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"A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES"

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Abstract

Enhancing drug solubility is critical for effective medication delivery. Techniques like particle size reduction, nanonization, cosolvency, hydrotropy, pH adjustment, supercritical fluid processing, solid dispersion, and liquisolid methods are used to overcome poor solubility issues. These methods improve drug dissolution and bioavailability,addressing a common challenge in pharmaceutical development.

Keywords

Solubility, Dissolution, Oral absorption, Solubility enhancement, Drug formulation, Solid dispersion, Solubility equilibrium, USP and BP expressions for solubility

Introduction

Solubility represents a substance's ability to dissolve in a specific solvent. When quantified, it signifies the concentration of solute in a saturated solution at a given temperature. In more qualitative terms, it refers to the ongoing interaction between multiple compounds, leading to a single-phase, transparent, and uniformly dispersed molecular mixture. Solubility is gauged by determining the highest quantity of solute that can dissolve in a solvent at equilibrium, resulting in what is known as a saturated solution.[1]

Solubility is a vital factor in getting the right amount of a drug into your body for it to work. When certain fat-loving drugs don't dissolve well in water, it causes issues when making medications and taking them by mouth. Scientists have come up with different ways to make these drugs dissolve better in water. To make poorly soluble drugs dissolve better, we use various methods like breaking them into tiny particles, changing their chemical structure, adjusting the pH, mixing them with other substances, forming complexes, using special solvents, and more. This is a common challenge when studying new drugs and when designing and making medications.[2]

For a drug to work in your body, its ability to dissolve and pass through is crucial. We can change or improve this using various techniques. Solubility means the maximum amount of a substance that can dissolve in a certain amount of liquid at a specific temperature and pressure. It can be described both in numbers and how well things mix together. In pharmaceuticals, we measure solubility in various ways like molarity, normality, and others when we have precise data.[3]

To make sure a drug is effective, we need to know how well it dissolves, what it does in a solution, and how easily it can get into your body when you take it by mouth. When you swallow a drug, it's important for it to dissolve quickly so it can be absorbed properly. This process of dissolving is called "solubility," and it's crucial when time is a factor in getting the drug into your system.[4-6]

Solid dispersion (SD) is a method often used to make drugs that don't dissolve well in water work better. It involves mixing at least two different things: a part that likes water and a part that doesn't, which could be a drug. This mixture can be either structured or not structured. Solid dispersion was first used to make drugs that love fats more available by mixing them with things that like water. About 40% of new drugs with great effects are hard to dissolve, which makes it tough to create medications from them.[7-8]

Solubility equilibrium happens when two actions are happening at a steady rate. At the equilibrium point, you can sometimes have more dissolved than the usual amount in a solution, called a "supersaturated" solution, but it's not very stable. Solubility isn't the same as the ability to dissolve a substance because it can involve not just dissolving but also chemical reactions. For example, zinc doesn't typically dissolve in hydrochloric acid, but it reacts with it to form zinc chloride and hydrogen, and zinc chloride can dissolve in hydrochloric acid because of this chemical reaction.[9]

Table No 1: USP and BP Expression for Approximate solubility[9]

Descriptive terms	Approximate volume of solvent in milli litre per gram of solute
Very Soluble	Less than 1
Freely Soluble	From 1-10
Soluble	From 10-30
Sparingly Soluble	From 30-100
Slightly Soluble	From 100-1000
Very Slightly Soluble	From 1000-10000
Insoluble	Greater than 10000

Solubility is described in many ways, and these descriptions often involve concentration measurements. It can be expressed as the amount of substance in relation to the amount of liquid, like grams of solute per kilogram of solvent or grams in 100 milliliters of solvent. Other methods include molarity, molality, mole fraction, and similar ways to show how much is dissolved.[9] (9)

Possible Causes for Poor Oral Absorption[10]

A drug is considered to have low solubility when it:

1. Doesn't dissolve well in water (less than 100 micrograms per milliliter.

2. Dissolves very slowly (less than 0.1 milligrams per square centimeter per minute.

3. Has a high molecular weight (more than 500) and tends to stick together.

4. Has a lot of energy in its crystal form, making it hard to dissolve.

Process of solubilization[11]

Step 1. To make something dissolve, you need to break the bonds between the particles in the substance you want to dissolve, make room in the liquid for the substance, and get the liquid and the substance to interact.

Step 2. The substance's particles separate from the big group of them.

Step 3. The particles of the substance fit into the spaces in the liquid.

Biopharmaceutics Classification System (BCS)[12-14]

The Biopharmaceutics Classification System (BCS) is a scientific way of sorting medicines based on how well they dissolve in water and how easily they pass through the intestines. When we also look at how these medicines dissolve in tests, we can understand three important things: how well they dissolve, how they move through the intestines, and how fast they dissolve. All of these factors affect how quickly and how much of the medicine your body can absorb when you take it in the form of a regular pill. According to the BCS, which was established by the US Food & Drug Administration (FDA), medicines are divided into four main groups based on how well they dissolve and how they move in the intestines. Medicines in class II and class IV often have trouble with dissolving, and making them dissolve better can improve how much of the medicine your body can use.

Table No 2: The Biopharmaceutics Classification System for drugs

Class	Solubility	Permeability	Absorption pattern	Rate limitingstep in the absorption	Example
I	High	High	Well absorbed	Well absorbed	Diltiazam
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeabilit	Insulin
IV	Low	Low	Poorly absorbed	Case by case	Taxol

Making medicines from drugs that don't dissolve well is often a big problem for the experts who create them. The usual methods, like using certain substances, breaking the drug into tiny particles, adjusting the pH, or using heat, don't always work very well.[15]

Importance of solubility enhancement

In simpler terms, oral ingestion (taking drugs by mouth) is the most common and convenient way to administer medications. It's widely used because it's easy for patients to do, cost-effective, doesn't require strict sterility, and allows flexibility in designing the drug's form. Many drug companies prefer making oral medications that work the same as the original. However, the solubility of a drug is a key factor in getting it into the bloodstream for the desired effect. Drugs that don't dissolve well in water often need higher doses. Water is commonly used as a solvent in liquid medicines. Drugs with poor water solubility can lead to slow absorption, resulting in inconsistent effects and possible side effects on the gastrointestinal system. So, improving a drug's solubility is a big challenge for chemists.[16]

Certainly! In simpler terms, the ability of a drug to dissolve in water is really important in making different types of medicines, like those you take by mouth or inject. If a drug doesn't dissolve well in water, you might need to take more of it to make it work in your body. This is a big problem when creating new medicines and working with genetic materials. When we make liquid medicines, water is a great choice because it can dissolve many different things. However, most medicines don't dissolve easily in water and can be a bit acidic or basic.[17-19]

Process of solubilization

Solubilization means making something dissolve in a liquid. It happens by breaking the bonds between the particles of the thing you want to dissolve and making space for it in the liquid. This process also involves the interactions between the particles of the substance you're trying to dissolve and the liquid itself.[20]

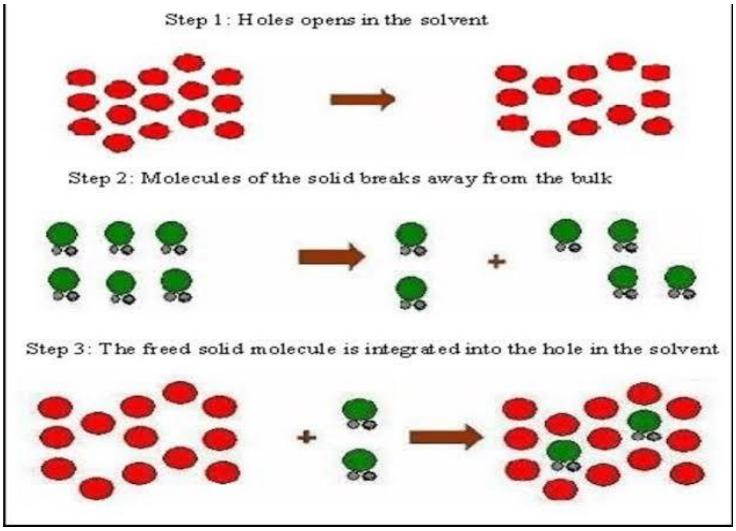
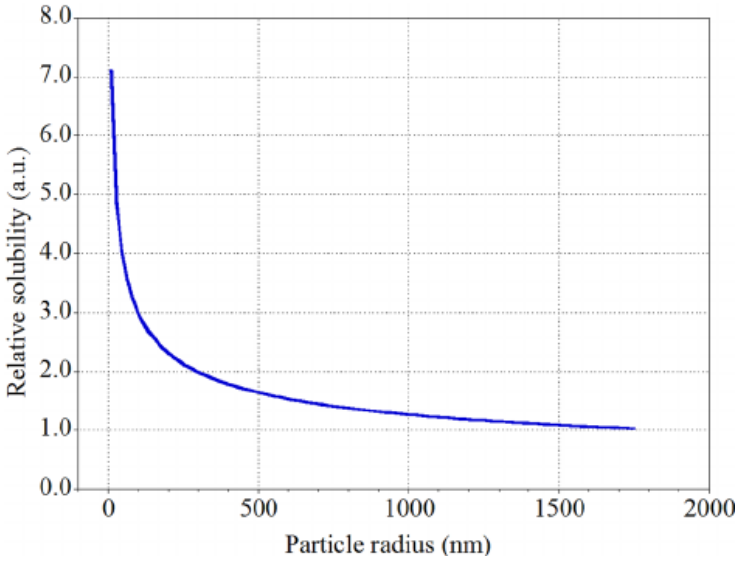


Fig 1:- process of Solubilization Factor affecting solubility

Factor affecting solubility enhancement

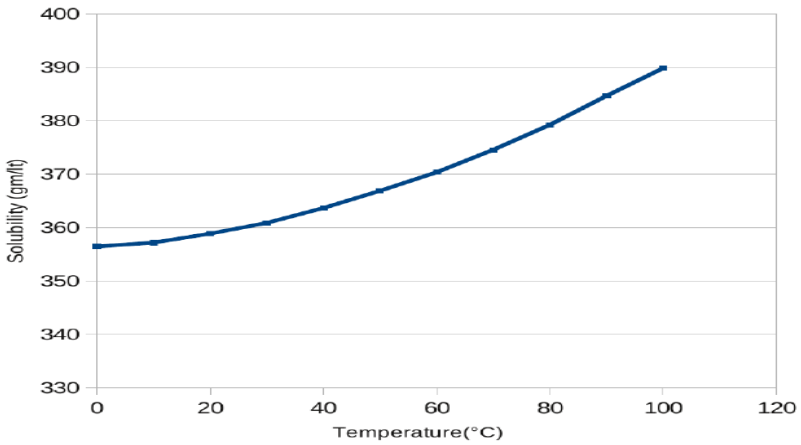
1. Particle size
2. Temperature
3. Molecular size
4. Pressure
5. Polarity
6. Solubilizing agent
7. pH

1. **Particle size -** When you make particles smaller, they have more surface relative to their size, which means they can interact with the liquid better. You can see this on a graph that shows how particle size affects solubility (like one by Alfred Martin in 1991). When particles are in contact with the liquid, their surface area affects how quickly they dissolve, but this only works when everything else like temperature and stirring is the same. If you make particles bigger, the rate at which they dissolve goes down. This change happens during the process of dissolving.[21]



Graph 1: Effect of particle size on solubility

2. **Temperature -** When you heat a substance, it gives its molecules more energy, making them spread out a bit. So, it dissolves better in a liquid, and its solubility goes up. You can see this on a graph that shows how temperature affects solubility. But when you cool things down, the molecules get closer together, and there's less space for them to mix with the liquid. So, solubility decreases with lower temperatures.[22]



Graph 2: Effect of solubility on temperature

3. **Molecular size -** when a substance has larger and heavier molecules, it's harder for them to mix with the liquid they are in the solvent. Think of it like trying to fit big puzzle pieces into a small puzzle. For example, at room temperature, you can only dissolve a tiny bit of lead (II) chloride in 100 grams of water, but you can dissolve more, like 200 grams of zinc chloride. So, it's about how big the molecules are and what they're made of that affects how much of a substance can dissolve in a given amount of liquid at a certain temperature.[23]
4. **Pressure -** Henry's Law states that the solubility of a gas in a liquid is directly related to the pressure of the gas above the liquid. When you increase the pressure, more gas dissolves into the liquid because the gas molecules are forced into it, reducing the space between them and making the gas more soluble. This is why carbonated beverages are bottled under pressure, which increases the solubility of carbon dioxide. When you open the bottle, the pressure decreases, causing the carbon dioxide to come out of the liquid as bubbles. This is why the drink becomes "fizzy" when you open it.[24]

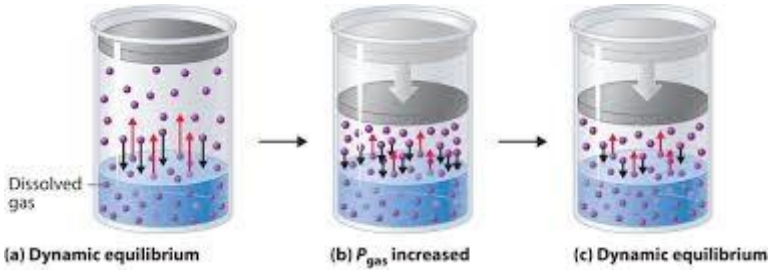


Fig 2: The solubility of gas in liquid can be increased by increasing pressure

5. **Polarity** - That's right, when it comes to dissolving things, it's all about being similar. Things that are alike in terms of polarity mix well together. So, nonpolar stuff dissolves better in nonpolar liquids, while polar and ionic substances dissolve better in polar liquids. This is why you often hear "like dissolves like.[25]

6. **Solubilizing agent** -Some substances can clump together in a liquid when their concentration is high enough. In water, these clumps act a bit like a separate oil-like phase, and they can "grab" organic substances, making them seem more soluble in water than they actually are. This is called solubilization. A similar thing happens in organic liquids with similar clumping agents, where the clumps have a more water-friendly center. If something water-friendly gets into these centers, it appears to dissolve better in the organic liquid.[26]

7. **pH** - A drug that doesn't dissolve well in water might become soluble if you change the pH of the water. To do this, you need to think about two things: the ability of the liquid to resist pH changes (buffer capacity) and making sure the pH change won't harm the drug. Some ingredients can raise the pH, making it more basic, which can help poorly soluble acidic drugs dissolve better. Other ingredients can make the liquid more alkaline, which can improve the solubility of weakly basic drugs.[27]

Solubility enhancement technique

1. Particle Size Reduction
2. Nanonization
3. Cosolvency
4. Hydrotrophy
5. pH Adjustment
6. Supercritical Fluid (SCF) Process
7. Solid Dispersion
8. Inclusion Complexation
9. Liquisolid Methods

1. Particle Size Reduction

Bioavailability is intrinsically linked to drug particle size. Reducing the particle size increases the surface area, thereby enhancing dissolution properties. Particle size reduction is typically achieved through various milling techniques, such as jet mills and rotor-stator colloid mills. However, it's important to note that this method may not be suitable for drugs with high dosages, as it doesn't alter the drug's saturation solubility.Nowadays Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different types of equipment for the reduction of the particle size. In micronization, the solubility of the drug is often intrinsically related to drug particle size. [28-29]

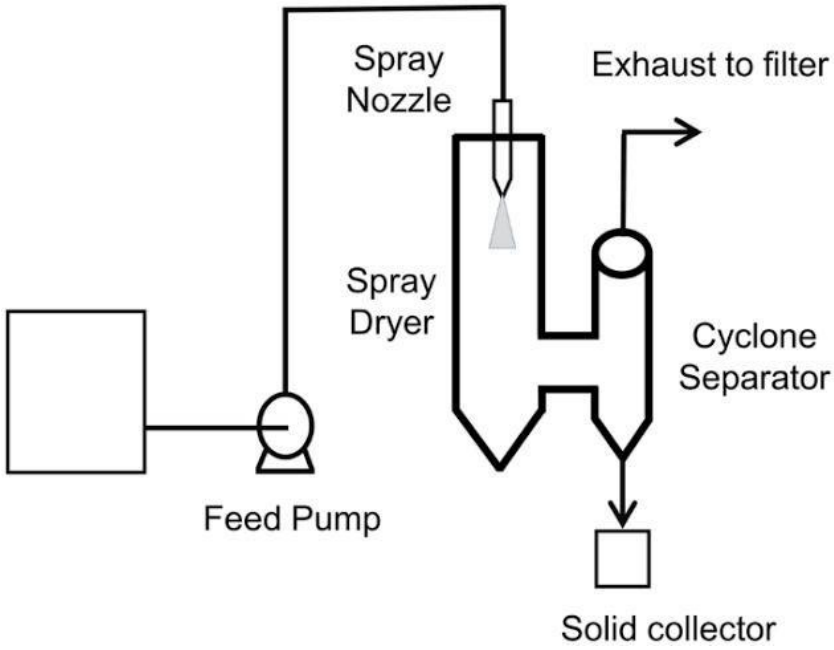


Fig 3 : partical size reduction process

Advantages

1. Liquid formulations can be rapidly developed for early-stage testing (pre-clinical) and later converted into solid forms for clinical development.
2. Typically, a low excipient-to-drug ratio is necessary.
3. Formulations are generally well-tolerated as long as potent surfactants are not needed for stabilization.
4. In general, crystal forms exhibit greater chemical and physical stability compared to amorphous particles.

Disadvantages

1. The strong tendency for particle agglomeration is a result of the high surface charge on small discrete particles.
2. From a technical standpoint, creating sterile intravenous formulations presents even greater challenges.

2. Nanonization[30]

The poor water solubility of numerous drugs presents a significant challenge in the development of potent pharmaceuticals. Approximately 40% of potential new drugs identified by pharmaceutical companies face this issue, impeding their clinical progress. This low water solubility limits their bioavailability and absorption. In recent times, several nanonization strategies have emerged to increase the dissolution rates and bioavailability of poorly water-soluble drugs. These strategies involve enhancing the surface area-to-volume ratios of drug powders, altering crystalline forms, and designing innovative nanomaterials for controlled release. Nanonization can lead to improved drug solubility, pharmacokinetics, and potentially reduced systemic side effects. Nanonization of hydrophobic drugs can be achieved by producing drug nanocrystals through chemical precipitation or disintegration. Alternatively, nanotechnology-based drug delivery systems like nanoemulsions and polymeric micelles can be employed. Over the past decade, various drug nanoformulations have gained clinical approval or are under clinical investigation. Extensive research has focused on developing enabling nanoformulation technologies, innovative pharmaceutical materials, and quality control to enhance product properties while reducing production costs. Ongoing technological advancements and unmet clinical needs drive the research and development of nanonization strategies.

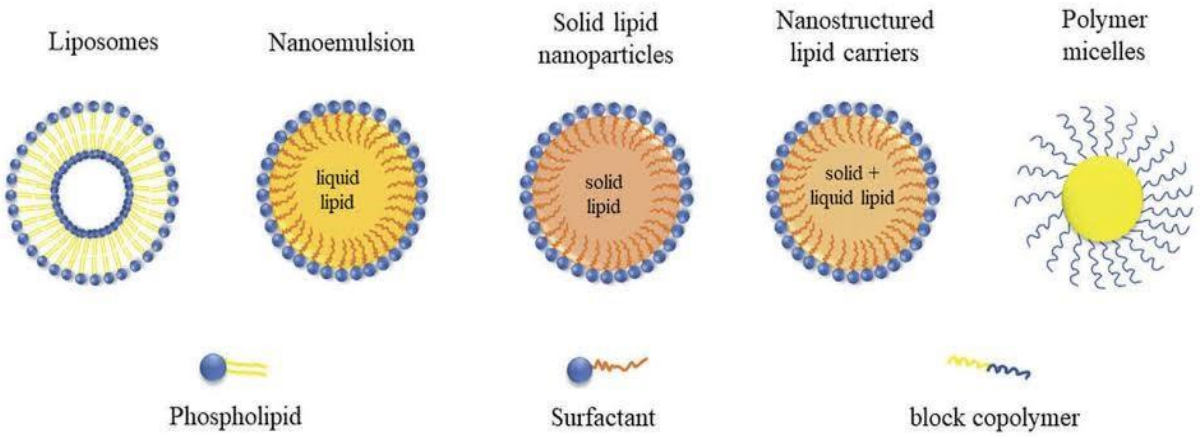


Fig 4 : nanonization process

Advantages	Disadvantages
Increased solubility of highly lipophilic drugs	Lack of proper knowledge about the effect of nanoparticles on bio-chemical pathways and processes in human body
Tunable physical and chemical properties	Unpredictable genotoxicity due to insufficient toxicological assess-ment studies
Targeted drug delivery	Carcinogenesis
Drug release in a sustained and controllable manner	Elimination and metabolism vary with different types of materials used in nanoparticle synthesis
Good biocompatibil-ity, bioavailability, and biodegradability	More expensive
Decreased toxicity or side effects of drugs	Short shelf life

Table No 3: Table advantages & disadvantages of nanonization [31]

3. Cosolvency[32]

The process you described, known as co-solvency, is a method to increase the solubility of poorly soluble drugs in water by mixing them with water-miscible solvents. Co-solvent systems work by reducing the interfacial tension between the drug and the aqueous solution, primarily by interfering with the hydrogen bonding network of water.These co-solvents, such as Dimethyl sulfoxide (DMSO) and dimethyl acetoamide (DMA), are chosen for their ability to solubilize poorly soluble drugs. However, it's important to consider the toxicity and tolerability of these solvents when formulating such solutions.Co-solvent formulations are advantageous for their simplicity and rapid formulation, but disadvantages include potential toxicity concerns and the possibility of uncontrolled precipitation when diluted with aqueous media. Proper consideration of these factors is crucial in the development of co-solvent-based drug formulations.

4. Hydrotropy[33]

Hydrotropy is a phenomenon in which the addition of a significant amount of a second solute increases the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions, including sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate, have been observed to enhance the aqueous solubilities of various poorly water-soluble compounds.

Advantages[34]

1. It eliminates the need for organic solvents, thus avoiding issues like residual toxicity, volatility-related errors, pollution, and cost concerns.
2. The process simply involves mixing the drug with a hydrotrope in water.
3. Hydrotropy is considered superior to other solubilization methods, such as miscibility, micellar solubilization, co-solvency, and salting in, because it is pH-independent, highly selective, and doesn't require emulsification.

Disadvantages[34]

1. Excessive use of hydrotropic agents can lead to concerns regarding toxicity.
2. The need for relatively high concentrations to reach the Maximum Hydrotropic Concentration (MHC) limits the practical use of hydrotropes in commercial applications.
3. Weak interactions between hydrotropic agents and drugs can occur.
4. Since water is used as a solvent, complete removal of water may not be achievable.

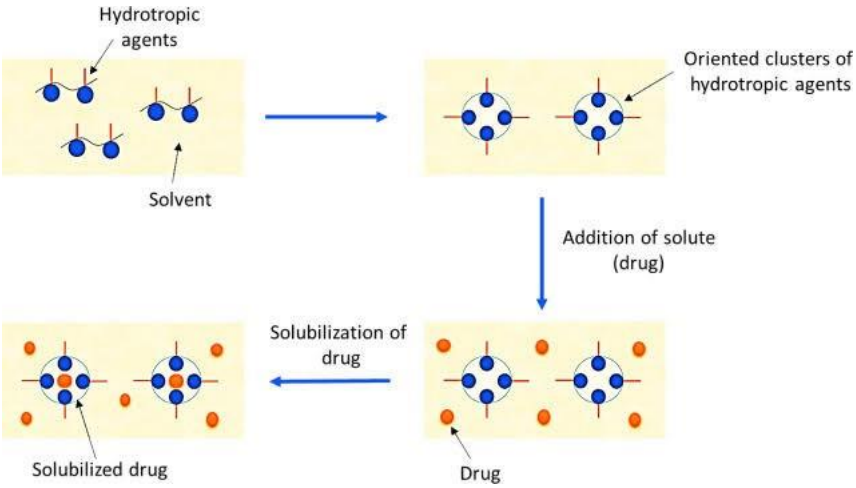


Fig 5 : hydrotrophy process

5. pH Adjustment[35]

A drug with low water solubility can potentially become soluble in water by adjusting the pH. When employing this approach to enhance solubility, it's crucial to consider the buffer capacity and tolerance of the selected pH.Furthermore, excipients that elevate the pH within the dosage form beyond the pKa of weakly acidic pharmaceuticals can boost drug solubility, while excipients functioning as alkalizing agents may enhance the solubility of weakly basic drugs. This method is applicable to both crystalline and lipophilic poorly soluble substances.

Advantages [36]

1. Both the formulation and analysis processes are straightforward.
2. Additionally, minimal quantities of chemicals are employed, rendering it suitable for high-throughput testing.

Disadvantages[37]

1. Tolerance and toxicity (both local and systemic) associated with non-physiological pH and extreme pH.
2. When diluted in aqueous fluid with a pH lower than the compound's solubility, there is a chance of precipitation. This can create emboli intravenously, and it can also cause variability when taken orally.

6. Supercritical Fluid (SCF) Process[38-39]

At its critical point, carbon dioxide becomes a supercritical fluid (SCF) that can dissolve non-volatile solvents. When operated above its critical temperature and pressure, an SCF exists as a single phase, offering a safe, environmentally friendly, and cost-effective solution. SCFs are particularly attractive in pharmacological research due to their low operating conditions in terms of temperature and pressure. They possess qualities that are advantageous for various product processing applications, bridging the gap between pure liquid and pure gas states.Furthermore, in the vicinity of the critical points, slight variations in operating temperature, pressure, or both can significantly impact properties such as density, viscosity, diffusivity, dielectric constant, and polarity. Common supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water.Various methods have been developed to address specific challenges in SCF processing, such as Precipitation with Compressed Antisolvents (PCA), Gas Antisolvent Recrystallization, Rapid Expansion of Supercritical Solutions, Precipitation with Impregnation of polymers with bioactive materials, Solution Enhanced Dispersion by Supercritical Fluid (SEDS), Compressed Fluid Antisolvent, and aerosol-based SCF processing.

Advantages[39]

1. Once drug particles are solubilized in supercritical fluids (SCF), they can be recrystallized into significantly smaller particle sizes.
2. Current SCF techniques have demonstrated the capability to generate nano suspensions with particle diameters ranging from 5 to 2,000 nanometers.
3. 3.Supercritical fluids are of particular interest in pharmacological research due to their ability to operate under low temperature and pressure conditions.
4. 4.SCF methods offer the flexibility and precision to micronize drug particles within specific size ranges, typically achieving sub-micron levels.

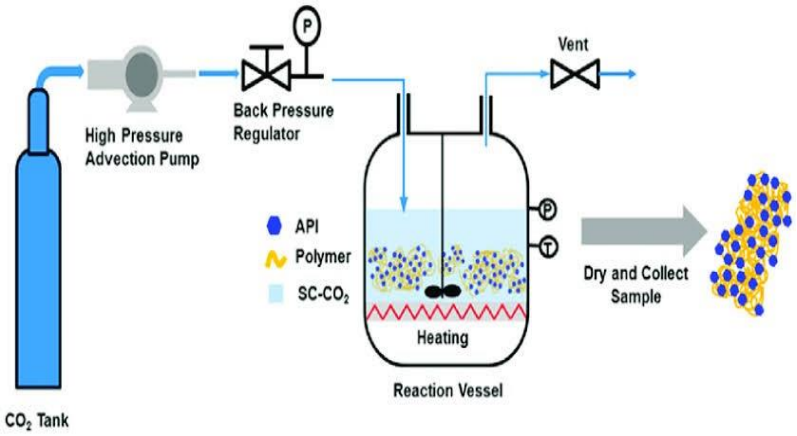


Fig 6 : supercritical fluid process

7. Solid dispersion[40]

A solid solution is a combination of two crystalline solids that results in the formation of a new crystalline solid. This mixed crystal is created when both components crystallize together within a homogeneous, single-phase system. Consequently, it is anticipated to exhibit significantly enhanced dissolution rates compared to simple eutectic systems. Amorphous precipitation, on the other hand, occurs when a drug precipitates in an amorphous form within an inert carrier. The higher energy state of the drug in this setup generally leads to much faster dissolution rates compared to the corresponding crystalline forms of the drug.

Advantages[41]

1. Accelerated drug absorption rates.
2. Improved water solubility of poorly water-soluble pharmaceuticals.
3. Transformation of the drug's crystalline structure into an amorphous form.
4. Creation of fast-disintegrating oral Enhanced dissolution rates.
5. tablets.
6. Concealment of the drug substance's taste.

Disadvantages [41]

1. Solid dispersion instability.
2. Vulnerability to deterioration from moisture and temperature. Development of crystallinity and a decrease in dissolution rate with time.

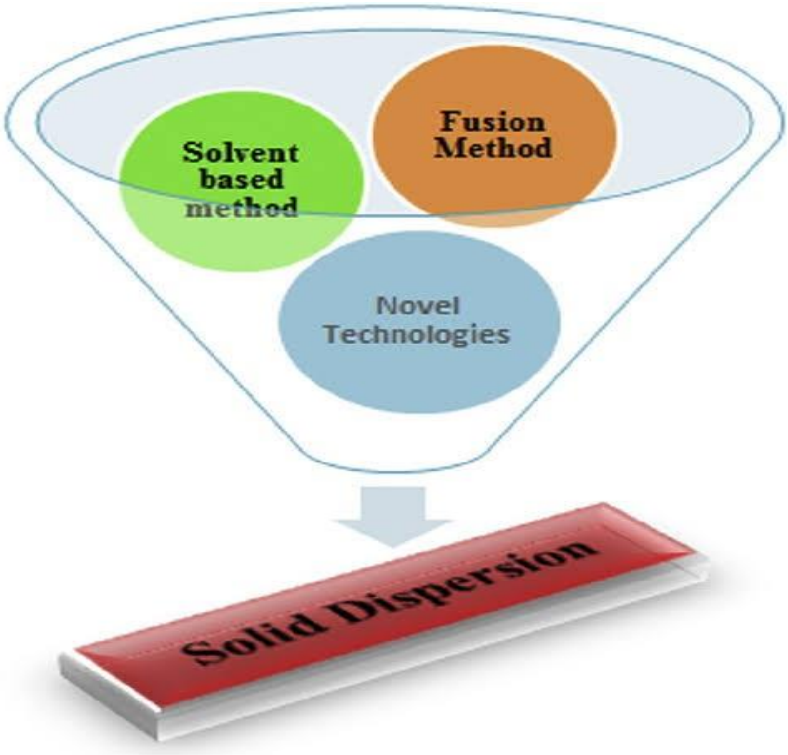


Fig 6 : solid dispersions process

8. Inclusion Complexation[42]

It is created by inserting a nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or a group of molecules. There are no intermolecular forces or chemical bonds involved in this interaction, making them known as no-bond complexes. Cyclodextrins (CD) are a family of cyclic oligosaccharides derived from the enzymatic degradation of starch. The three primary cyclodextrins, namely α, ß, and γ-CD, consist of six, seven, and eight D-(+)-glucopyranose units. Cyclodextrins have a hydrophilic outer surface and a hydrophobic internal cavity. They are frequently utilized in complexation, forming complexes with drugs to enhance the solubility and bioavailability of poorly soluble drugs. Derivatives of R-cyclodextrin with improved water solubility, such as hydroxypropyl-R-cyclodextrin (HP-R-CD), are commonly employed in pharmaceutical formulations.

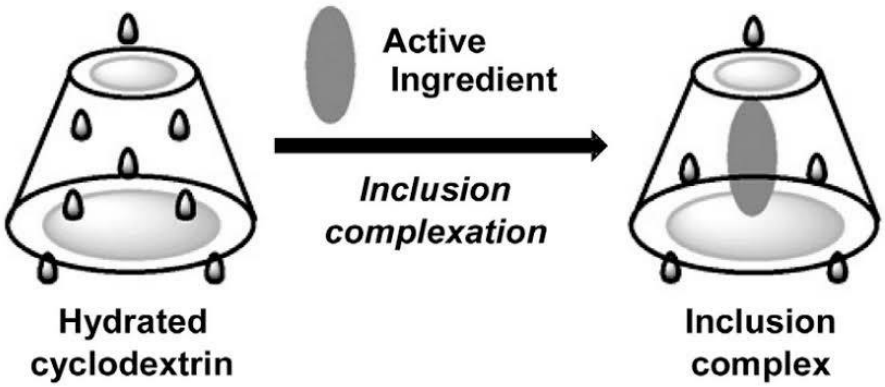


Fig 7 : Inclusion complexation process

9. Liquisolid Methods[43]

When a drug is mixed with a liquid vehicle and introduced into a carrier material with a porous surface and fibers inside, both absorption and adsorption processes occur. Initially, the liquid is absorbed into the interior of the carrier particles, filling their internal structure. Once this saturation point is reached, the liquid is then adsorbed onto both the internal and external surfaces of the porous carrier particles. This results in a liquisolid system with favorable flow characteristics, thanks to the coating material, which possesses high adsorption capabilities and a significant specific surface area. Coating materials like microcrystalline cellulose, amorphous cellulose, and silica powders can be used in this process.

Advantage [43]

1. Provides easily manageable and compressible powdered forms of liquid medications.
2. This method enhances the solubility and bioavailability of orally administered water-insoluble drugs and has applications in the pharmaceutical industry.
3. Suitable for creating formulations for both oily and liquid drugs.
4. This system can be employed to formulate a variety of poorly soluble drugs.
5. Specifically designed for transforming liquid medications into a powdered form.
6. Offers a cost-effective alternative to the preparation of soft gelatin capsules.

Disadvantages[43]

1. This process demands materials with strong adsorption properties and a substantial specific surface area.
2. It is not suitable for use with highly concentrated insoluble drugs exceeding 100 milligrams.

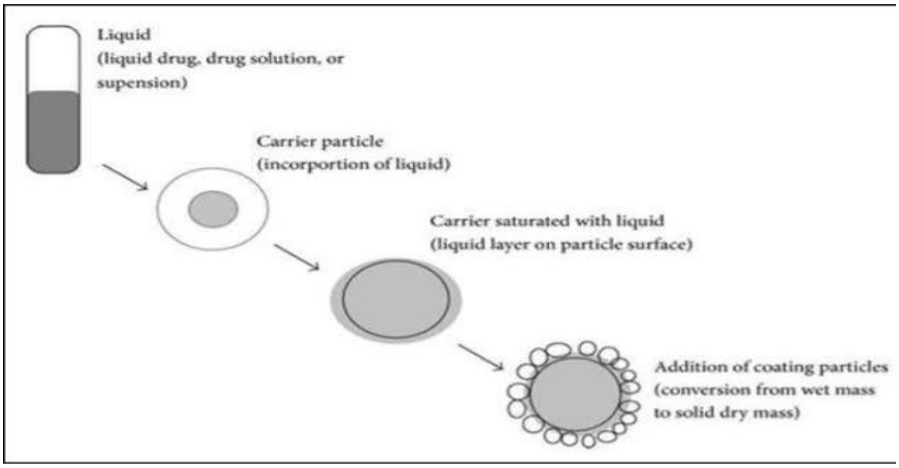


Fig 8 : schematic representation of liquisolid systems

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