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Solubility Enhancement Techniques: A comparative study

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ABSTRACT: The solubility process refers to the amount of solute dissolved in the solvent under specific gravity and temperature conditions. Solubility is one of the rate-limiting parameters for orally delivered drugs to acquire their required concentration in systemic circulation for the pharmacological response. To obtain therapeutic plasma concentrations after oral administration, a weakly water-soluble medication requires substantial doses. According to the Biopharmaceutics Classification System, class II medications undergo a preventative step in which the drug is released from the dosage form and solubility in stomach fluid, but is not absorbed, therefore when solubility increases, bioavailability increases for BCS class II drugs. The BCS drug parameter represents the drug's solubility and permeability. The rate of dissolution is higher when the surface area is larger. As a result, various techniques are being exposed in order to improve drug bioavailability. This article aims to describe various solubility enhancement techniques that can be used to improve the solubility of a drug-using advanced and traditional methods.

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INTRODUCTION:

Solubility refers to the ability of a substance to dissolve in a solvent and form a solution under specific gravity and temperature conditions [1]. Solubility is important in the dissolution process in order to complete a movement and achieve the desired pharmacological response and drug solubility for better bioavailability. Solubility Enhancement Techniques are a set of techniques that can help with the formulation process. Solubility is a unique concept in physical and chemical science, including pharmacokinetics therapy, which is more useful in medicine and biopharmaceutical [2]. Micronization, solid dispersion, pH adjustment, Micelle solubilization, co-

solvency Complexation, and hydrotropic are all solubility enhancement techniques for determining drug solubilization [3]. Furthermore, the solubility enhancement technique distinguishes between physical and chemical modifications of the drug substance for the purpose of determining the drug's solubility parameter. This method is used to improve the solubility and dissolution of drugs for oral and Parenteral administration [4]. Traditional methods include PH, Particle Size Distribution, Co-solvency, Micro-emulsion Complexation, Micelle Solubilization, Supercritical Fluid Process, Solid Dispersion, and Hydrotrophy. Micronization, Nano-suspension, homogenization, salt formation, spray drying, hot-melt extrusion, solvent evaporation, and conventional solid dispersion techniques are now available for enhancement of the solubility of poorly water-soluble drugs [5].

IMPORTANCE OF SOLUBILITY:

The path of drug delivery that is most suitable and commonly used for the purpose of absorption. In line with its flexibility in the modified dosage form, ease of administration, high patient compliance, rate effectiveness, and smallest sterility restraints. The majority of drugs, such as pharmacologic reactions, can be directly linked to drug plasma levels, which show the drug's effect on the body. Bioavailability can help determine a drug's solubility and how it affects pharmacological response. Solubility is one of the most important parameters to determine when a drug is in complete movement in order to achieve the desired pharmacological response. Any drug that is administered or fascinated must be present in an aqueous solution in front of the absorption site so that the response to the site of action can be easily seen. For liquid pharmaceutical formulations or any solubility process, the liquid is the most commonly used solvent [6]. Aqueous solubility is poor for drugs that are weakly acidic or weakly basic. Drug solubility in bioavailability development is a unique and interesting/challenging part of the drug development process and drug solubility is important for drug delivery systems [7]. Inadequate bioavailability is frequently caused by low solubility and dissolution rates of poorly water-soluble drugs in aqueous stomach liquids. According to the Biopharmaceutical Classification System, class II drugs have a rate preventive step in which the drug is released from the dosage form and has a solubility in stomach fluid but does not have absorption, so as the solubility increases, the bioavailability increases for BCS class II drugs. The BCS drug parameter represents the drug's solubility and permeability [8]. Has a larger surface area and a faster rate of dissolution? As a result, if the area increases as the particle size decrease, predictable methods such as ball milling, trituration, grinding fluid energy micronization, controlled precipitation and salt formation can be used. As a result, design approaches are being exposed in order to improve drug bioavailability [9] and the solubility expression of the drug is represented in (Table 1) [10].

Table 1. Solubility classification.

Classification	Volume of solvent need to dissolve 1 g/ml drug
Very soluble drug	Less than
Free soluble drug	From 1-10
Soluble drug	From 10-30
Sparingly soluble drug	From 30-100
slightly soluble drug	From 100-1000
Very slightly soluble drug	From 1000-100000
In-soluble drug	Greater than 100000

Physical investigational changes:

- Micronization, homogenization, nanosuspension, supercritical fluid process, and spray drying are examples of size reduction techniques.
- Polymorphs and pseudo-polymorphs are examples of crystal habit modification.
- Eutectic combination, Hot plate method, a Solvent evaporation method, and Melting Solvent method, are examples of drug dispersion in the carrier.
- Molecular complexes, Chelates, and Inclusion Complexes are examples of complex activity.
- Micro-emulsion is an example of solubilization by surfactants.
- Salt formation is an example of chemical identification.
- Co-crystallization, co-solvency, and solubilizing agents are examples of other approaches [11,12].

Method of solubilization [13]:

It depicts the breakage of inter ionic or intermolecular bonds in the solute parting molecule in the solvent, allowing space in the solvent for solute particle interaction with ions and solvent. The solid particles break the particles that are separated from the bulk substances. Finally, solid molecules are mixed with solvents.

Biopharmaceutics Classification System:

It is classified into four classes according to the solubility and permeability depending on the nature of the drug as shown in Table 2 [14].

Table 2. Biopharmaceutical classification of drugs.

Class	Perme-ability	S	Example
I	High	High	Propranolol, diazepam, Acyclovir, Levodopa, Metoprolol.
II	High	Low	Nifedipine, Naproxen, Amlodipine, Itraconazole.
III	Low	High	Cimetidine, Nephazolin, Metformin
IV	Low	Low	Taxol, Clorthiazol, Colistin

S – Solubility.

Factors affecting solubility [15]:

***Particle Size*:**

The solubility of a particle is affected by its size. The surface area to volume ratio increases as particle size decreases. The amount of interaction a particle has with the solvent is determined by its surface area.

***Temperature*:**

Drug solubility is affected by temperature. If the solution process absorbs the energy, the solubility will increase as the temperature rises. As the temperature rises, the solubility will decrease if energy is released during the solution process.

***Molecular size*:**

The solubility of material is diminished when molecules have a higher molecular weight and a bigger molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

***Solute and solvent nature*:**

The solute's and solvent's natures are determined by the solute's concentration in a certain quantity of solvent at a specific temperature. Only 1 gm of lead (II) chloride can be dissolved in 100 gm of water at room temperature, whereas 200 g of zinc chloride can be dissolved.

***Pressure*:**

While pressure has no influence on the solubility of liquids or solids, it does have an impact on the solubility of gaseous solutes, which increases as pressure rises and decreases as pressure falls.

***Polarity*:**

The polarity of both the solute and the solvent molecules affects solubility. Non-polar solute molecules dissolve in non-polar solvents, while polar solute molecules dissolve in polar solvents.

***Polymorphs*:**

A substance's ability to crystallize in various crystalline forms is referred to as polymorphism. A polymorph is a material that has the ability to crystallize in a variety of crystalline shapes. A solid can crystallize in a variety of shapes, known as polymorphs. Polymorphs have different melting points. Polymorphs will have variable solubility since the solubility is proportional to a solid's melting point.

***pH*:**

The majority of medications are weak electrolytes, which ionize in the solution as weak bases and acids. Drugs that have been ionized are more soluble in water. The unionized drug is a poorly water-soluble drug.

TRADITIONAL SOLUBILITY ENHANCEMENT TECHNIQUES [16,17]:

Surfactants:

Surfactant molecules have polar and non-polar regions. A hydrocarbon segment is usually connected to a polar group in most surfactants. An anionic, cationic, zwitterionic, or non-ionic polar group can exist. Small polar molecules can accumulate in the micelles' hydrophobic core when they are added. This solubilization process is critical in both industrial and natural processes. Surfactants reduce surface tension between liquid-solid, liquid-liquid, or liquid-gas interfaces, increasing drug solubility by increasing lipophilic drug dissolution in the aqueous medium. Surfactants are also used to keep drug suspensions stable. It also helps to improve wetting and penetration in solid drug dissolution when used as a fluid. Micelle formation occurs when the concentration of surfactants exceeds their critical micelle concentration (CMC), which for most surfactants is in the range of 0.05 to 0.10 %. Micelle formation entraps the drugs within the micelles and is known as micellization and predominantly results in elevated solubility of poorly soluble drugs [19]. Examples are Soap (fatty acid), propylene glycol, and Sodium lauryl sulfate (SLS).

Its advantage is to improve drug stability. Its disadvantage is Micelle development happens when it entraps with the drugs within micelles and mostly results in the raised solubility of below-par soluble drugs.

pH-adjustment:

Using a pH change, poorly water-soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may be dissolved in water. In theory, pH adjustments can be used for both oral and parenteral administration. Because blood is a strong buffer with a pH between 7.2 and 7.4, the poorly soluble drug may precipitate after intravenous administration. The buffer capacity and tolerability of the chosen pH are important factors to consider when evaluating the approach's suitability. Because the pH in the stomach is around 1 to 2, and the pH in the duodenum is between 5 to 7.5, the degree of solubility is likely to be influenced as the drug passes through the intestines after oral administration. The best candidates are ionizable compounds that are stable and soluble after pH adjustment. Acids, bases, and zwitterionic compounds are all possible. It can be used for both crystalline and lipophilic poorly soluble compounds. Solubilised Excipients that raise the pH of the environment within a dosage form, such as a tablet or capsule, to a level higher than the pKa of weakly acidic drugs increase the drug's solubility; similarly, excipients that act as alkalizing agents may increase the solubility of weakly basic drugs. Because the solubility of the poorly soluble drug is increased when compared to water alone, the fraction of orally absorbed drugs may be increased if compounds can permeate through the epithelium orally. To increase the solubility of a poorly soluble drug, pH adjustment is frequently combined with co-solvents [20].

***Advantages*:**

- Simple to formulate and analyse.
- Simple to produce.
- Using small quantities of the compound, amenable to high throughput evaluations.

***Disadvantages*:**

- Dilution with aqueous media at a pH where the compound is less soluble increases the risk of precipitation. This may cause emboli intravenously, and it may cause variability orally.
- Tolerance and toxicity (local and systemic) are associated with non-physiological pH.
- A dissolved drug in an aqueous environment, like all solubilized and dissolved systems, is frequently less chemically stable than crystalline solid formulations. The chosen pH could hasten hydrolysis or catalyse other degradation processes.

Co-solvency:

Co-solvents, which are water-miscible solvents in which the drug has good solubility, can be used to increase the solubility of a poorly water-soluble drug. When compared to the aqueous solubility of the drug alone, co-solvents can increase the solubility of poorly soluble compounds thousands of times. Co-solvents are solutions made up of water and one or more water-miscible solvents that improve the solubility of poorly soluble compounds. Because it is simple to produce and evaluate, this has been one of the most widely used techniques in the past.

PEG 300, propylene glycol, and ethanol are examples of solvents used in co-solvent mixtures. Poorly soluble drugs can be given orally or Parenteral in co-solvent formulations. To lower the solvent concentration before administration, Parenteral formulations may require the addition of water or a dilution step with an aqueous media. A co-solvent approach may be appropriate for poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the solvent mixture.

To increase the solubility of poorly soluble compounds, co-solvents can be combined with other solubilization techniques and pH adjustments. The use of co-solvents to improve the solubility of poorly soluble drugs is a highly effective technique. Propylene glycol, ethanol, glycerine, and polyethylene glycol are the most commonly used low-toxicity co-solvents for Parenteral use. Because of their large solubilization capacity for poorly soluble drugs and low toxicity, dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been widely used as co-solvents [21,22].

***Advantages*:**

- It can be used with other solubilization procedures and pH modification to further boost the solubility of poorly soluble substances.
- It has a substantial solubilization capacity for poorly soluble pharmaceuticals, and is easy and rapid to formulate, produce, and analyze simple and rapid to formulate and produce.

***Disadvantages*:**

- As with other excipients, the toxicity and tolerability of the solvent level provided must be taken into account.
- When diluted with aqueous media, uncontrolled precipitation occurs. Precipitates can be amorphous or crystalline, and their size varies.
- Many of the insoluble chemicals Phases works with are unsuitable for intravenous delivery without the use of co-solvents. This is due to the fact that the medications are exceedingly water-insoluble and do not quickly re dissolve after being precipitated from the co-solvent mixture. There is a danger of embolism and local adverse effects at the injection site in certain cases.
- The chemical stability of the insoluble drug is worse than in a crystalline state, as it is with all solubilized forms.

Co-crystallization:

Co-crystallization modifies molecular interactions and is considered a viable strategy for increasing therapeutic properties. "A multicomponent crystal is generated between two solid substances under ambient conditions, where at least one component is an acceptable ion or molecule," according to a more detailed definition of a co-crystal. Co-crystallization aids in the correction of an API's physical, chemical, and physiological flaws. The physical state of the components is the only difference between solvates and co-crystals. A solvate is formed when one of the components is liquid and the other is solid; a co-crystal is formed when both components are solid. An API and a co-crystal former are the two main components of pharmaceutical co-crystals [23].

Solubilizing agent:

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 like cross-carmellose sodium and sodium starch glycolate are used as solubilizing compounds in a variety of preparations to increase drug solubility and dissolve. Improved gum Arabic or gum karaya, a well-known material, was estimated as a dissolution carrier and improved the low soluble of drugs like Nimotop. The addition of caffeine and niacinamide to the drug antimalarial agent tablet of halofantrine HCl increased its water solubility [24].

Salt formation:

An API is frequently unable to be constructed in its purest form due to different issues of instability. As a result of the conversion, salts, co-crystals, solvates, hydrates, and polymorphs are generated. Each one imparts a distinct physiochemical feature that enhances drug performance parameters like stability, bioavailability, purification, and manufacturability. To increase the solubility of poorly soluble therapeutic candidates (weak acids and bases), salt production has been employed for decades. Salts are generated when a substance is ionized in a solution. It's effective in Parenteral and other liquid formulations, as well as solid dosage forms. When an acidic or basic medicine is transformed into the salt with a better solubility than the original drug, it is called a salt. The FDA approved around 300 novel chemical entities for marketing between 1995 and 2006, 120 of which were salt forms. Furthermore, hydrochloric acid was used to produce 54 of the 101 approved salts of basic medicines, indicating that hydrochloride was the most common salt type. 12 Ionisable groups that help with salt formation should be present in the medicine [25]. The following factors were utilized to choose counter ion;

- There should be at least a 2 to 3 pKa differential between the medication and the counter ion.
- Crystal lattice forces should be reduced by counter ions.
- It should be FDA authorized or have sufficient toxicological evidence to support the counter ion selection.

This approach has a lot of potential for increasing the dissolution rate, but it has several drawbacks, such as the time it takes to approve salts and the fact that it isn't beneficial for neutral molecules. There should be a minimum difference of 2 to 3 pKa units between the drug and the counter ion.

***Advantages*:**

The best method to increase the solubility and dissolution rate of acidic nature substances and all basic drugs.

***Disadvantages*:**

It is the high reaction with atmospheric co_2 and water high is resultant in the precipitation in low water-soluble drugs and displays in the epigastric stress due to alkalinity.

Polymeric alterations:

Polymorphs are different crystalline forms of the same medicine, each with its own set of characteristics. Physical and chemical stability, melting point, vapor pressure, shelf life, dissolving rate, form, density, biological activity intrinsic solubility, and bioavailability are all physicochemical properties of polymorphs. Metastable crystalline polymorphs are associated with higher energy, increased surface area, solubility, bioavailability, and efficacy the stable, unstable, and metastable crystalline polymorphs. In terms of bioavailability, it is preferable to convert pharmaceuticals from crystal to metastable or amorphous forms during their shelf life in a range of real-world storage conditions [26].

***Advantages*:**

Include high molecular weight polymers and a rapid rate of polymerization.

***Disadvantages*:**

Bioavailability, which is necessary to alter the drug and the crystal forms in meta-stable has done shelf-life under a variety of storage conditions.

Size reduction of particle:

The surface area to volume ratio of a particle decreases as it gets smaller, resulting in a higher surface area to volume ratio. Because of the larger surface area, there is more interaction with the solvent, resulting in an increase in solubility. Particle size is a critical parameter that should be closely monitored during any formulation's pre-formulation studies. Although particle size reduction is a successful way to increase solubility, if it is not controlled and optimized, it can result in recrystallization and re-aggregation of the drug during storage [27].

***Advantages*:**

- Liquid forms can be developed quickly for preclinical testing and then converted to solids for later clinical development.
- Low Excipients-to-drug ratios are usually required.
- If no strong surfactants are required for stabilization, formulations are generally well tolerated.
- Crystal forms are generally more chemically and physically stable than amorphous particles.
- A method to consider for stubborn compounds that have failed to increase solubility in the past.
- In the case of chemical substances, increase the rate of the solution because particle size reduction increases the surface area available for solvent action.

***Disadvantages*:**

- There is a strong tendency for particle agglomeration due to the high surface charge on discrete small particles.
- It may be technically difficult to develop a solid dosage form with a high payload without encouraging agglomeration.
- Developing sterile intravenous formulations is even more difficult from a technical standpoint.
- Physical and mechanical stress can cause the active compound to degrade.
- Thermal stress caused by comminution can cause issues with the processing of thermosensitive agents.
- There is a strong trend for element gathering because of the increased surface control on distinct lesser elements**.**

Microemulsions:

A microemulsion is an optically clear pre-concentrate, isotropic, thermodynamically stable transparent, translucent system containing a mixture of oil, and hydrophilic surfactant, often in combination with a co-surfactant, with droplet sizes ranging from 20 to 200 nanometres and a hydrophilic solvent that dissolves a poorly water-soluble drug. HLB and non-toxicity are the criteria for selecting a surfactant. When the formulations come into contact with water, they self-emulsify, forming a very clear emulsion of small, uniform oil droplets containing the solubilized poorly soluble drug. Many drugs that are practically insoluble in water have been increased in solubility using micro-emulsions, as well as the incorporation of proteins for oral and Parenteral administration. The most suitable formulation is an oil-in-water (o/w) microemulsion, which is expected to increase solubility by dissolving compounds with low water solubility in an oil phase. Even if the microemulsions are diluted below the critical micelle's concentration after oral administration, the resultant drug precipitates have a fine particle size allowing enhanced absorption. They can also enhance oral bioavailability by reducing the droplet size (< 100 nm), and hence increase the rate of absorption due to surfactant-induced permeability changes [28].

***Advantages*:**

- Ease of preparation, clarity, filterability, and ability to incorporate a wide range of drugs with varying solubilities and bioavailability.

- Thermodynamic stability is a technique that leads to increased drug loading and penetration.
- Pre-concentrates are relatively simple to produce.
- Drug release from well-developed micro emulsion pre-concentrates is normally independent of digestion. As a result, without the use of food, optimal bioavailability and reproducibility can be expected (i.e., the fasted state).

***Disadvantages*:**

- The drug's affinity for precipitation on dilution, causes it to advance due to polar head solvent dilution influences. Authorizing formulas with multiple components become more difficult.
- In cases where long-term chronic administration is intended, the tolerability of formulations containing high levels of synthetic surfactants may be poor.
- Formulations containing multiple components become more difficult to validate.

Solvent evaporation:

Tachibana and Nakumara were the first to combine the drug and the carrier in a single solvent, then evaporate the solvent under a vacuum to produce a solid solution [29]. They were able to make a solid solution of the highly lipophilic -carotene in the highly water-soluble carrier polyvinyl pyrrolidone as a result of this. Using the solvent evaporation technique, many researchers investigated the solid dispersion of meloxicam, naproxen, and nimesulide [30]. These findings suggest that the above-mentioned technique can be used to improve and stabilize solid dispersions of drugs that are poorly water-soluble.

The main advantage of the solvent method is that due to the low temperature required for the evaporation of organic solvents, the thermal decomposition of drugs or carriers can be avoided. The higher cost of preparation, the difficulty in completely removing the liquid solvent, the possible adverse effect of the supposedly negligible amount of solvent on the chemical stability of the drug, the use of a common volatile solvent, and the difficulty in reproducing crystal forms are all disadvantages of this method.

Sonocrystallization:

Melt Sono-Crystallization (MSC): Sonocrystallization can be utilized to impart a range of desired properties to high-value products. The Dow Chemical Company in the United States is already crystallizing adipic acid via Sonocrystallization, but it is a well-guarded secret. Impurities were reduced from 800 parts per million to less than 50. Ultrasound can be useful in a variety of crystallization situations, including:

- Primary nucleation begins, narrowing the metastable zone's breadth.
- Secondary nucleation is the second stage of the nucleation process.
- Perfection and the crystal habit.
- Agglomeration is reduced.
- In a sterile environment, a non-invasive alternative to seed crystal addition (seeding).
- Controlled nucleation to manipulate crystal dispersion.

The creation of primary nuclei is influenced by ultrasonic parameters such as oscillation frequency, irradiation intensity, physical features of the liquid such as degree of super-saturation, and operating parameters such as temperature [31].

Inclusion complexation:

Among all the solubility enhancement techniques, the inclusion complex creation technique has been employed more specifically to improve the aqueous solubility, dissolution rate, and bioavailability of weakly water-soluble medicines. When a nonpolar molecule or a nonpolar section of a molecule (referred to as a guest) is inserted into the cavity of another molecule or group of molecules, inclusion complexes are produced (known as a host). The cavity of the host must be large enough to hold the guest while still being small enough to keep water out. The most common host molecules are cyclodextrins. Cyclodextrins are non-reducing, crystalline, and water-soluble cyclic oligosaccharides. Cyclodextrins are composed up of a ring of glucose monomers. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin [32].

The greater the relative solubility enhancement obtained through cyclodextrin complexation, the lower the pure drug's aqueous solubility. Cyclodextrins pharmaceutical applications in drug solubilization and stabilization, in vivo drug delivery, toxicological issues and safety evaluation, and mechanisms of Cyclodextrins modifying drug release from polymeric drug delivery systems have all been previously reviewed [33].

This cavity allows cyclodextrins to interact with guest drug molecules, changing properties including solubility, stability, bioavailability, and toxicity profiles [34]. The forces that cause complexation have been linked to;

- The exclusion of high-energy water from the cavity.

- Vander Waal's interactions.
- The release of ring strain particularly in the case of CD.
- Hydrogen and hydrophobic bindings.

ADVANCE TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

Micronization:

Micronization is a high-energy particle size reduction technique that can reduce coarse particles to a diameter of fewer than 5 µm. Micronization produces a narrow and constant particle size distribution, which is necessary for the creation of a homogeneous dosage form. Micronization increases surface area and solubility as particle size decreases. The micronization technology used has an impact on the attributes of the micronized therapeutic ingredient, such as particle size, size distribution, shape, surface properties, agglomeration behavior, and powder flow. The most often used processes for generating micronized pharmaceutical particles include mechanical communication, spray drying, and supercritical fluid (SCF) technologies. Micronized drug delivery, according to the Noyes–Whitney hypotheses, is a prominent method for increasing the bioavailability of weakly water-soluble drugs [35].

***Techniques for Micronization*:**

- Jet milling /fluid energy mill or micronizer.
- Micro precipitation & micro crystallization.
- Controlled crystallization.
- Spray freezing into liquid.
- Rotor stator colloids mills.
- Spray freezing into liquid.

***Advantages*:**

- Produces a more uniform particle with a larger surface area and a narrower particle size distribution.

***Disadvantages*:**

- A high-energy procedure disturbs the crystal structure of the drug, possibly resulting in disordered or amorphous portions in the final product.
- When stored in hot and humid settings, amorphous regions are thermodynamically unstable and prone to recrystallization.

Homogenization:

Homogenization is the method that is used to make a mixture of two equally non-soluble liquids the similar through. This is found by revolving one of the liquids into a state containing very small particles circulated uniformly throughout the other liquid [36].

Using high-pressure homogenization, many poorly water-soluble medicines have been nano suspended. In the high-pressure homogenization process, a drug and surfactant suspension is driven under pressure through a nano-sized aperture valve of a high-pressure homogenizer. This approach works on the basis of aqueous phase cavitation. The particles' cavitation forces are strong enough to transform drug microparticles into nanoparticles. The requirement for small sample particles prior to loading, as well as the numerous homogenization cycles necessary, are also drawbacks of this approach. R.H. Muller's Disso Cubes technique, which uses a piston-gap-type high-pressure homogenizer, is an example of this technology [37].

The drug is broken down from micro particles to nanoparticles by the cavitation force. The hardness of the drug material, processing pressure, and the number of cycles employed all influence particle size [38].

The following are some of the potential benefits of nanosuspensions:

- Increased drug saturation solubility and dissolution rate.
- Improved bioavailability due to an increase in adhesive nature.
- Increase the amorphous proportion in the particles, which could result in a crystalline structural change and increased solubility.
- Surface modification of nano-suspensions for site-specific delivery is a possibility.
- Large-scale production capability is required for the market introduction of a delivery system.

This technique, however, may only be used to break up brittle drug candidates into nanoparticles. The chemical instability of fragile drugs under harsh manufacturing conditions, Ostwald ripening in long-term storage, the toxicity of surfactants, dispersibility of the dried powder, batch-to-batch variation in crystallinity level, and finally the difficulty of quality control and stability of partially amorphous nano suspensions must all be taken into account.

Nanosuspension:

This technology is used on drugs that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system made up of nano-sized drug particles suspended in an aqueous vehicle stabilized by surfactants and intended for oral, topical, Parenteral, or

pulmonary administration. Solid particles in nanosuspensions typically have a particle size distribution of 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 employs a variety of techniques, including nano engineering, nanotech technology, and milling technology (Nanocrystals) [39].

***Advantages*:**

- Nanosuspension reduces drug particles, enhancing surface area, solubility, dissolution rate, and, ultimately, bioavailability.
- Permeability is improved by nanosuspension.
- Bio adhesion and residence time are improved by nanosuspension.
- Organic solvents should be avoided whenever possible, and nano-formulation has the advantage of high drug loading.

***Disadvantages*:**

- Nanosuspension has the disadvantage of being unstable due to agglomeration, crystal formation, and Ostwald ripening.

Supercritical fluid process:

Supercritical fluids (SCFs) can dissolve non-volatile solvents due to the critical point of carbon dioxide. It is safe, environmentally friendly, and cost-effective. A SCF exists as a single-phase above its critical temperature and pressure. SCFs have qualities that are advantageous in product processing since they are midway between a pure liquid and pure gas. Small variations in operating temperature, pressure, or both affect density, transport qualities (such as viscosity and diffusivity), and other physical parameters near critical points (such as dielectric constant and polarity). Because of their particular processing characteristics, which have long been recognized and employed in the food sector, SCFs have lately been adapted to pharmaceutical applications. Carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, and ammonia are some of the most commonly utilized supercritical solvents. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed anti solvents process (CAP), 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 anti solvents processes (SAS) [40].

***Advantages*:**

- SCFs are appealing for pharmacological research because of their low operating conditions (temperature and pressure).
- The drug particles may be recrystallized at considerably decreased particle sizes after being solubilized in SCF.
- SCF techniques allow micronization of drug particles within restricted particle size ranges, often to sub-micron levels, owing to their flexibility and precision.

***Disadvantages*:**

Precipitation by infusion or impregnation of the polymers with the bioactive product, Anti-solvent, Compressed Fluid, Solution improved Dispersal by the Supercritical Fluid techniques.

Spray drying:

In an appropriate solvent, the active component and the carrier are dissolved and suspended. This solvent is evaporated by drying it out and blowing it away with a jet of hot air. Because of the enormous surface area of the droplets, the solvent evaporates quickly, and a solid dispersion occurs soon. An aqueous, organic, aqueous-organic co-solvent solution, aqueous-organic emulsion, or suspension containing a drug and pharmaceutical Excipients is atomized using this process. Following that, the frozen particles are lyophilized to produce dry, free-flowing micronized powders. The use of acetonitrile as a solvent increased drug loading and reduced lyophilization drying time [41].

***Advantages*:**

It is a technology system for the mass production method.

***Disadvantages*:**

Spray drying is a method of experimental use to mechanical force comminution it may degrade in certain pharmaceuticals development, and drying might cause the thermal pressure and dreadful conditions of some products use are used of the organic solvents.

Hydrotrophy:

Hydrotrophy is a solubilization process in which a substantial amount of a second solute is supplied, increasing the first solute's water solubility. The solute is made up of alkali metal salts of different organic acids. Hydrotropic agents are ionic organic salts. Salts that improve a solute's solubility in a particular solvent are referred to as "salting in," while salts that decrease solubility are referred to as "salting out." The phenomenon of hydrotropism causes numerous salts with large anions or cations that are themselves very soluble in water to "salt in" non-electrolytes called hydrotropic salts. The hydrotropic agent and the solute have a weak interaction, making hydrotropic solutions non-colloid. The term "hydrotrophy" refers to the increase in water solubility that occurs when a large number of additives are present. Complexation, which involves a mild interaction between hydrotropic substances such as sodium benzoate, sodium acetate, sodium alginate, and urea and weakly soluble medicines, is more closely related to its process for enhancing solubility [42].

***Advantages*:**

- Hydrotrophy is suggested to be superior to other solubilization methods, such as miscibility, micelle solubilization, co-solvency, and salting in, because the solvent character is independent of pH, has high selectivity, and does not require emulsification.
- Solvent character is independent of pH, hydrotrophy has high selectivity, and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water and does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of an emulsion system.

Disadvantages:

Hydrotrophy has an influence on the surfactant combination that is necessary for micelle formation and stage presentation of multiple systems with a position toward Nano-dispersions, and it conducts percolation, clouding of the polymer, and surfactants, and so on.

CONCLUSION:

We have concluded in this review paper that the solubility of any molecule is critical and plays a significant role in drug formulation and development. These strategies are used to improve the drug's solubility by adjusting various parameters. Solubility refers to any physical or chemical property, including pharmacokinetics treatment in medical and biopharmaceutical applications. Solubility is one of the rate-limiting parameters for orally delivered drugs to acquire their required concentration in systemic circulation for a pharmacological response. For formulation scientists, the problem of solubility is a key concern. Traditional methods include pH, particle size distribution, salt formation, co-solvency, and solvent evaporation, whereas modern methods include micronization, nano-suspension, homogenization, and spray drying. Nano suspensions, Super Critical Fluid, Cryogenic, and Inclusion Complex Formation are the most advanced strategies for resolving hydrophobic drug solubility problems.

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