [12].

The improvement of drug solubility and, subsequently, its oral bioavailability, remains one of the most challenging areas of drug research, especially for oral drug delivery systems. A number of methods that have been documented in the literature can be used to increase the solubility of drugs that are not very water-soluble. The methods are selected based on a variety of criteria, such as the characteristics of the drug being considered, the kind of excipients to be chosen, and the type of dosage form planned. Insufficient bioavailability is frequently caused by the poor solubility and slow dissolution rate 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 the rate-limiting step for BCS class II medications is drug release from the dosage form and solubility in stomach fluid rather than absorption, boosting solubility also increases the drugs' bioavailability [9, 12, 13]. Poor absorption and bioavailability, insufficient solubility for IV dosing, development issues that increase the development cost and time, and burden shifting to the patient (regular high-dose administration) are all adverse effects of drugs with low solubility [11].

Techniques for Solubility Enhancement

Techniques used to increase solubility can be divided into two categories: physical modifications and chemical changes to the medicinal ingredient.

Physical Modifications. Drug dispersion in carriers such as eutectic mixes, solid dispersions, solid solutions, and cryogenic procedures. Modification of the crystal habit such as polymorphs, amorphous form, and cocrystallization.

Chemical Modifications. Derivatization, complexation, usage of a buffer, and salt production.

Miscellaneous Methods. Using a supercritical fluid technique, solubilizers, cosolvency, hydrotrophy, and new excipients as adjuvants.

Particle Size Reduction

Drug particle size is frequently intrinsically correlated with drug solubility; as a particle gets smaller, the surface area to volume ratio rises. Greater contact with the solvent is made possible by the bigger surface area, increasing solubility.

The active ingredient is disaggregated by mechanical stress in conventional particle size reduction techniques including comminution and spray drying. Thus, solubility augmentation is now possible through an effective, repeatable, and affordable method thanks to particle size reduction. However, the physical stress that is frequently applied to the therapeutic product during comminution processes like milling and grinding could lead to degradation. a thermal Processing thermosensitive or unstable active chemicals raises additional concerns about stress that could develop during comminution and spray drying.

For medications that are nearly insoluble, using conventional methods may not be able to increase the solubility to the appropriate level. Another usual technique for reducing particle size is micronization. Through increased surface area, micronization speeds up the pace at which pharmaceuticals dissolve; it does not speed up equilibrium solubility. These medications' rate of dissolution is increased by reducing the particle size of the pharmaceuticals, which results in an increase in surface area. Medications are micronized using milling techniques such as jet mills, rotor stator colloid mills, and other devices. Micronization is not appropriate for drugs with a high dosage number since it does not alter the drug's saturation solubility [14]. These procedures were used with fenofibrate, progesterone, spironolactone diosmin, griseofulvin, and Each drug's digestive absorption, and as a result, its bioavailability and clinical effectiveness, were increased via micronization. In 30 minutes in biorelevant medium, micronized fenofibrate showed a more than 10-fold (1.3% to 20%) increase in dissolution[15, 16].

Solid Dispersion

When Sekiguchi and Obi examined the production and efficacy of eutectic melts of a sulphonamide medication and a water-soluble carrier in the early 1960s [17], they first put up the idea of solid dispersions. Solid dispersions are an effective pharmaceutical approach for boosting the drug dosage forms' ability to dissolve, absorb, and provide therapeutic benefit. 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. For solid dispersions, polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and plasdone-S630 are the most often utilised hydrophilic carriers. The formulation of solid dispersion includes surfactants like Tween-80, sodium docusate, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS). Celecoxib with povidone (PVP) and ritonavir with gelucire are two examples of acceptable hydrophilic carriers that can be used to solid disperse medications to increase their solubility. Here is a list of various methods for preparing hydrophobic medication solid dispersions in an effort to increase their aqueous solubility. [18–20].

Hot-Melt Method (Fusion Method). The simplicity and economy of this direct melting approach are its key benefits. Sekiguchi and Obi were the ones who originally suggested using melting or fusion to create fast-acting solid dispersion dosage forms. This method involves immediately heating the physical mixture of a medication and a water-soluble carrier until the two melt. The melted slurry is then vigorously stirred while fast cooling and solidifying in an ice bath. The resultant solid mass is then broken down, pulverised, and sieved before being compressed with tableting agents into tablets. The composition of a binary system, or the choice of the carrier and the weight percentage of the medication in the system, determines the melting point of the system [21]. The miscibility of the medication and the carrier in the molten form is a crucial need for the hot-melt method's ability to create solid dispersion. The thermostability of the medicine and the carrier is a crucial need.

Solvent Evaporation Method. The first to combine the drug and carrier in a common solvent, evaporate the solvent under vacuum, and then make a solid solution was Tachibana and Nakamura [22]. In the highly water soluble carrier povidone, they were able to create a solid solution of the highly lipophilic -carotene as a result. Numerous researchers used the solvent evaporation approach to examine the solid dispersion of meloxicam, naproxen, and nimesulide. These results imply that the aforementioned technique can be successfully used to enhance the stability of solid dispersions of medicines that are poorly water soluble [14, 16]. Due to the low temperature needed for the evaporation of organic solvents, the fundamental benefit of the solvent evaporation method is that thermal breakdown of pharmaceuticals or carriers can be avoided. The drawbacks of this approach include the higher cost of preparation, the challenge of completely eliminating the organic solvent (from a regulatory perspective), the potential negative impact of the solvent's purportedly negligible amount on the chemical stability of the drug, the choice of a common volatile solvent, and the challenge of duplicating crystal forms [23].

Hot-Melt Extrusion Heat-sensitive materials have a challenge. But unlike the conventional fusion approach, this technique allows for continuous production, which qualifies it for large-scale production. Additionally, the product is simpler to handle because, at the extruder's outlet, the shape can be modified without grinding for the following processing step [19].

Nanosuspension

The development of nanosuspension technology makes it a promising contender for the effective delivery of hydrophobic medications. Drugs that are poorly soluble and insoluble in both water and oils are treated with this method. A pharmaceutical nanosuspension is a biphasic system made up of nanoscale drug particles stabilised by surfactants for parenteral and pulmonary delivery as well as oral and topical application. The average particle size is between 200 and 600 nm, and the particle size distribution of the solid particles in nanosuspensions is typically smaller than one micron [24, 25].

Precipitation technique, media milling, high pressure homogenization in water, high pressure homogenization in non- aqueous media, and a combination of Precipitation and high-Pressure homogenization are some of the several techniques used to prepare nanosuspensions [26, 27].

Precipitation Technique. In the precipitation method, the medication is dissolved in a solvent before being combined with an antisolvent to form crystals. The primary benefit of the precipitation method is the employment of straightforward, inexpensive equipment; however, the addition of drug crystals that are increasing presents a difficulty in order to prevent the production of microparticles. The need that the drug be soluble in at least one solvent and that this solvent be miscible with an antisolvent is the technique's limitation. Additionally, the precipitation approach cannot be used with pharmaceuticals because they are both weakly soluble in aqueous and nonaqueous media [28]. Danazol and naproxen have been produced as nanosuspensions using the precipitation approach to increase their oral bioavailability and dissolving rate. Additionally, a 4-fold apparent increase in the rate of absorption was linked to thesize reduction of naproxen. [29, 30].

Media Milling. High-shear media mills are used to create the nanosuspensions. For several days, the milling chamber is rotated at a very high shear rate under controlled temperatures while being charged with milling media, water, medication, and stabiliser (at least 2–7 days). Glass, zirconium oxide, or a strongly cross-linked polystyrene resin make up the milling media. The impaction of the milling media with the drug results in the breaking of microparticulate drug into nanosized particles, which generates high energy shear forces [27].

High Pressure Homogenization
Numerous medications that are poorly water soluble have been prepared as nanosuspensions using high-pressure homogenization. This method involves pushing a drug and surfactant suspension through a nanosized aperture valve of a high pressure homogenizer while it is under pressure. This technique's foundation is cavitation in the aqueous phase. Drug microparticles can become nanoparticles when the cavitation forces within the particles are strong enough. This method's drawbacks include the need for small sample particles prior to loading and the numerous cycles of homogenization necessary [31]. By decreasing their particle size using high pressure homogenization, poorly soluble medications such spironolactone, budesonide, and omeprazole have increased bioavailability and dissolution rates [32– 34].

Combined Precipitation and Homogenization. Precipitation and homogenization combined The drug nanoparticles that precipitate often continue to build crystals until they reach the size of microcrystals. It is necessary to process them using high-energy forces (homogenisation). They are either completely crystalline, partially crystalline, or completely amorphous, which causes issues with long-term stability and bioavailability. As a result, the precipitated particle suspension is then homogenised to maintain the particle size that was achieved during the precipitation step.

Supercritical Fluid (SCF) Process
Particle size reduction via supercritical fluid (SCF) techniques is another revolutionary nanosizing and solubilization technology whose application has grown in recent years. Supercritical fluids can take on the characteristics of both a liquid and a gas because their temperature and pressure are higher than their critical temperatures (Tc) and critical pressures (Tp). Since SCFs are extremely compressible at near-critical temperatures, even small changes in pressure can significantly influence the fluid's density and mass-transport properties, which are key factors in determining its solvent power. The drug particles may be recrystallized at significantly smaller particle sizes after being solubilized within the SCF (often carbon dioxide).

The SCF techniques' flexibility and precision enable the micronization of medication particles within certain particle size ranges, frequently to submicron levels. The ability to produce nanoparticulate suspensions of particles with a diameter of 5-2,000nm has been established by current SCF techniques. In order to reduce particle size and improve solubility, a number of pharmaceutical companies, including Nektar Therapeutics and Lavipharm, are focusing in particle engineering. Precipitation with compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions (RESS), gas anti solvent recrystallization (GAS), and aerosol supercritical extraction system (ASES) are some of the SCF processing methods that have been developed to address specific aspects of these shortcomings [35, 36].

Cryogenic Techniques
By forming nanostructured, amorphous drug particles with a high degree of porosity under extremely low temperature conditions, cryogenic procedures have been developed to speed up the dissolving rate of medications. Capillary, rotary, pneumatic, and ultrasonic nozzle types, location of the nozzle (above or below the liquid level), and the make-up of the cryogenic liquid can all be used to categorise cryogenic inventions (hydrofluoroalkanes, N2, Ar,O2, and organic solvents). Dry powder can be produced after cryogenic processing by a number of drying techniques, including spray freeze drying, air freeze drying, vacuum freeze drying, and lyophilization [37–39].

Spray Freezing onto Cryogenic Fluids. On cryogenic fluids, Briggs and Maxvell developed the spray-freezing technique. This method involved dissolving the medication in water and atomizing it over the surface of a boiling, agitated fluorocarbon refrigerant. The carrier might be mannitol, maltol, lactose, inositol, or dextran. To improve the aqueous solution's dispersion, a sonication probe can be inserted into the stirred refrigerant [40].

Spray Freezing into Cryogenic Liquids (SFL). High surface area, well-wettable amorphous nanostructured drug powder aggregates have been created using the SFL particle engineering method. In order to achieve strong atomization into microdroplets and thus noticeably higher freezing rates, it integrates direct liquid-liquid impingement between the automated feed solution and cryogenic liquid. The lyophilized frozen particles are subsequently milled into dry, free-flowing powders [41].

Spray Freezing into Vapor over Liquid (SFV/L) Drug solutions are frozen in cryogenic fluid vapours, and the frozen solvent is then removed, creating fine, highly wettable drug particles. The atomized droplets usually begin to freeze in the vapour phase during SFV/L before they come into contact with the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen areas of the atomized droplet, so small drug particles may nucleate and proliferate [42].

Ultra-Rapid Freezing (URF). Using solid cryogenic materials, ultra-rapid freezing is a revolutionary cryogenic technique that produces nanostructured drug particles with significantly increased surface area and desired surface morphology. When a drug solution is applied to the solid surface of a cryogenic substrate, it instantly freezes, and when the solvent is removed through lyophilization, a micronized drug powder with increased solubility is created. The phase separation and crystallisation of the pharmaceutical ingredients are hampered by ultra-rapid freezing, resulting in closely combed, amorphous drug-carrier solid dispersions and solid solutions [43].

Inclusion Complex Formation-Based Techniques

The inclusion complex creation technique has been used more accurately than any other solubility enhancement method to increase the aqueous solubility, dissolving rate, and bioavailability of medicines that are not very 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). Cyclodextrins are the most popular host molecules. Cyclodextrins are produced as a result of the enzymatic breakdown of starch by cyclodextrin- glycosyltransferase (CGT) (CDs). As shown in Figure 1, these cyclic oligosaccharides are nonreducing, crystalline, water soluble, and composed of glucose monomers organised in a donut-shaped ring with a hydrophobic cavity and a hydrophilic outer surface. Cyclodextrin, Cyclodextrin, and Cyclodextrin are three naturally occurring CDs. [44].

Kneading Method. This method is based on turning CDs into a paste by impregnating them with a little amount of water or hydroalcoholic solutions. The medicine is subsequently mixed with the aforementioned paste for a predetermined amount of time. The kneaded mixture is next dried and, if necessary, sieved. A mortar and pestle can be used to knead on a laboratory scale. Extruders and other machinery can be used for large-scale kneading operations. This is the most popular and straightforward technique for creating inclusion complexes, and it has a very cheap manufacturing cost. [45].

Lyophilization/Freeze-Drying Technique The lyophilization/freeze drying method is thought to be suitable for producing a porous, amorphous powder with a high level of drug and CD interaction. In this method, the drug and CD are present in a solution that is first frozen and then dried at low pressure to remove the solvent system from the solution. By using this technique, thermolabile compounds can be successfully transformed into complex forms.

This method's drawbacks include the need for specialised equipment, a lengthy manufacturing process, and poorly flowing powdered product. As an alternative to solvent evaporation, the lyophilization/freeze drying process involves molecularly combining the medication and carrier in a shared solvent.
[46]

Microwave Irradiation Method. This method uses a microwave oven to microwave irradiate the reaction between the medication and the complexing agent. In a precise proportion, the medication and CD are dissolved in a solution of water and an organic solvent before being added to a flask with a circular bottom. In the microwave, the combination reacts for a brief period of one to two minutes at 60 degrees Celsius. A sufficient amount of solvent mixture is added to the aforesaid reaction mixture after the reaction is finished in order to eliminate any remaining free drug and CD that are not complexed.

The precipitate that results from this process is separated using Whatman filter paper and dried at 40°C in a vacuum oven. Shorter reaction durations and a higher product yield make the microwave irradiation method a unique technique for industrial scale production. [47].

Micellar Solubilization

The simplest, most well-established, and oldest technique is undoubtedly the employment of surfactants to enhance the performance of poorly soluble medicinal compounds during dissolution. Surfactants lower surface tension and enhance lipophilic medication solubility in aqueous media. Additionally, they help stabilise drug suspensions. Surfactants generate micelles that enclose the pharmaceuticals when their critical micelle concentration (CMC), which is typically between 0.05 and 0.10 percent for most surfactants, is exceeded. This process, called micellization, usually makes medications that aren't very soluble more soluble. Additionally, surfactant enhances the wetting of solids and accelerates the decomposition of solids into smaller particles. [10]. Polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides, and mono-

and di-fatty acid esters of low molecular weight polyethylene glycols are examples of frequently used non-ionic surfactants. Surfactants are frequently employed to stabilise drug-containing microemulsions and suspensions [48, 49].

Anti-diabetic medications such as gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone are examples of poorly soluble substances that utilise micellar solubilization [50].

Hydrotrophy

The process of hydrotrophy increases the first solute's solubility in water by adding a significant amount of the second solute, the hydrotropic agent. Ionic organic salts, or hydrotropic agents, are composed of different organic acids and alkali metal salts. The solute is said to be "salted in" by additives or salts that improve solubility in a particular solvent, and "salted out" by additives or salts that decrease solubility. The phenomenon of "hydrotropism" refers to the "salting in" of non-electrolytes dubbed "hydrotropic salts" by a number of salts with big anions or cations that are also extremely soluble in water. Hydrotrophy is the term used to describe the increase in solubility in water brought on by the presence of many additions. The process that makes the medications more soluble is more directly linked to complexation, which involves a minimal contact between the hydrotrophic substances like sodium benzoate, sodium acetate, sodium alginate, and urea and the drugs that aren't very soluble. [51, 52].

It is known that the hydrotropes self-assemble in solution. Since a wide range of substances have been reported to display hydrotropic behaviour, it is challenging to classify hydrotropes based on molecular structure. Alcohol, aromatic alcohols like resorcinol, pyrogallol, catechol, - and -naphthols, salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene are some examples that may be used specifically. The majority of investigated compounds are aromatic hydrotropes with anionic head groups. Due to isomerism, they are numerous, and the existence of interacting pi (π) orbitals may be the reason of their effective hydrotrope action. [53].

Rare hydrotropes include salts of aromatic amines like procaine hydrochloride, which have cationic hydrophilic groups. They are known to have effects on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, and other processes in addition to improving the solubilization of compounds in water. [54].

Crystal Engineering

The amount of a drug's surface that can be dissolved depends on the size of its particles and how well luminal fluids can moisten them. This particle size, which is crucial to the pace at which drugs dissolve, depends on the crystallisation conditions or comminution techniques like impact milling and fluid energy milling. The extremely heterogeneous, charged, and cohesive particles that might result from comminution processes have the potential to impair product performance and downstream processing. In order to create high purity powders with well-defined particle size distribution, crystal habit, crystal shape (crystalline or amorphous), surface nature, and surface energy, crystal engineering techniques are being created for the controlled crystallisation of pharmaceuticals [55]. It is possible to create crystals with varied packing arrangements by changing the crystallisation circumstances (using other solvents, changing the stirring, or adding additional ingredients to the drug solution). These crystals are referred to as polymorphs.

As a result, the physicochemical characteristics of polymorphs of the same medication, such as solubility, dissolving rate, melting point, and stability, may vary. For predictable bioavailability of the product over the course of its shelf life under a variety of real-world storage settings, it is preferred to produce the drug's most thermodynamically stable polymorph. Chloramphenicol palmitate solutions are a well-known illustration of the significance of polymorphism on bioavailability. When given the identical amount of chloramphenicol palmitate, it was demonstrated that the stable polymorph produced low serum levels while the metastable polymorph produced significantly greater serum levels [56]. In a different investigation, it was discovered that tablets made from the oxytetracycline form A polymorph dissolved noticeably more slowly than the form B polymorph tablets [57]. About 55% of the form A polymorph tablets started to dissolve after 30 minutes, but practically all (95%) of the form B polymorph pills started to dissolve at the same time.

Sublimation, crystallisation from solutions, evaporation, thermal treatment, desolvation, or grinding/milling are a few examples of conventional crystallisation processes. To create pharmaceutical solids with the correct dissolving rate and stability, these are being replaced by cutting-edge crystal engineering techniques such SCF technologies [58, 59]. Another cutting-edge technique, known as melt so no crystallization, creates porous, quickly dissolving particles for hydrophobic medicinal compounds [60]. These fascinating studies suggest that crystal engineering techniques need to be used more for improving the pace at which poorly soluble medicines dissolve. Salt production, a change in the solvent's dielectric constant, chemical alteration of the drug, the use of

hydrates or solvates, the use of soluble prodrugs, the use of ultrasound, and spherical crystallisation are other methods for improving the solubility of weakly water- soluble drugs.

CONCLUSION

Medication solubility is a prerequisite for drug absorption from the gastrointestinal tract (GIT), and drug dissolution is the rate-determining stage for oral absorption of pharmaceuticals that are weakly water soluble. The various methods mentioned above can be employed separately or in combination to increase the solubility of the medicines. The secret to achieving the objectives of a good formulation, such as good oral bioavailability, decreased frequency of dose, and improved patient compliance, combined with a cheap production cost, is proper process selection for solubility improvement. The choice of a method for solubility enhancement depends on the properties of the drug, such as solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behaviour, and so forth. It also depends on the dosage form requirements, such as the formulation of tablets or capsules, strength, immediate, or modified release, and so forth.

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