A BRIEF REVIEW ON : SOLUBILITY ENHANCEMENT TECHNIQUES OF POORLY SOLUBLE DRUGS.

Corresponding Authors : Durga M. Choudhari, Rutuja S. Divekar, Ajinath R. Sabale.

Co – Author : Dr. Amita B. Dongare, Prof. Sandhya R. Kolekar.

Ekanath Sitaram Divekar College Of Pharmacy, Varvand 412215.

Emails-durgachoudhari7906@gmail.com, rutujadivekar7917@gmail.com,

ajinathsabale045@gmail.com, amitapadalkar172@gmail.com,Kolekar2sandhya@gmail.com.

ABSTRACT:

Poor water solubility remains a challenge in pharmaceutical development, particularly for biopharmaceutical classification system (bcs) class ii and iv drugs, which frequently display low dissolution rates and limited bioavailability. This review explores a spectrum of strategies both conventional and advanced for enhancing the solubility of such poorly soluble drugs. Techniques are categorized into chemical modifications (including salt formation, co-crystallization, co-solvency, hydrotropy, and the use of novel solubilizers), physical modifications (such as particle size reduction via micronization and nanosuspensions, crystal habit alteration through polymorphs and pseudopolymorphs, complexation including inclusion complexes, and drug dispersion in carriers via solid solutions and dispersions), and other innovative methods (notably ph adjustment, supercritical fluid processing, the liquisolid technique, and polymer-based approaches). Each method is evaluated based on its impact on key performance parameters such as dissolution rate, saturation solubility, and bioavailability and its practicality for formulation development. The scope of this review emphasizes how crucial it is to choose suitable modification methods based on the physicochemical characteristics of potential drugs and the routes of administration they are intended to use. Finally, there is great potential for enhancing the therapeutic results of hydrophobic medications through the successful use of these solubility-enhancement techniques.

KEY WORDS : solubility, modification ,conventional method, particle size, solvency.

INTRODUCTION :

To improve the solubilization and bioavailability of medications that are poorly soluble in water, a number of strategies can be employed. Micronization, ph adjustment, chemical manipulation and medication solubilization frequently involves the use of solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy and other techniques. In both formulation design & development and novel chemical entity screening studies, solubilization of poorly soluble medicines is a frequent challenge.[1] solubility is the maximum amount of analyte that can dissolve in a volume of solvent. It can be described using both qualitative and quantitative methods. It can be characterized as spontaneous in qualitative terms. Combining two or more substances to create a uniform mixture. Quantitatively, a homogeneous solution is created by the concentration of a material (solute) in a specific volume of solvent at a specific temperature. Molality, molarity, volume fraction, mole fraction, percentage, and parts can all be used to express a drug's solubility. Solubility equilibria play a critical role in drugs. Drugs with low water solubility (bcs classes ii and iv) exhibit issues relating to dissolution. [2] the bcs is a scientific framework for classifying medications according to their intestinal permeability and water solubility. Three crucial aspects solubility, intestinal permeability, and dissolution rate are taken into account by the bcs in conjunction with the drug product's in vitro dissolving capabilities. These factors all affect the rate and volume of oral drug absorption from sudden release solid oral dosage forms. The us food & drug administration (fda) developed the bcs, which divides drugs into four basic classifications according to permeability and solubility (table 1). Class ii and class iv drugs have solubility issues. [3, 4] therefore, increasing the solubility of bcs class ii and class iv medicines increases their bioavailability. [5]

Table 1: Biopharmaceutical classification system.

Class	Solubility	Permeability	Absorption pattern	Rate l.s in absorption
I	High	High	Well absorbed	Gastric emptying
Ii	Low	High	Variable	Dissolution
Iii	High	Low	Variable	Permeability
Iv	Low	Low	Poorly absorb	Case by case

Potential reasons for poor oral absorption [4]

A medication is considered poorly soluble if its :

1.Aqueous solubility is less than 100 µg/ml.
2.poor dissolution: intrinsic dissolution rate <0.1 mg/cm2/min.
3. High molecular weight: (>500), self association and aggregation;

4. Elevated crystal energy.

Table 2 :Relative terms of solubility[47]

Descriptive terms	**Parts of solvent required for 1 part 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

[14]

Techniques for solubility enhancement[6-13]

There are several methods to increase a drug's solubility in aqueous medium when it is limited.

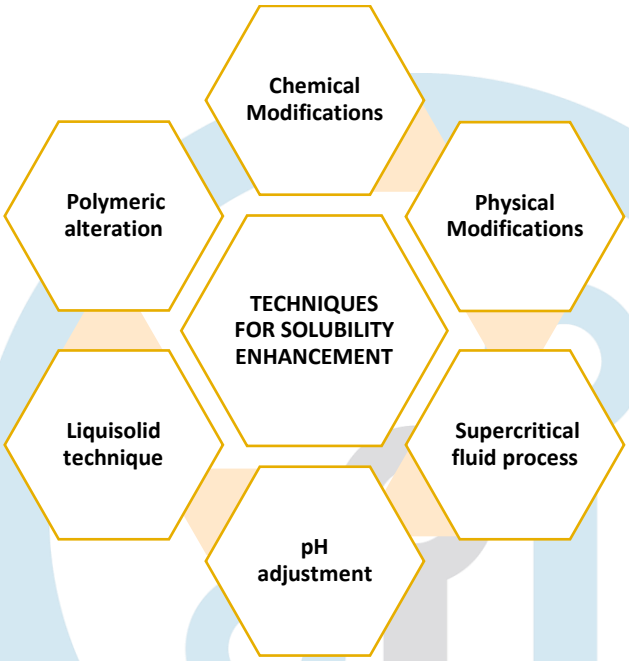

Fig no 1. Techniques for solubility enhancement

The following are some new and conventional methods to improve solubility :

A. Chemical Modifications:

1) Salt formation
2) Co-crystallization
3) Co-solvency
4) Hydrotropy
5) Use of novel solubilizer
6) Nanotechnology

B. Physical modifications:

1) Particle size reduction
    a. Conventional method
    b. Micronization
    c. Nanosuspension
2) Modification of the crystal habit
    a. Polymorphs
    b. Pseudopolymorphs
3) Complexation
    a. Physical mixture
    b. Kneading method
    c. Co-precipitate method
4) Inclusion complex formulation based techniques
    a. Kneading method
    b. Lyophilization/ freeze- drying technique
    c. Microwave irradiation method
5) Solubilization by surfactants
    a. Microemulsions
    b. Self microemulsifying drug delivery system
6) Drug dispersion in carriers
    a. Solid solution
    b. Solid dispersions

i. Fusion process
ii. Solvent method
iii. Fusion solvent method
iv. Spray drying
v. Lyophilization (spray freeze drying method)
vi. Hot melt extrusion
vii. Dropping method

C. Ph adjustment
D. Supercritical fluid process
E. Liquisolid technique
F. Polymeric alteration

A. CHEMICAL MODIFICATIONS :

1) Salt formation [15]

Many times, a variety of instability problems prevent an api from being created in its pure form. As a result, they transform into solid forms including hydrates, solvates, salts, co-crystals, etc variations. Each of them contributes a distinct physiochemical characteristic that influences the drug's performance attributes, stability, bioavailability, purification, and manufacturing feasibility in a more effective manner.for a while, the process of salt-forming weak acids and bases—drug candidates that are not very soluble—has been used to increase solubility. Ionization of a chemical in solution results in the formation of salts. It works effectively for both solid dosage forms and parenteral and other liquid formulations. A salt that is more soluble than the acidic or basic medication is produced. For example, barbiturates, theophylline, and aspirin. Progesterone is a commercially available example of this strategy; it is a water-insoluble steroid that dissolves in peanut oil.

2) Co-crystallization[16]

Co-crystallization is taking over the field with the most development and attention. Cocrystallization is only possible when the physiochemical characteristics (hydrophobicity, the formulation's overall solubility and compaction characteristics are enhanced. The api and the former are the two main components that make up co-crystals. The former might now be any additional excipient or api that, when taken together, lowers the dosage and minimizes adverse effects. The pharmacological qualities (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, etc.) Will therefore alter even if the api is the same.the most rapidly evolving class of solid pharmaceutical compounds is co-crystallization, which is a very broad field. Cocrystal anhydrates, cocrystal hydrates (solvates), anhydrates of salt cocrystals, and hydrates (solvates) of salt cocrystals are thus the categories into which they can be separated. Apis in classes ii and iv, as defined by the bcs classification, have consistently presented difficulties when it comes to improving solubility. Two or more molecules joined by a hydrogen bond form co-crystals. Numerous analytical methods and logical physicochemical examinations, such as solubility and stability tests, can be used to choose the best co-crystal.instances of hydrogen bond co-crystallization include the co-crystals of rac-ibuprofen, racflurbiprofen, and aspirin. Using 4,4v-bipyridine, the carboxylic acid dimmers were broken down to create these. Despite being nominally molecular compounds (or co-crystals), these structures do not involve charge transfer from or to the active ingredient or the creation of covalent bonds. Therefore, high-throughput (ht) crystallization methods have recently been created to gain a detailed understanding of this. This method is essentially combinatorial, employing a variety of conditions and compositions. To lower the material need and provide the greatest number of circumstances feasible, experiments are conducted on a small scale.

"multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule" is a more precise definition of a co-crystal.

Self-assembly units based on supramolecular synthons, which are generated from motifs frequently seen in crystal structures, are frequently present in co-crystals. Pharmaceutical co-crystals typically require at least one

api component, with the remaining co-crystal former or formers being pharmaceutically acceptable substances such commonly used food additives and excipients.

3) Co-solvency[17]

The most often used method to improve a drug's aqueous solubility is cosolvency, which involves combining water with an approved harmless organic solvent. In the pharmaceutical sector, ethanol, propylene glycol, glycerine, glycofural, and polyethylene glycols are often utilized cosolvents.[18]

There are multiple uses for the cosolvency phenomena in various domains. Apart from uses in medication preparation, to dissolve cholesterol gallstones, solubilizing chemicals such as tert-butyl ether were employed in clinical settings. Because organic solvents have the ability to alter the distribution and mobility of hydrophobic pollutants in the environment, cosolvency is a crucial topic from the perspective of environmental scientists.[19] the chemist has some theoretical support from the solubility behavior of a solute in mixed solvents. Some concepts regarding solute-solvent and solvent-solvent interactions in the solution can be gathered from this.

From a pharmaceutical perspective, cosolvency of non-aqueous solvent combinations is particularly crucial since the mixtures may be utilized as synthesis media or re-crystallization solvents for drug purification. The drug's chemical stability, the solute's acid dissociation constants, and other factors may be impacted by the addition of a cosolvent to the aqueous solution.
Viscosity and surface tension of the solution, which are important considerations for using cosolvents in pharmaceutical applications. Reviewing the available cosolvency models, their predictive power, and the error ranges of the anticipated solubilities in the pharmaceutical domains are the objectives of this work. Along with the model's accessible accuracy tests, the fundamental models and their recent extensions were covered.

4) Hydrotropy

Hydrotropes, also known as hydrotropic agents, are substances used to increase the solubility of solutes that are weakly soluble in solvents. Salting-in and salting-out procedures are commonly used to improve solubility. Salts that exhibit the "salting in" of non-electrolytes are referred to as "hydrotropic salts," and the phenomenon is called "hydrotropism." this salting-in process differs from salting-out. Although no colloidal property is displayed as a result of the interaction, hydrotropic salts strengthen the solute's solubilizing ability by forming a weak association with them. Similar to surface active agents, hydrotropes improve the aqueous solubility of solutes that are only weakly soluble in water at room temperature. There is potential for hydrotropy to become an industrial technology.[20] since the mechanism of action of hydrotropes is still up for debate and far from definitive, it is by no means apparent. Numerous scholars offered their own theories regarding the potential hydrotrope mechanism. The following three theories have been put forth to explain hydrotropic activity:

(a) complex formation between solute and hydrotrope,
(b) disintegrating or shattering tetrahedral complex of water molecules,
(c) self-association of hydrotrop

Table 3 :Classification of hydrotropesaliphatics and linear

Category	Example
Aromatic anionics	Sodium benzoate, sodium salicylate
Aromatic cationics	Paba, procaine hydrochloride, caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

5) Use of novel solubilizer

Different solubilizing compounds can also increase the solubility of drugs that are poorly soluble. Examples of conventional solubilizers that increase the solubility of hydrophobic apis include dendrimers, peg 400 sepitrap, soluplus povacoat, and polysorbates.[46,47]

6) Nanotechnology

Utilizing their ultra-small size, high-energy catalytic activity of surface atoms and protective properties for the encapsulated pharmaceuticals, nanomaterials are used as carriers in nanoparticle drug delivery systems. These methods target pharmaceuticals for cellular or subcellular-level delayed release, circumvent physiological barriers, decrease or prevent immune clearance, and lessen the impact of body fluids on the

medication . These techniques main objectives are to reduce drug toxicity and adverse effects and improve drug consumption by addressing some of the main drawbacks of traditional drug delivery techniques, these systems present a viable path forward in the field of drug delivery, especially for medications that struggle with solubility, stability, and targeted distribution.[21] their current form is ineffective due to issues with side effects, degradation, and inadequate absorption. Conversely, nanoparticles can deliver the medication to the desired tissues or cells, improve the drug's permeability and retention period in the body, and stop the medicine from degrading. Additionally, it lessens adverse effects on the patient's body and increases therapeutic efficacy, making the course of therapy more comfortable.[22]

B. PHYSICAL MODIFICATIONS :

1) Particle size reduction

The size of the drug particle has an intrinsic relationship with bioavailability. Increased surface area enhances the dissolving characteristics by decreasing particle size. Nowadays particle size reduction can be achieved by micronisation and nanosuspension.

a. Conventional method :

Cutting, compression, impact, attrition, and combined impact and attrition are some of the mechanisms involved in the traditional method of particle size reduction. Traditional techniques for reducing particle size, like spray drying and comminution, depend on mechanical stress to break down the active ingredient. Thus, particle size reduction is enabling a cost-effective, repeatable, and efficient method of improving solubility. However, the mechanical forces inherent in comminution, including grinding and milling, frequently cause the medicinal product to undergo considerable physical stress, which may result in degradation. When processing thermally sensitive or unstable active substances, the thermal stress that can happen during comminution and spray drying is also taken into account. It is impossible to raise the solubility of poorly soluble medications to a suitable level solely by employing conventional methods of solubility enhancement.[34]

b. Micronization :

Coarse particles can be reduced in size to less than 5 μ in diameter with this high energy particle size reduction approach. In order to create a homogeneous dosage form, micronization produces a uniform and narrow particle size distribution. Surface area rises as particle size decreases and solubility rises as micronization takes place. The type of micronization technology employed affects the characteristics of the micronized drug material, including particle size, size distribution, shape, surface qualities, agglomeration behavior, and powder flow. The most widely used methods for creating micronized medicine particles include mechanical communication, spray drying, and supercritical fluid (scf) technologies. . According to the noyes–whitney postulations, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water soluble drug substances.[30]

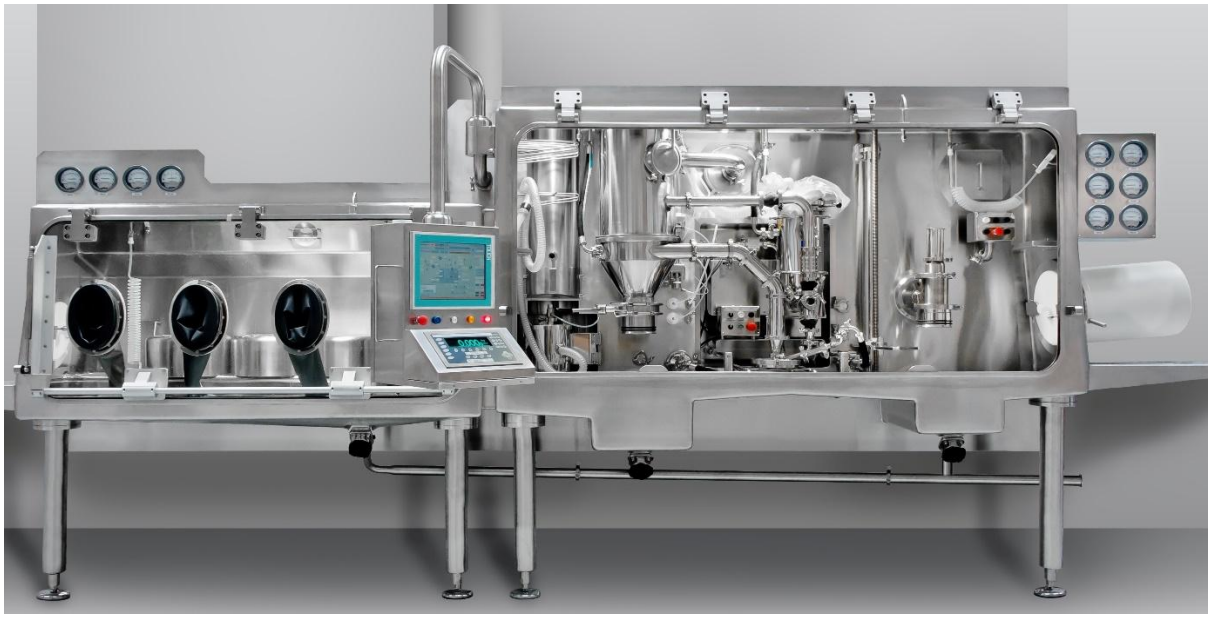

Fig no 2. Micronization

c. Nanosuspension

nanosuspensions can be formulated bybottom-up technology and top-down. Both top-down and bottom-up approaches can be used to formulate nanosuspensions.
Media milling and jet milling, two common methods for creating nanosuspensions, can both make advantage of the micronization concept. There are several benefits and drawbacks of micronization. Micronization, for instance, speeds up the rate of dissolving but reduces the drug's saturation solubility. Some new and traditional techniques for creating nanosuspensions are discussed in the sections that follow.[26,27,28,29]

2) Modification of the crystal habit :

a. Polymorphs

b. Pseudopolymorphs :

The capacity of an element or compound to crystallize in multiple crystalline forms is known as polymorphism. Despite having the same chemical makeup, different pharmacological polymorphs have distinct physicochemical characteristics, such as solubility, melting point, density, texture, and stability. Similar to this, a drug's amorphous form is always better than its crystalline form because of the higher energy involved and the larger surface area. Order for the breakdown of various solid medication types polymorphs that are amorphous, metastable, and stable.[33]

3) Complexation :

Drug stability and aqueous solubility have been improved through the complexation of medicines with cyclodextrins. Pharmaceutically significant cyclodextrins are composed of six, seven, or eight dextrose molecules (α, β, or γ-cyclodextrin) that are joined in a 1,4 configuration to create rings with different diameters. The ring's lipophilic center and hydrophilic perimeter allow for the formation of noncovalent inclusion complexes by suitably sized organic molecules, which improves chemical stability and aqueous solubility.london forces, hydrogen bonds, and hydrophobic contacts are examples of relatively weak forces that are essential to complexation.

a. Physical mixture :

In a mortar, the active medication and the appropriate polymer were combined in various ratios and stirred continuously for almost an hour. After passing through sieve number 80, the slurry is placed over fused calcium chloride in a desiccator.

b. Kneading method :

To create a slurry, an active medication and an appropriate polymer in various ratios are added to the mortar and triturated with a little amount of ethanol. The medicine is gradually added to the slurry while being continuously triturated. After that, the produced slurry is air dried for 24 hours at 250c. After being ground up and run through sieve number 80, the final product is kept in a desiccator above fused calcium chloride.

c. Co-precipitate method :

At normal temperature, the active medication dissolves in ethanol, and the appropriate polymer dissolves in distilled water. The active medication and appropriate polymers are combined in varying molar ratios. After an hour of stirring at room temperature, the solvent is removed from the mixture. After being ground up and sent through sieve number 80, the resulting mass is kept in desiccators.

4) Inclusion complex formulation based techniques :

a. Kneading method :

b. Lyophilization/ freeze- drying technique :

This method involves first freezing the solution containing the medication and cds or an appropriate polymer at low pressure, followed by drying the solution to remove the solvent system.
The primary factors influencing lyophilization are the special qualities of water and its functions as a solvent,

gas, diluent, plasticizer, and stabilizer. Drug and carrier molecules are mixed in a common solvent as an alternative to solvent evaporation.

c. Microwave irradiation method :
This technique was created for quick organic synthesis and reactions, which call for a greater target product and a shorter reaction time.[31]
Involves using a microwave oven to perform a microwave irradiation reaction between a drug and a complexing agent. The drug and cd are dissolved in a mixture of water and organic solvent in a specific proportion into a round-bottom flask, and the mixture is reacted for a brief period of time—roughly one to two minutes—at 60°c in the microwave oven. Following the completion of the reaction, a sufficient amount of solvent mixture is added to the reaction mixture above to remove any remaining, uncomplexed free drug and cd. The precipitate is then separated using whatman filter paper, and it is dried in a vacuum oven set at 40°c for 48 hours.

5) solubilization by surfactants :
a. Microemulsions :

b. Self microemulsifying drug delivery system :
A microemulsion is an isotropic translucent system that is optically clear, transparent, thermodynamically stable, and composed of a combination of hydrophilic solvent, oil, and surfactant that dissolves a medication that is poorly soluble in water. Non-toxicity and hlb are the criteria used to choose a surfactant. The formulations self-emulsify when they come into contact with water, resulting in a very transparent emulsion of tiny, uniform oil droplets that contain the weakly soluble drug that has been solubilized. In addition to adding proteins for oral, parenteral, and intravenous delivery, microemulsions have been employed to increase the solubility of many drugs that are almost insoluble in water. In order to improve solubility by dissolving molecules with poor water solubility into an oil phase solubility, an oil-in-water (o/w) microemulsion is the most appropriate formulation.[32]

6) Drug dispersion in carriers :
a. Solid solution :

b. Solid dispersions :
A mixture of two crystalline solids that results in a new crystalline solid is called a solid solution. When the two components crystallize together in a homogenous one-phase solution, a mixed crystal is created. Therefore, compared to simple eutectic systems, it is anticipated to produce. When a drug precipitates in an inert carrier in an amorphous state, this is known as amorphous precipitation. In this arrangement, the drug's higher energy state typically results in significantly higher rates of dissolving than the analogous crystalline forms.

i. Fusion process :
The medicine is added to the matrix after the carrier is heated to a temperature slightly over its melting point. To evenly distribute the medication throughout the matrix, the mixture is chilled while being continuously stirred. Additional elements that could be involved include the carrier's own solubilizing impact, enhanced wetting or reduced surface hydrophobicity, complexation, and crystallization of the medication in a metastable polymorphic form with changed thermodynamic characteristics.[39]
ii. Solvent method :
An appropriate organic solvent is used to dissolve the active substance and the carrier. Either a high temperature or a vacuum is used to evaporate this solvent. Super saturation and concurrent precipitation of the components, which leaves a solid residue, happen as the solvent is being withdrawn. To remove any solvent that may have freely adhered to the particle, the co-precipitate is then vacuum-dried. It is implied that even minute amounts of the solvent have been removed. Complete solvent removal can be demonstrated using less sensitive methods like spectroscopy and gravimetry as well as highly sensitive ones like differential thermal analysis (dta), differential scanning calorimetry (dsc), and thermogravimetric analysis (tga). [40]

iii. Fusion solvent method :

The drug or drugs are incorporated as a solution after the carrier or carriers are melted. The necessity for solvent removal is removed if the liquid is safe and the carrier can contain a specific amount of liquid while keeping its solid qualities. The method works well for medications that are thermolabile or have high melting points.

iv. Spray drying :

In an appropriate solvent, the active component and carrier are suspended and dissolved. In order to evaporate this solvent, a stream of hot air is applied after it has dried. The solvent evaporates quickly and solid dispersion forms soon because of the droplets' enormous surface area.

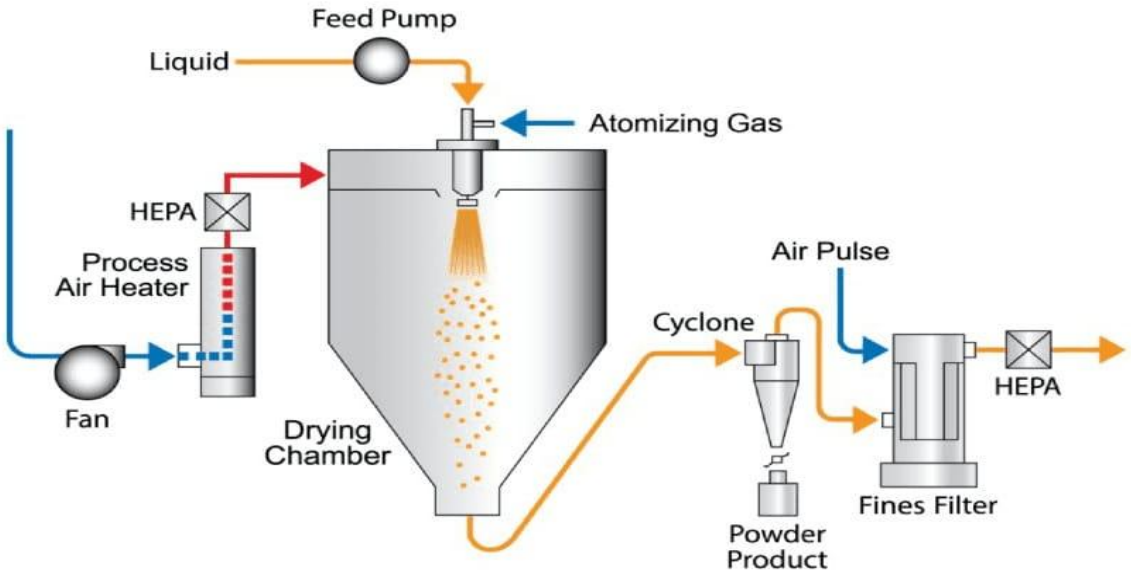

Fig no 3. Spray drying

V. Lyophilization (spray freeze drying method) :

Spray freeze drying (sfd) is a technique that has been effectively developed to create solid dispersions at room temperature without the need for heating while making thermosensitive medications. Sfd technology creates a frozen micronized powder that is then dried by atomizing a feed liquid comprising insoluble or poorly water-soluble apis and excipients straight into a cryogenic liquid at room temperature. For solid dispersions, this method has several benefits over conventional technologies, such as increased surface area and amorphous structure.[41-43]

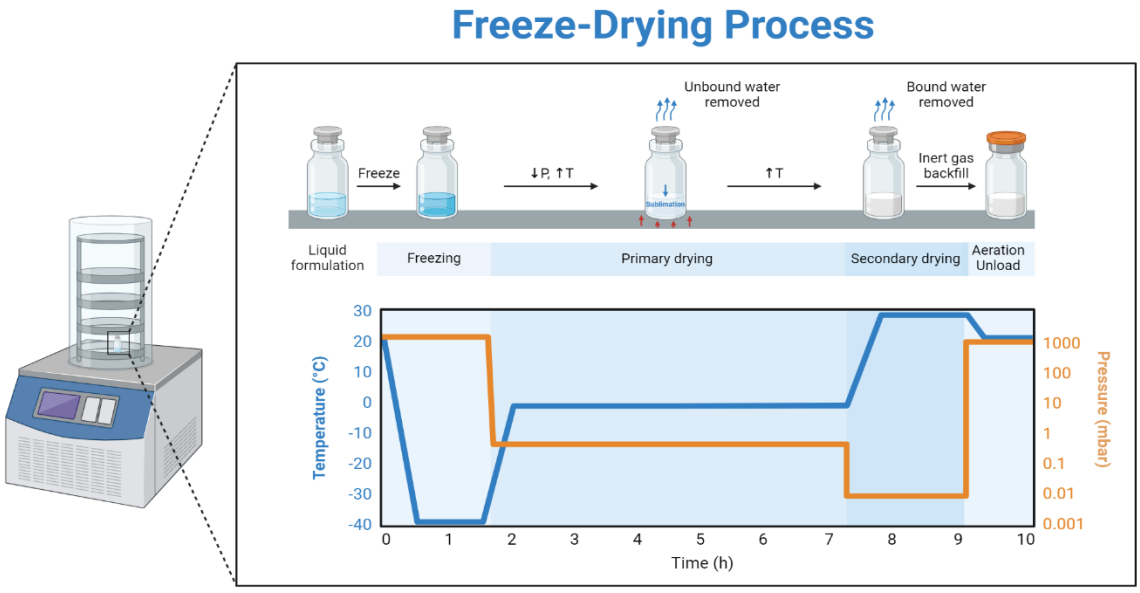

Fig no 4 . Lyophilization (spray freeze drying process)

Vi. Hot melt extrusion :

In the polymer business, this is the preferred technique. However, the first people to apply this technology for pharmacological purposes were speiser and huttenrach.

The following sections make up a melt extrusion: an exit port with an optional die to shape the extruding mass, a heated barrel with extruder screws to transport and mix the fed ingredients, and an opening to feed raw materials. The carrier and active chemicals are continuously delivered into the heated extruder barrel. The active ingredient and carrier mixture changes into its "fluid like state" as it is passed through heated screws. This condition enables close and even mixing due to the extruder screws' high shear.The melt is shaped into the necessary form, such as granules, pellets, films, or powder, using an exit outlet that includes an optional die. [44]

Vii. Dropping method :

A melting drug carrier combination is pipetted into a solid dispersion, which is then put onto a plate to solidify into spherical particles. The size of the pipette and the viscosity of the melt are two examples of variables that can affect the size and shape of the particles. It is crucial to regulate the temperature since viscosity is very temperature sensitive. This will ensure that the melt solidifies into a spherical shape when it is deposited onto the plate.[45]

C. pH adjustment :

By altering the ph, a medicine that is poorly soluble in water may dissolve in it. The buffer capacity and tolerability of the chosen pH are crucial factors to take into account in order to determine the solubility of this method. Excipients that function as alkalizing agents may enhance the solubility of weekly basic medications, while soluble excipients that raise the ambient ph within the dosage form to a range higher than the pka of weekly acidic drugs increase the solubility of such drugs.[23]

D. Supercritical fluid process :

A minimum of two distinct components make up a solid dispersion (SD), often a hydrophilic matrix and a hydrophobic medication.[24] the drug in these systems is distributed within the crystalline or amorphous matrix, either molecularly or as particulates. A solid solution with a molecularly dispersed drug is of particular interest as it can result in dissolution rate enhancement owing to the decrease in drug crystallinity and an increase in the specific surface area. Generally, techniques used to obtain SDs include: spray-drying , co-evaporation or co-precipitation , freeze-drying , and hot-melt extrusion (hme) . However, each of these processes has its own disadvantages that might restrict its use. Hme is extremely popular in sd preparation but the possible thermal degradation of drugs and/or polymers caused by the high processing temperatures can be considered as a principle drawback of this technique.

SCF can be defined as a substance above its critical pressure and temperature, where it possesses properties of both liquids and gases (density similar to liquids, whereas the diffusivity and viscosity are akin to gases) [25]

E. Liquisolid technique [38] :

One of the newest and most promising methods for increasing the pace at which water-insoluble medications dissolve is the use of liquidsolid compacts. Liquisolid compact refers to tablets or capsules that have either immediate or sustained release along with the proper adjuvant needed for tableting or encapsulation.

Liquisolid systems are often regarded as powdered forms of liquid medications that flow and compress well; this suggests that the drugs are either water-insoluble solids dissolved in appropriate water-miscible nonvolatile solvent systems or liquid lipophilic (oily) drugs. A straightforward admixture with certain powder excipients known as the carrier and coating materials can transform such liquid medications into dry-looking, non-adherent, free-flowing, and readily compressible powders. Liquisolid compacts are formulated using three main ingredients: coating substance, carrier, and liquid drug. Disintegrants, release-retard polymers, and other excipients are also utilized, depending on the formulation's needs and goals.[35,36,37]

F. Polymeric alteration :

Polymorphs are distinct crystalline forms of a medication that may have various characteristics. Physical and chemical stability, melting point, vapor pressure, shelf life, rate of dissolution, shape, density, inherent

solubility, biological activity, and bioavailability are only a few examples of the physicochemical characteristics that might differ across polymorphs. Crystalline polymorphs can be classified as stable, unstable, or metastable; metastable forms are associated with higher energy and enhanced surface area, solubility, bioavailability, and efficiency. In terms of bioavailability, it is preferred to transform drugs from crystal forms into amorphous or metastable forms during the course of their shelf life under a range of actual storage circumstances.

CONCLUSION :

To sum up, increasing the solubility of medications that are poorly soluble in water is essential for boosting their bioavailability and therapeutic effectiveness. To improve solubility, a variety of tactics can be used, such as physical and chemical changes as well as creative approaches. Co-crystallization, salt production, and the application of new solubilizers are examples of chemical changes. Physical changes include complexation, crystal habit modification, and particle size decrease. Additionally promising are cutting-edge techniques like polymer-based strategies, liquisolid technology, and supercritical fluid processing. The drug's physicochemical properties and the way it will be administered determine which approach is best. For poorly soluble medications, researchers can create efficient solubility-enhancement strategies by comprehending the advantages and disadvantages of each strategy.

REFERENCE' S :

1.Vemula vr, lagishetty v, lingala s. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research, 2010; 5(1): 41-51.

2.Kshirsagar s, choudhari m, sathyan r, dhore s. Solubility enhancement by various techniques based on pharmaceutical and medicinal chemistry approach: an overview. Asian journal of pharmacy and technology, 2019; 9(2): 141-146

3.Yaris m, asif m, kumar a, aggarval a. Biopharmaceutical classification system: an account. International journal of pharmtech research, 2010; 2(3): 1681-1690. 4. Cook j, addicks w, wu yh. Application of the biopharmaceutical classification system in clinical drug development—an industrial view. The aaps journal, 2008; 10(2): 306-310. 5. Brahmankar dm, jaiswal sb, biopharmaceutics and pharmacokinetics, 2009; 349-357.

4.Vilas, p. B., vinayta, r. A., anirudha, v. M., arunadevi, s. B., sanjay, bais., j. Innov. Pharm. Biol. Sci.2015, 2 (4), 482-494.

5.Brahmankar dm, jaiswal sb, biopharmaceutics and pharmacokinetics, 2009; 349-357.

6.Kadam, s.v., shinkar, d.m., saudagar, r.b., int. J. Pharm. Biol. Sci. 2013, 3 (3), 462-475.

7.Blagden, n., matas, m., gavan, p.t., york, p., adv. Drug delivery rev. 2007, 59(7), 617–630.

8.Meera, c., j pharmacy res. 2010, 3(10), 2494-2501.

9.Thorat, y. S, gonjari i. D, hosmani a. H., int j pharm sci res.2011, 2(10), 2501-2513.

10.Shinde a., pharminfo.net. 2007, 5(6), 1-9.

11.Brahmnkar, d.m., jaiswal, s.b., biopharmaceutics and pharmacokinetics treatise. Vallaabh prakashan, delhi 2009.

12.Leuner, c., dressman, j., euro j pharm biopharm. 2000, 50, 47-60.

13.Kumar, s., singh, p., the pharm innov j. 2016, 5(1), 23-28.

14.Limbachiya mi. Solubility enhancement techniques for poorly soluble drugs: a review. Ijprd, 2011; 4(4):71-86

15.Serajuddin, a.t, adv drug deliv rev. 2007, 59(7), 603-16.Patole, t. And deshpande, a., 2014. Co-crystallization-a technique for solubility enhancement. Int j pharm sci res, 5(9), pp.3566-76.

16.Jouyban, a., 2008. Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixtures. *Journal of pharmacy & pharmaceutical sciences*, *11*(1), pp.32-58.

17.Allen mj, borody tj, bugliosi tf, may gr, larusso nf, thistle jl. Rapid dissolution of gallstones by methyl tert-butyl ether- preliminary observations. New eng j med, 312: 217-220, 1985.

18.Li a, andren aw. Solubility of polychlorinated biphenyls in water/alcohol mixtures. 1. Experimental data. Environ sci technol, 28: 47- 52, 1994

19. namdev, b., venkatachalam, s., jawahar, n. And chorsiya, a., 2022. A brief review on solubility enhancement technique: hydrotropy. *Indian j pharm educ res*, *56*(2), pp.347-355.

20.Liu, y., liang, y., yuhong, j., xin, p., han, j.l., du, y., yu, x., zhu, r., zhang, m., chen, w. And ma, y., 2024. Advances in nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs. *Drug design, development and therapy*, pp.1469-1495.

21.Chenxi, z., hemmat, a., thi, n.h. and afrand, m., 2025. Nanoparticle-enhanced drug delivery systems: an up-to-date review. *Journal of molecular liquids*, p.126999.

22.Kumar, s. And singh, p., 2016. Various techniques for solubility enhancement: an overview. *The pharma innovation*, *5*(1, part a), p.23.

23.Dhirendra, k.; lewis, s.; udupa, n.; atin, k. Solid dispersions: a review. *Pak. J. Pharm. Sci.* **2009**, *22*, 234–246.

24.Nandi, u., ajiboye, a.l., patel, p., douroumis, d. And trivedi, v., 2021. Preparation of solid dispersions of simvastatin and soluplus using a single-step organic solvent-free supercritical fluid process for the drug solubility and dissolution rate enhancement. *Pharmaceuticals*, *14*(9), p.846.

25. pu x., sun j., li m., he z., "formulation of nanosuspensions as a new approach for the delivery of poorly soluble drugs", current nanoscience, vol. 5, no. 4, pp. 417-427, 2009. Doi: 10.2174/157341309789378177

26. mohanty s., boga p., "role of nanoparticles in drug delivery system", international journal of research in pharmaceutical and biomedical sciences, vol. 1, no. 2, pp. 41-66, 2010.

27. nagare k., ghughure s., salunke s., jadhavg., dhore r., "a review on nanosuspension an innovative acceptable approach in novel delivery system", universal journal of pharmacy, vol. 1, no. 1, pp-19-31, 2012.

28.Jadhav, s.p., singh, s.k. and chawra, h.s., 2023. Review on nanosuspension as a novel method for solubility and bioavailability enhancement of poorly soluble drugs. *Advances in pharmacology and pharmacy*, *11*(2), pp.117-130.

29.Jagtap, s., magdum, c., jadge, d. And jagtap, r., 2018. Solubility enhancement technique: a review. *Journal of pharmaceutical sciences and research*, *10*(9), pp.2205-2211.

30.Devil nkd, rani ap, javed m, kumar ks, kaushik j, sowjanya. Cyclodextrins in pharmacy-an overview, pharmacophore, 2010; 1(3):155-165.

31.Khatri, h., hussain, m.s. and tyagi, s., 2022. Solubility enhancement techniques: an overview. *World journal of pharmaceutical research*, *11*(5), pp.34-40.

32.Jagtap, s., magdum, c., jadge, d. And jagtap, r., 2018. Solubility enhancement technique: a review. *Journal of pharmaceutical sciences and research*, *10*(9), pp.2205-2211.

33.Yadav, k., sachan, a.k., kumar, s. And dubey, a., 2022. Techniques for increasing solubility: a review of conventional and new strategies. *Asian journal of pharmaceutical research and development*, *10*(2), pp.144-153.

34.Spireas s. Liquisolid systems and methods of preparing same. U.s. patent 6423339b1. 2002.

35. fahmy rh, kassem ma. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 2008; 69:993-1003

36. spireas s, sadu s. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int. J. Pharm. 1998; 166:177-88

37.Patel, b.b. and shah, c., 2016. Recent research on liquisolid technology for solubility enhancement-a review. *International journal of advances in pharmaceutics*, *5*(1), pp.01-07.

38.Sareen, s., mathew, g., joseph, l., int j pharma investig. 2012, 2(1), 12-17.

39. yella, s.r., krishnalah., inventi spreading knowledge.10-18.

40. kushwaha, a., inter j pharm sci res. 2011, 2(8), 2021-2030.

41.Kalyanwat, r., patel, s., inter j drug formu res. 2010, 1 (3), 1-14.

42.Verma, s., rawat, a., kaul, m., saini, s., inter j pharmacy tech. 2011, 3(2), 1062-1099.

43. habib, m.j., technomic publishing company, inc. Lancaster, pennsylvania (u.s.a.). 2001, 1-36.

44.Pawar, a.r., choudhari, p.d., asian j. Biomed. Pharm. Sci. 2012, 13, 9-14.

45.Ahmad, d., setouh., emad, a.l., , abdelmelek n.s., eur j pharm biopharm.2015, 94, 386-392.

46.Naveen, k., thakral, a., r. Ray., bar-shalom, d., eriksson, a. H., majumdar, d. K., aaps pharm scitech. 2012, 13, 1.

47.Ansel's pharmaceutical dosage forms and drug delivary systems