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SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

The ability of a solid to dissolve in a liquid phase and produce a uniform molecular dispersion is known as solubility, and it is crucial to the effectiveness of drugs. However, most active pharmaceutical ingredients are hydrophobic and poorly soluble in water. The solubility of the medicine can be one of the hardest things to work with when creating a formulation. Important compounds with poor aqueous solubility never make it to the final pharmaceuticals because their full therapeutic range and potential are not realized. Therefore, despite their potential for pharmacokinetic activity, many new drugs' poor water solubility is a major barrier to their successful market launch. If a molecule's solubility in water limits its bioavailability, then it would not be possible to develop molecules that would have a highly beneficial effect on their physiological target.

KEYWORDS: Solubility, bioavailability, pharmacokinetic activity, physiological target.

INTRODUCTION

Solubility is a substance's property in a solvent and concentration of dissolved solute in a saturated solution at a given temperature as an obvious homogenous molecular dispersion in terms of quality. This is the highest amount of the solute that occurs while a solvent is in equilibrium so a saturated solution is the name given to the resulting solution. Ions and their propensity to precipitate or stay aqueous when combined with other particles are listed in a solubility chart.[1] When a solid chemical substance exhibits chemical equilibrium with a compound's solution, it is supposed to be in soluble equilibrium. Drugs are dependent on solubility equilibria. Class II or even Class IV BCS chemicals with poor aqueous solubility have problems with absorption and dissolution. Parts, molarity, normalcy, formality, mole fraction per percent solution, volume fraction, and molality are quantitative terms that can be used to characterize solubility.[2]

Table 1: Solubility Expression.[3]

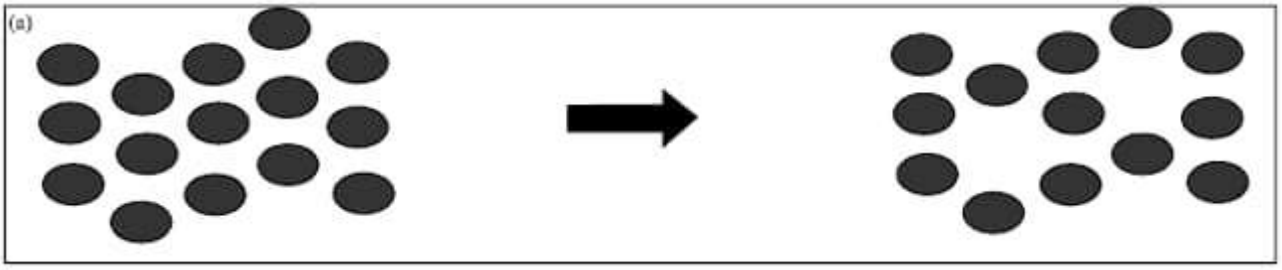
Definition	Parts of solvent required for one part of
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly	From 1000-10,000
Insoluble	Greater than 10,000

Possible Causes for Poor Oral Absorption:[4] A drug is considered poorly soluble.

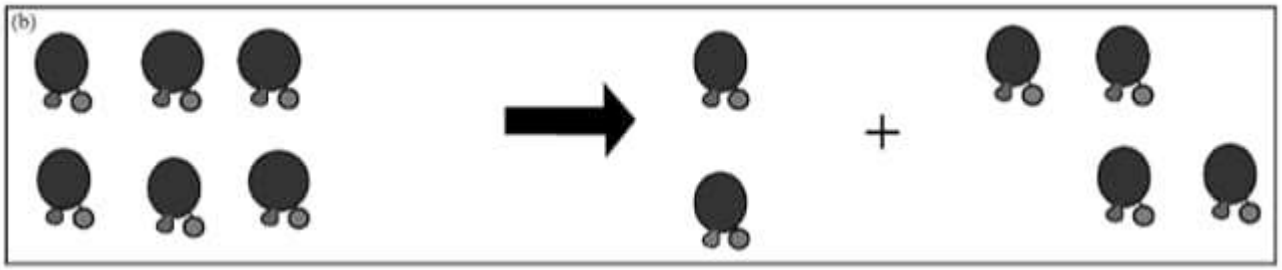
Aqueous solubility <100µg/ml, Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm²/min, High molecular weight: (>500), Self-association and aggregation, High crystal energy.

Process of Solubilization[5]

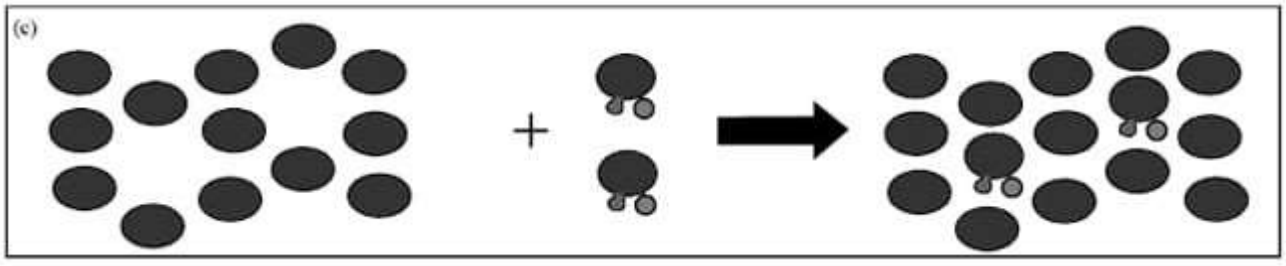
Step 1: Breaking down ionic or molecular bonds within the solute and separating the interactions between the solvent and the solute molecule or ion are both parts of the solubilization process.



Step 2: A solid molecule breaks off from the mixture.



Step 3: Insert solid molecule feed into the Solvent hole.



Biopharmaceutics classification system (BCS)

The FDA introduced the Biopharmaceutics Classification System (BCS) which divides drugs into four classifications based on permeability and solubility. Due to low solubility, Class II and IV of the system encounter dissolution as the rate-limiting step for drug absorption.

Table 2: 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: The solubility of the particles is influenced by their size. As the particle size reduces, the surface area to volume ratio rises. A particle's interaction with the solvent increases with increasing surface area.[5] The relationship between solubility and particle size can be expressed using the following equations

$$\log \frac{S}{S_o} = \frac{2\gamma V}{2.303RTr}$$

Where,

S is the solubility of infinitely large particles
So is the solubility of fine particles
V is the molar volume
λ is the surface tension of the solid
r is the radius of the fine particle
T absolute temperature in degrees Kelvin.
R universal gas constant.

Temperature: The solubility is affected by temperature. The procedure of solution absorbs energy, which causes the solubility to increase and the temperature to rise. If energy is released during the solution process, the solubility reduces as the temperature rises.[8]

Molecular size: The difficulty of solvating substances with larger molecular weights and sizes by surrounding them with solvent molecules is the cause of this decrease in solubility.

Nature of solute and solvent: The concentration and mixing temperature of solutes and solvents affect how they interact with one another. At room temperature, 100 grams of water dissolve one gram of lead (II) chloride,

but 200 grams of zinc chloride dissolve in 100 grams of water with the same water concentrations.[4]

Pressure: When pressure rises, gaseous solutes become more soluble, and when pressure falls, they become less soluble.

For both solids and liquids, pressure differences do not affect solubility.

Polarity: The polarity of the solvent and solute molecules has an impact on solubility. In general, polar solute molecules will dissolve in polar solvents, while those that are non-polar will dissolve in non-polar solvents.

Polymorphs: A substance's capacity to crystallize in multiple crystalline states is referred to as polymorphism. An agent's polymorphism is its capacity to crystallize in several forms. A solid can take on multiple forms if it crystallizes in different ways. The melting point of a polymorph might vary. Since a solid's solubility and melting point are related, polymorphs will differ in their solubility.[4]

TECHNIQUES TO OVERCOME POOR SOLUBILITY[7,14]

Chemical Modifications

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropy
- Use of novel solubilizer
- Nanotechnology

Physical Modifications

- Particle size reduction
- Conventional method
- Micronization
- Nanosuspension

Modification of the crystal habit

- Polymorphs
- Pseudopolymorphs
- Complexation
- Physical mixture
- Kneading method
- Co-precipitate method

Inclusion Complex Formulation-Based Techniques

- Kneading method
- Lyophilization/ Freeze-drying Technique
- Microwave irradiation method

Solubilization by surfactants

- Microemulsions
- Self-micro emulsifying drug delivery system

Drug dispersion in carriers

- Solid solutions
- Solid dispersions
- Fusion Process
- Solvent Method
- Fusion solvent method
- Spray drying
- L lyophilization (Spray Freeze Drying Method)
- Hot melt Extrusion
- Dropping Method
- pH adjustment
- Supercritical fluid process
- Liquisolid technique
- Polymeric alteration

Chemical Modifications

Salt formation

There are situations when instability issues make it impossible to define an API in its purest form. As a result, they change into polymorphs, solvates, co-crystals, salts, and hydrates. All of them have an impact on the drug's performance characteristics, including manufacturability, stability, bioavailability, and purification. It has been the practice for decades to increase the solubility of therapeutic candidates that are weakly soluble (weak acids and bases). Salts are created in solutions when a compound ionizes. It performs well in dose forms that are liquid, solid, or parenteral. Acid or basic medication converted to a more soluble salt. Theophylline, barbiturates, etc. Commercial progesterone is a water-insoluble steroid that comes in peanut oil.[15]

Co-crystallization:[16] Co-crystallization affects molecular interactions and may be used to improve medicinal characteristics.

A co-crystal is a "multi-component crystal formed between two chemicals that are solids at ambient conditions, with at least one component being an acceptable ion or molecule." (Source) Co-crystallization addresses the physiological, chemical, and physical shortcomings of an API. Co-solvency reduces interfacial tension, which increases the solubility of nonpolar solutes. The optimal co-crystal can be chosen by rational physicochemical research and analytical methods. Solvates and co-crystals are identical in all respects except for their physical state. A solvate is produced when two components are one liquid and the other solid when both constituents are solid, co-crystals are created. The two primary components of co-crystal (s) are the co-crystal former and pharmaceutical API.

Various methods for co-crystallization 1) Evaporation of solvents 2) Slurry Co Crystallization 3) Grinding 4) Solvent drop grinding (grinding modification) Five-times faster co-crystallization (17) 6) Hot extrusion melting 7) Crystallization of sons Crystal Characterization Method Specifications 1) Dissolvability 2) Wavelength

maximum 3) Stability 4) Internal dissolution 5. Bioavailability 6) Point of Melting 7) Melt (microscopy at the hot stage) 8) DSC, or scanning calorimetry Vibrational spectroscopy 10) XRD 9.

Co-solvency/Solvent Blending: It improves the solubility of poorly water-soluble drugs by lowering the interfacial tension between an aqueous solution and a hydrophobic solute. The drug is always liquid poorly soluble lipophilic or crystalline substances with high solubility in the solvent combination may be co-solvent candidates. It is used in parenteral dosage forms because of the low toxicity of different co-solvents and their capacity to solubilize nonpolar medicines. Co-solvents include glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol.[18]

Advantages of co-solvency/solvent Blending

Despite its high solubilization capacity for poorly soluble pharmaceuticals, the formulation, production, and evaluation of this medication are straightforward and quick, it can be combined with other techniques to improve the solubility of weakly soluble substances by using a variety of solubilization techniques and pH manipulation.

Disadvantages of co-solvency/solvent Blending

The solvent's tolerance and toxicity must be investigated concerning the specified concentration, Precipitation can happen when diluted with an aqueous medium, sometimes uncontrollably, The nature of precipitates can be either amorphous or crystalline, and they come in different sizes, A large number of the insoluble compounds are inappropriate as co-solvents, which makes them especially inappropriate for intravenous administration, As is true of all solubilized drugs, the chemical stability of the insoluble drug is reduced when compared to when it is in its crystalline form If the medications used are particularly insoluble in water and do not rapidly redissolve following precipitation from the co-solvent mixture, there may be a risk of embolism and other local adverse effects at the injection site.

Hydrotrophy solubilization phenomenon occurs when a significant amount of a second solute is added to an existing solute, increasing the solubilization of the original solute in aqueous solution. More precisely, complexation—which entails only a slight interaction between hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, or urea and poorly soluble medications—is more directly linked to the mechanism by which it improves solubility. Hydrotropic agents are made from ionic organic salts. Only a weak contact exists between the hydrotropic agent and the solute in hydrotropic solutions, which lack colloidal characteristics.[20]

Table 3: Classification of Hydrotropes.

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate.
Aromatic cationic	Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

Advantages of Hydrotrophy

It is proposed that hydrotrope is a better solubilization technique than other techniques including miscibility, micellar solubilization, cosolvency, and salting in because its solvent nature is pH-independent, highly selective, and emulsification-free, It just involves mixing the medication with the hydrotrope in water; it does not require the use of organic solvents, the development of an emulsion system, or the chemical modification of hydrophobic pharmaceuticals, The solvent character is independent of pH, and hydrography has great selectivity and does not require emulsification, Wide variety of compounds has been reported to exhibit hydrotropic behavior. Examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, and B b-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulfate) and dodecylated oxidibenzene.[19]

Mixed Hydrotropy:[21] It is a new, simple, cost-effective, safe, accurate, and precise method that involves the blends of hydrotropes which gives a synergistic effect on the solubility of poorly water-soluble drugs.

Advantages of mixed hydrotropic

By using a combination of agents at lower concentrations, it may be possible to lessen the large total concentration of hydrotropic agents required to produce a modest increase in solubility, the application of hydrotropic solubilizers to improve permeation, Application of hydrotropic solubilization in nanotechnology (by controlled precipitation).

Use of novel solubilizer*:* A variety of solubilizing agents can also increase the solubility of poorly soluble medications. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap[22], Soluplus[23] Povacoat, and dendrimers, improve the solubility of hydrophobic API.

***Sepitrap as a novel Solubilizer*:** in less than 5 minutes, 80% of solubilizers are desorbed from Sepitrap M (Microencapsulated solubilizer for solid dosage

application) and therefore is available to solubilize the drug substance. The ratio of spectral and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect tablet characteristics and can be used without any formulation constraints.[24]

Dendrimers[25] are recognized for their three-dimensional, monodispersed, highly branching, macromolecular nanoscopic architecture with several reactive end groups generated by reiterative reaction sequences. Dendrimers are static unimolecular micelles whose structure is stable at high solvent concentrations. Dendrimers' micelle-like behavior led to their use to solubilize hydrophobic medicines. Dendrimers increase hydrophobic contacts, hydrogen bonding, and electrostatic interactions between dendrimer terminal functional groups and hydrophobic groups. Polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers are the most frequent.

PAMAM dendrimers appear to be the most studied in solubilization. Brabander and Meijer discovered an important family of dendrimers called poly (propylene) imine dendrimers (PPI). They resemble PAMAM dendrimers (except repeating units).

Nanotechnology: Refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. Because the micronized product has a very small effective surface area for dissolution, oral bioavailability enhancement by micronization is insufficient for many new chemical entities with very low solubility, and nanonization was the next step taken.[26] It is possible to employ preparatory techniques like high-pressure homogenization, vacuum deposition, high-temperature evaporation, and milling.

Advantages of nanotechnology

It produces spherical particles that are nano- or micro-sized, have smooth surfaces, a narrow particle size distribution, and high specific surface areas. As a result, it increases the rate of dissolution and solubility.

Disadvantage of nanotechnology

The agglomeration problem is inherent and difficult to overcome.

PHYSICAL MODIFICATIONS

Particle size reduction The Solubility of the drug is often intrinsically related to drug particle size. As particle size becomes smaller, the surface area to volume ratio increases. Greater solubility results from greater interaction with the solvent made possible by a larger surface area. Drug particle size and bioavailability of poorly soluble medications are frequently correlated. Reducing particle size increases surface area, which enhances dissolution characteristics and opens up more formulation and delivery option options.[27,28]

Advantages of particle size reduction

It is a cost-effective, scalable, and effective method of improving solubility, In the case of chemical substances, increases the rate of solution because the solvent's action is enhanced by a reduction in particle size.

Disadvantages of particle size reduction

There is a considerable tendency for particle agglomeration due to the high surface charge on discrete tiny particles, the active compound may degrade as a result of mechanical or physical stress, and Thermo mechanical stress that develops during comminution can cause issues when processing thermosensitive agents.

It is theoretically difficult to create a solid dosage form with a high payload that prevents agglomeration and sterile intravenous formulation.

Conventional method of particle size reduction

The traditional method of reducing particle size involves several mechanisms, including cutting, compression, impact, attrition, and combined impact and attrition. The active component is broken down by mechanical stress in conventional particle size reduction techniques like comminution and spray drying. Thus, solubility improvement is now possible through an affordable, scalable, and effective method of particle size reduction. However, the drug product frequently experiences significant amounts of physical stress from the mechanical forces inherent in comminution, such as milling and grinding, which may cause degradation. Thermally sensitive or unstable active agents are processed with consideration for the potential for thermal stress during comminution and spray drying. Poorly soluble medications cannot have their solubility increased to a desirable level solely by employing conventional solubility enhancement techniques.

Micronization: This method of high energy particle size reduction can reduce coarse particles to smaller than 5 µ diameter particles. The development of a uniform dosage form requires a uniform and narrow particle size distribution, which is produced by micronization. Particle size decreases as micronization takes place, increasing surface area and solubility. The type of micronization technique used affects the properties of the drug substance that has been micronized, including shape, size distribution, agglomeration behavior, and powder flow. The methods most frequently used to produce micronized drug particles are mechanical mixing, spray drying, and supercritical fluid (SCF) technology. The Noyes- Whitney postulations state that one common way to increase the bioavailability of drugs with low water solubility is to administer the drug in micron size.

Techniques for Micronization

- Jet milling/fluid energy mill or micronized
- Rotor stator colloid mills
- Microprecipitation & micro crystallization

- Controlled crystallization
- Supercritical fluid technology
- Spray freezing into liquid.

Advantages of micronization
Gives uniform particles with an increase in surface area and narrow particle size distribution.

Disadvantages of micronization
The drug's crystal lattice may be disrupted by a high-energy process, which could lead to the final product having disordered or amorphous regions, these regions are unstable due to thermodynamics and can recrystallize when stored, especially in hot and humid conditions.

Nanosuspension
Drugs that are poorly soluble and insoluble in both water and oils are treated with this technology. Pharmaceutical nanosuspensions are biphasic systems that can be administered parenterally and pulmonaryly or orally. They are composed of nanoscale drug particles stabilized in an aqueous medium by surfactants. With an average particle size ranging between 200 and 600 nm, the solid particles in nanosuspensions typically have a particle size distribution of less than one micron.[29] Both top-down and bottom-up technologies can be used to create nanosuspension. A variety of techniques, including nanotechnology, nanojet technology, and nanocrystal milling technology, are used in top-down technology.

Advantages of nanosuspension
The drug's particle size is lowered in nanosuspension, increasing surface area and, ultimately, solubility, dissolution rate, and bioavailability, the process of nanosuspension increases permeability, and the duration of residence action and bio adhesion are increased by nanosuspension, High drug loading is a benefit of nanoformulation, Avoidance of organic solvent.

Disadvantages of nanosuspension
Suffers from problems of instability due to agglomeration, crystal growth, and Ostwald ripening.

MODIFICATION OF THE CRYSTAL HABIT

- Polymorphs
- Pseudopolymorphs

An element or compound that exhibits polymorphism can crystallize in multiple different forms. Despite having the same chemical makeup, different drug polymorphs have distinct physicochemical characteristics, such as solubility, melting point, density, texture, and stability. Similar to this, an amorphous drug is always preferable to a crystalline one because of the increased surface area and higher energy involved. Order for dissolution of different solid forms of drug Amorphous >Metastable polymorph >Stable polymorph.

Complexation: it is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry.[30]

Two types of complex
Stacking complexes*:* This is caused by the drug's non-polar area attaching to the complexing agent, which keeps the non-polar area from coming into contact with water. Stacking produces a distinct solution whether it is mixed or homogeneous.

Inclusion complexes*:* These forms when a nonpolar molecule or a portion of a molecule is inserted into the cavity of another molecule or collection of molecules. The common use of cyclodextrin and its derivatives in complexation.

Solid ternary complexes can be formed with
Carboxylic acid[31] - e.g. Citric acid, tartaric acid Water soluble polymer[32] Soluplus[23], Povacoat, Kollidon, Amino acid[33] Arginine, tryptophan, leucine, phenylalanine, methionine, and isoleucine Sugar alcohol[34] – Mannitol.

A ternary agent helps in the binding of drugs and with complexing agents. Most probably use of the acidic ternary compound in the case of a basic drug or vice versa that is use of a basic ternary compound with the acidic drug is done to form a solid ternary complex. Water soluble polymer may be used in specific concentrations for example 0.5% or 1% by preparing its aqueous solution. Drug, B-CD, and amino acids such as L- Lysine and Arginine ternary complexes may be prepared at 1:1:2 molar ratios, weight ratios, or another suitable ratio.

Physical mixture**:** To achieve the required particle size in the finished product, the CDs or appropriate polymer and drug are thoroughly mixed by trituration in a mortar and then passed through an appropriate sieve. It's an easy trituration technique.

Kneading method*:* CDs or other appropriate polymers are soaked in water or hydroalcoholic solutions to form a paste. Next, the medication is added and mixed for a while. The dough is kneaded, dried, and sieved.

Co-precipitate method*:* The right amount of medication is added to the CDs or polymer solution. Magnetic stirring of the mixture under regulated circumstances. The whole complex is in the dark. To stop the inclusion complex structure water from escaping, the precipitate is vacuum-filtered and then dried at room temperature. This process is very industrialized.

INCLUSION COMPLEX FORMULATION BASED TECHNIQUES
Inserting guest molecules or nonpolar areas into holes of other molecules (known as inclusion complexes) (known as a host). Cyclodextrins are hosts. The host cavity must

be big enough for visitors but small enough to drain water. Included in the preparation are kneading, co-precipitation, neutralization, and co-grinding.[35]

Kneading method: Discussed in complexation.

Lyophilization/Freeze-Drying Technique*:* The solvent system can be eliminated from the solution without endangering the sample by first freezing and then drying the mixture. The lyophilization process depends on the special qualities of water as a plasticizer, stabilizer, solvent, gas, and more. The drug and carrier are molecularly combined in a shared solvent as opposed to being evaporated.

Microwave Irradiation Method

Incorporates the use of a microwave oven to irradiate a drug and complexing agent. A solution of water and organic solvent in a predetermined ratio dissolves the medication and CD in a round-bottom flask. In the microwave oven, the mixture reacts for a brief period—one to two minutes—at 60 °C. A sufficient amount of solvent mixture is added to the reaction mixture above once the reaction is finished to eliminate any remaining, uncomplexed free drug and CD. Whatman filter paper is used to separate the precipitate, and it is then dried in a vacuum oven at 40 °C for 48 hours.

Solubilization by surfactants

Both polar and nonpolar substances are surfactants. They have a polar group joined to a hydrocarbon segment. These polar groups can all be either cationic or anionic. In the hydrophobic center of the micelle, small polar molecules can gather. Both natural and industrial processes depend on this process. Surfactants facilitate lipophilic drug dissolution in aqueous media, thereby lowering surface tension and increasing drug solubility. Moreover, surfactants stabilize drug suspensions. Micelle formation occurs at low concentrations (0.05-0.10 percent for most surfactants) when surfactant concentration surpasses critical micelle concentration (CMC), encasing pharmaceuticals within micelles. Micellarization is the process that makes poorly soluble drugs more soluble.

Microemulsion

In an optically clear pre-concentrate, a hydrophilic surfactant and a hydrophilic solvent dissolve a poorly water-soluble medication. The surfactant needs to be non-toxic and HLB. It produces a transparent emulsion of uniformly sized, tiny oil droplets that contain the medication that has been solubilized but is poorly soluble. Many medications that are nearly insoluble in water have been made more soluble by using micro-emulsions. A microemulsion of oil in water, known as the best formulation, is used to increase solubility by dissolving molecules with low water solubility into an oil phase. Consequently, surfactant-induced permeability modifications have the potential to enhance oral bioavailability.[14]

Drug dispersion in carriers[36]

A blend of two crystalline solids that results in a new crystalline solid is called a solid solution. Because the two components crystallize together in a homogenous one-phase system, a mixed crystal is created. Therefore, compared to basic eutectic systems, it is anticipated to produce much higher rates of dissolution. When a drug precipitates in an inert carrier in an amorphous form, this is known as amorphous precipitation. Compared to the corresponding crystalline forms of the drug, the higher energy state of the drug in this system typically results in much higher dissolution rates.

Applications of solid dispersions: Such a technique may be used.[37]

Obtaining a homogenous dispersion of a minute amount of medicine in a solid state is the goal of this procedure.

- To keep the medication from becoming unstable.
- The ability to administer liquids (up to 10% of the total volume) or gaseous substances in a solid dose.
- To create a fast-acting main dose in a sustained-release dosage form for administration
- To minimize the amount of time that medications such as morphine and progesterone are inactive before they enter the system.
- To incorporate poorly soluble or insoluble carriers into an extended-release schedule for soluble drugs.
- To combine polymorphs in a given system to create isomorphous solids.

Advantages of solid dispersion[38]

It has a high rate of dissolution and is easy to use, Boost the absorption rate of prescription drugs, Improves a pharmaceutical formulation's poorly water-soluble medication's water solubility, Heat the medication to cause its crystalline structure to become amorphous, Prepares rapid disintegration oral tablets, Mask the taste of the drug substance, Avoid degradation or decomposition of drugs. Transformation of the liquid form of the drug into a solid form (Ex. Clofibrate and Benzoyl benzoate can be incorporated into PEG-6000 to give a solid.), Avoidance of polymorphic changes and thereby bioavailability problems.

Disadvantages of solid dispersion[38]

The instability of a solid mixture Deterioration of solid dispersion as a result of moisture and temperature; shows signs of crystallinity and a slowdown in disintegration rate with aging.

Limitations of solid dispersion system

• The behavior of solid dispersion is unpredictable because material properties are unknown.

• During processing (mechanical stress) or storage (stress from temperature and humidity), the amorphous state may crystallize.

• The majority of polymers used in solid dispersions absorb moisture, causing crystal formation, phase separation, or conversion from amorphous to crystalline

state during storage, reducing solubility and dissolution rate.

• Moisture can affect the storage stability of amorphous medicines by increasing drug mobility and crystallization.

METHODS OF PREPARING SOLID DISPERSIONS

Fusion Process[39]

The drug is mixed into the matrix by heating the carrier to a temperature slightly above its melting point. The mixture is continuously stirred while it cools to ensure that the drug is evenly distributed throughout the matrix. The solubilizing effect provided by the carrier itself, enhanced wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form with modified thermodynamic properties are additional factors that might be involved.

Solvent Method

An organic solvent is used to dissolve them. High temperatures cause this solvent to evaporate. Supersaturation happens after the solvent is removed, and the contents then precipitate. After that, the co-precipitate is vacuum-dried to get rid of any solvent that might still be on the particle. The solvent needs to be eliminated. Total solvent elimination can be demonstrated by highly sensitive methods such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), and differential thermal analysis (DTA).[40]

Fusion-Solvent Method

Carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. The method is useful for drugs with high melting points or that are thermolabile.

Spray Drying

After being dissolved in an appropriate solvent, the carrier and the active ingredient are suspended. The solvent is removed by drying it and then applying a heated air stream to evaporate the solvent. The droplets' large surface area causes the solvent to evaporate quickly, forming solid dispersion quickly.

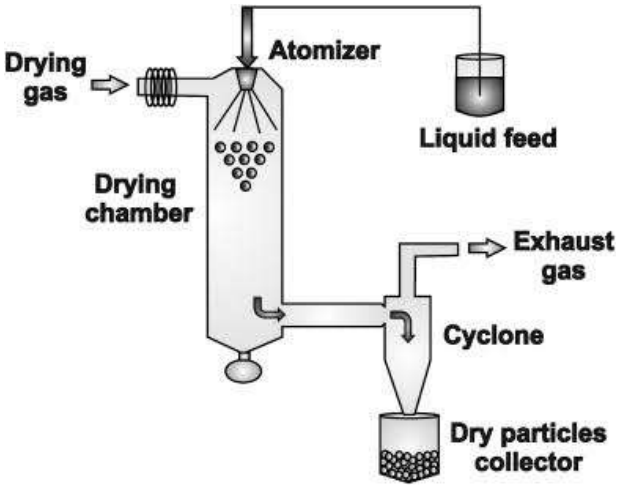


Figure 1: Spray Drying Process.

Lyophilization (Spray Freeze Drying Method)

The polymer industry has made this decision. But Huttenrach and Disperse were the ones who employed this technique with drugs. The following are the sections of melt extrusion: heating and combining the feed ingredients in a barrel, with an optional die to create the extruding mass, and an exit outlet. The carrier and active components are fed by the heated extruder barrel.

The "fluid-like state" is created by heating the screws that carry the active component. Extruder screw shear allows for close and homogeneous mixing. A die shapes the melt into granules, pellets, films, or powder. Hot melt extrusion heats the drug/carrier mix for roughly a minute, allowing the processing of thermolabile medicines.[41]

Hot-melt Extrusion

The polymer industry prefers this technology. However, it was Speiser and Huttenrach that used this technology for pharmacological purposes. Sections of a melt extrusion include a heated barrel with extruder screws to convey and mix the fed materials, and an exit outlet with an optional die to shape the extruding mass. The active components and carrier are fed continuously into the heated extruder barrel. The "fluid-like state" is achieved by conveying the active component and carrier through heated screws. The strong shear of extruder screws facilitates close and homogenous mixing. An optional die molds the melt into granules, pellets, films, or powder. The drug/carrier mix is only heated for about a minute in hot melt extrusion, which allows the processing of thermolabile drugs.[41]

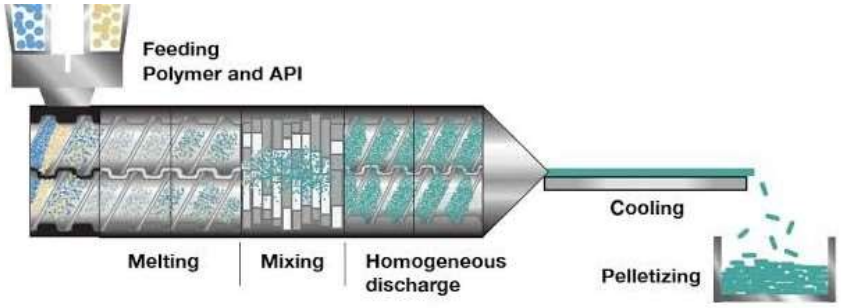


Figure 2: Hot Melt Extrusion Process.

Dropping Method

The drug-carrier mixture is resolidified and then pipetted into a solid dispersion, where it solidifies into spherical particles. The viscosity of the melt and the pipette size have an impact on the size and shape of the particles. The melt must solidify spherically when dropped onto the plate because viscosity is highly temperature-dependent.[43]

PH ADJUSTMENT

By changing the ph., medications that are not very water-soluble can become soluble. When trying to access solubility in this way, consideration must be given to the buffer capacity and tolerability of the selected pH. Thus, solubilized excipients raising pH inside the dosage form to a range greater than or equal to pKa may increase the solubility of weekly basic drugs, while alkalizing excipients may improve the solubility of weekly acidic medications.[42]

Advantages of pH adjustment

Easy to formulate and evaluate, Makes use of small amounts of the compound, making it suitable for high throughput analyses.

Disadvantages of pH adjustment

The possibility of precipitation when diluted with aqueous media that have a pH lower than that of the compound's solubility. When taken orally, this may cause variability, and intravenously, emboli may result, It is important to take into account the tolerance and systemic and local toxicity associated with using an extreme pH and non-physiological pH, A dissolved drug in an aqueous environment is often less stable chemically than formulations that are crystalline solid, as is the case with all solubilized and dissolved systems. The chosen pH could catalyze additional degradation processes or speed up hydrolysis.

SUPERCRITICAL FLUID PROCESS

Supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide. It is safe, environmentally friendly, and economical. A SCF exists as a single phase above its critical temperature and pressure. SCFs have properties useful to product processing because they are intermediate between pure liquid and gas. Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Unique processing capabilities of SCFs, long recognized and applied in the food industry have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents are carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvents processes (SAS).[43]

Advantages of supercritical fluid process

SCFs are appealing for pharmaceutical research because of their low operating temperatures and pressures, the drug particles may be recrystallized at significantly smaller particle sizes after becoming dissolved in SCF. Particles with a diameter of up to 2,000 nm can be created in nanosuspensions using current SCF processes, Because of the accuracy and flexibility provided by SCF processes, drug particles can be micronized within identical specific particle size ranges, frequently down to sub-micron levels.

LIQUISOLID METHODS

Liquids are absorbed and adsorbed by carrier materials with porous surfaces, such as cellulose. This indicates that the liquid is first taken up by the inside of the particles, where it becomes saturated before being released onto the outside. This procedure takes place both before and following the drug's dissolution in liquid. Because of the coating material's high adsorptive capacity and large specific surface area, the liquisolid system gains the required flow properties once it is added. Coating materials consist of crystalline and amorphous silica powders and cellulose.[43]

Advantages of Liquisolid Methods

Offers compressible and reasonably flowing powdered versions of liquid medications, The method is useful in industry and enhances the bioavailability and solubility of water-insoluble substances when taken orally, Useful for the formulation of oily drugs/liquid drugs, Drug release can be modified by using different carrier and additives like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit, etc., Several poorly soluble drugs can be formulated into the system, This system is specifically for the powdered liquid medications, the Production cost is low compared to that of preparation of soft gelatin capsules.

Disadvantages of the liquisolid method

Recipients with high specific surface area and adsorption capabilities are needed, It does not apply to insoluble drugs at high doses (>100 mg).

POLYMERIC ALTERATION

Polymorphs are unique crystalline forms of a drug with different properties. Numerous polymorphs exist, each with a different set of physicochemical characteristics, including melting point, vapor pressure, shelf life, dissolution rate, morphology, and density. Bioavailability. In comparison to stable, unstable, and unstable polymorphs, metastable crystalline polymorphs have greater energy, surface area, solubility, bioavailability, and efficacy. Throughout their shelf life, medications should change from crystal to metastable or amorphous forms to optimize bioavailability.

Table 4: Example of Latest Research on Solubility Enhancement Techniques.

Drug	Dosage form	Indication	Reference
Fenofibrate	Tablet	Hypercholesterolemia	[44]
Carvedilol	Tablet	Heart Failure	[45]
Ritonavir	Tablet	Antiretroviral	[46]
Nimodipine	Powder	Calcium Channel Blocker	[47]
Aprepitant	Powder	Prevent Nausea And Vomiting In Cancer Patients.	[48]
Paclitaxel	Powder	Treatment For Various Types Of Cancer.	[49]
Amlodipine Besylate	Powder	Treat High Blood Pressure.	[50]
Ibuprofen	Powder	Non-Steroidal Anti-Inflammatory	[51]

CONCLUSION

One of the most crucial things to take into account is the solubility of medications taken orally since it is one of the rate-limiting parameters in reaching the required concentration in systemic circulation for pharmacological response. The solubility issue is a major challenge for formulation scientists to solve. To improve the oral bioavailability of hydrophobic medications, it is possible to effectively implement the strategies discussed in this review, either separately or in combination. However, the method employed will largely determine how effective the improvement is. Of all the available solubility techniques, Nanosuspension, Super Critical Fluid, Cryogenic, and Inclusion Complex Formation are the most promising for use in addressing the solubility issues of hydrophobic pharmaceuticals.

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