IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

Enhancing the Dissolution of Hydrophobic Actives: A Comparative Review of Traditional and Advanced Formulation Technologies

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Abstract

Over 40% of newly discovered drug candidates fail to progress through the development pipeline due to inadequate biopharmaceutical properties, primarily poor aqueous solubility and slow dissolution. For molecules belonging to BCS Classes II and IV, these solubility restrictions dictate poor oral absorption and highly variable bioavailability. To address this challenge, this review delivers a comprehensive and comparative analysis of conventional, advanced, and emerging solubilisation technologies. Traditional formulation approaches including pH adjustment, co-solvency, salt formation, hydrotropy, cyclodextrin inclusion complexes, and polymeric solid dispersions are reviewed alongside their key benefits and limitations, such as physical instability and precipitation risks. This work subsequently transitions into modern physical modifications, evaluating advanced nanoscale systems (such as nanosuspensions, solid lipid nanoparticles, polymeric micelles, and electrospun nanofibres) and supercritical fluid processing. Special attention is paid to emerging chemical and molecular strategies, namely mesoporous silica adsorption, deep eutectic solvents (DESs), and ionic liquids (ILs), which offer highly tunable polarities and strong molecular interactions. Through a detailed case study of the hydrophobic active curcumin, we compare the quantitative dissolution efficiencies, scalability, and pharmacokinetics of these diverse techniques. Ultimately, we conclude that achieving reproducible bioavailability depends on selecting a tailored solubilisation platform that balances the unique crystal properties of the drug with industrial scalability and formulation stability.

Suggested Keywords

- Solubility enhancement
- BCS Class II and IV drugs
- Solid dispersions & Hot-melt extrusion
- Nanotechnology & Nanosuspensions
- Deep eutectic solvents & Ionic liquids
- Dissolution efficiency (Curcumin)

1. INTRODUCTION

1.1 SOLUBILITY

Solubility refers to the ability of a solid, liquid, or gas known as solute to dissolve in a solid, liquid, or gas called solvent, resulting in a uniform solution of the solute within the solvent. A substance's solubility primarily relies on the solvent employed, in addition to temperature and pressure.[1] As a highly debated yet still unresolved topic, techniques for enhancing solubility or dissolution continue to be a dynamic area for researchers in formulation science. Solubility and dissolution are fundamental principles in all physical and chemical sciences, encompassing biopharmaceutical and pharmacokinetic aspects in the treatment of any medication. However, as the synthetic method continues to thrive in providing numerous promising lead compounds across various pharmacological categories, they are also guiding the molecules towards larger structures. Consequently, over 40% of new candidates entering the drug development pipeline fail due to suboptimal biopharmaceutical characteristics. Factors such as absorption rate and extent, distribution rate, necessary dose for minimum effective concentration, and those to prevent side effects can greatly impact the drug's absorption, distribution, metabolism, excretion, and toxicity. Throughout the years, drug discovery tools have led to a noticeable change in biopharmaceutical characteristics.[2]

Solubility equilibrium is a dynamic state of balance that takes place when a solid chemical compound reaches chemical equilibrium with a solution containing that compound. Solubility equilibria play a crucial role in the pharmaceutical industry. Drugs with low solubility in water (specifically Class II or Class IV compounds of BCS) face absorption issues linked to dissolution. In pharmaceutical sciences, when quantitative data exist, solubility can be represented as parts, molarity, normality, formality, mole fraction percent solution, volume fraction, and molality.[3]

Definition	**Parts of solvent required for one part 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 1000-10,000
Insoluble	Greater than 10,000

Table 1: Solubility Expression [3]

1.2 POSSIBLE CAUSES FOR POOR ORAL ABSORPTION

Any drug is said to be poorly soluble when:

1. Aqueous solubility <100µg/ml.

2. Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min.

3. High molecular weight: (>500), Self-association and aggregation.

4. High crystal energy.[4]

1.3 PROCESS OF SOLUBILIZATION

It requires the disruption of intermolecular or interionic bonds in the solute, the separation of solvent molecules to create space for the solute, and the interaction between the solute ion or molecule and the solvent.

Solubilisation process occurs in three parts as shown in fig1:

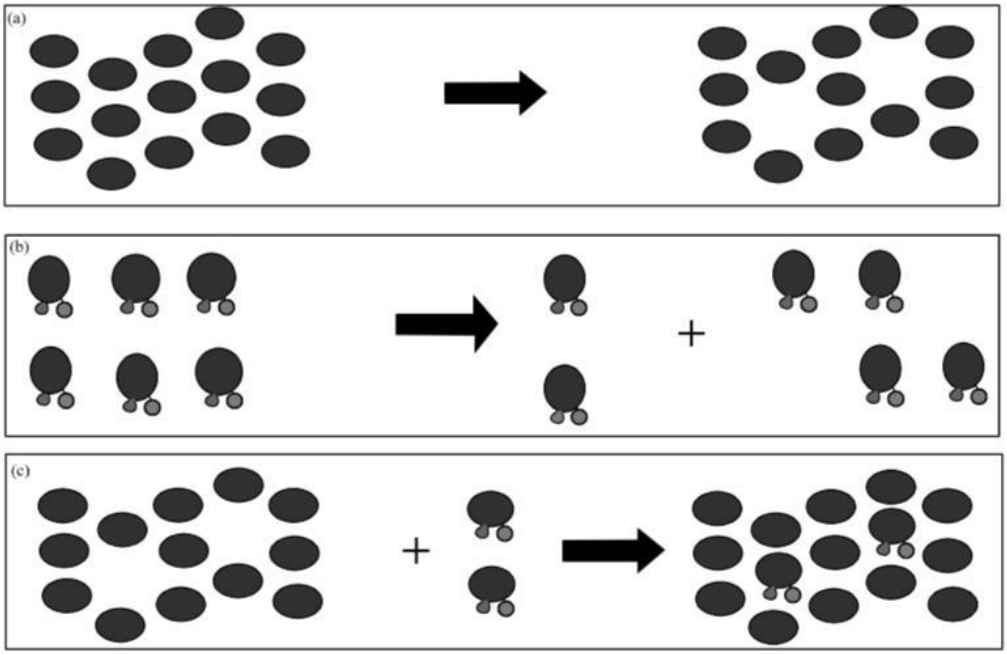


Fig 1(a-c): Solubilisation Process

(a) Holes are put in the solvent

(b) Molecules of the solid breaks away from the bulk

(c) Freed solid molecule is integrated into the holes in the solvent.[5]

1.4 FACTORS AFFECTING SOLUBILITY

- **Particle size**

Solubility is influenced by particle size. The surface area to volume ratio rises with decreasing article size. Particle surface area increases lead to increased solvent interaction.

The effect of particle size on solubility can be described by,

$$\frac{S}{S_0} \text{ LOG } \frac{2\gamma V}{2.303\, R\, T\, r}$$

Where,

S is the solubility of infinitely large particles

s_0 is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle

T absolute temperature in degree Kelvin.

R universal gas constant.[6]

- **Temperature**

Temperature affects solubility. The solubility will rise with temperature if energy is absorbed during the solution process. If energy is released during the solution process, the solubility will decrease as the temperature rises.[7]

- **Molecular size**

The solute's molecular weight and size increase with the size of its molecules. Larger molecules are harder for solvent molecules to encircle. Larger particles are often less soluble if all of the aforementioned elements are taken out of the equation. When two solutes of the same polarity are subjected to the same pressure and temperature, the one with smaller particles is typically more soluble.

- **Nature of solute and solvent**

The concentration of the solute in a given amount of solvent at a certain temperature determines the nature of the solute and solvent.

- **Pressure**

For gaseous solutes, solubility increases with increasing pressure and decreases with decreasing pressure. Pressure variations have little influence on the solubility of solid or liquid solutes.

- **Polarity**

The solubility will be impacted by the polarity of the solute and solvent molecules. In general, like dissolves like indicates that polar solute molecules dissolve in polar solvents and nonpolar solute molecules dissolve in nonpolar solvents. Both positive and negative ends are present in polar solute molecules. The positive ends of the solvent molecule will draw the negative ends of the solute molecule if the solvent molecule is likewise polar. This kind of intermolecular force is referred to as dipole-dipole interaction, or London dispersion forces, in which the negative electrons of solvent molecules are drawn to the positive nuclei of solute molecules. This allows the solute molecules to be solvated by the non-polar solvent.

- **Polymorphs**

Since a solid's melting point is correlated with its solubility, polymers can differ in their solubility. Due to comparatively tiny variations in free energy, the range of solubility discrepancies between various poly balls is often just two to three times.

- **Rate of solution**

The rate of solution is a measure of how fast substances dissolve in solvents.

✓ **Size of particles**
A solute dissolves more quickly when its surface area is increased by breaking it up into tiny pieces because the process only occurs at each particle's surface, increasing the solute's rate of solution.

✓ **Temperature**
Raising the temperature causes both liquid and solid solutes to dissolve more quickly and in larger quantities. The opposite is true for gas.

✓ **Amount of solute already dissolved**
Dissolution happens really quickly when there is minimal solute already in the solution. Dissolution happens more slowly when the solution gets closer to the point where no solute can be dissolved.

✓ **Stirring**
Studying which liquid and solid solutes increase the rate of solution by bringing a new portion of solvent into contact with the solute.[3,5]

1.5 BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The US Food and Drug Administration came up with BCS, which divides drugs into four classifications based on their solubility and permeability. Due to low solubility, the rate-limiting step in the class 2 and class 4 system resolution is little drug absorption. [3]

Class I High solubility and high permeability (HS,HP) Eg: propranolol Metoprolol	**Class II** Low solubility and high permeability (LS,HP) Eg: ketoprofen Carbamazepine
Class III High solubility and low permeability (HS,LP) Eg: ranitidine,atenolol	**Class IV** Low solubility and low permeability (LS,LP) Eg: Hydrochlorthiazide Furesemide

Table 2: Biopharmaceutics Classification Of Drugs[8]

Class 1: the medication dissolves quickly and quantitatively, is easily absorbed by the intestine, and eventually reaches its intended location in the body.

Class 2: drugs with low solubility in aqueous bodily fluids that readily cross the physiological barrier are becoming more and more prevalent in contemporary drug delivery systems.

Class 3: Unlike class to actives, these are soluble in the gastrointestinal tract but are not absorbed by the body. They run the risk of being eliminated without having any physiological impact.

Class 4: medication that doesn't disintegrate or cross a barrier.[9,10]

2. TECHNIQUE FOR SOLUBILITY ENHANCEMENT

Methods of solubility enhancement

PH adjustment, co-solvency, microemulsification, self-emulsification, micelles, liposomes, and emulsions are some of the traditional and widely used methods for improving the aqueous solubility and, consequently, the bioavailability of poorly soluble drugs, particularly BCS class 2 drugs.[11] Each method is dealing with some merits and demerits. Hence the decision of the method is a crucial step in the formulation process.

CONVENTIONAL METHODS

2.1 SURFACTANTS

Reducing the interfacial tension between the solute and solvent surfaces to improve wetting and salvation contact is the traditional method of solubilizing a poorly soluble material. Polyglycolized glyceride, Tweens, Span, Polyoxyethylene stearates, and synthetic block copolymers such as Poly (propylene oxide)-poly (ethylene oxide)-poly (propylene oxide) like Poloxamers-based micelles, Poly (beta-benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide), etc., are highly effective excipients and carriers for improving dissolution. By reducing the surface tension between the drug and solvent, improving wetting properties, and micellar solubilization, amphiphilic surfactants increase drug solubility.[12]

2.2 pH ADJUSTMENT

By changing the pH, a medicine that is poorly soluble in water may dissolve. The buffer capacity and tolerability of the chosen pH are crucial factors to take into account in order to access the solubility using this method. The solubility of weekly acidic medications is increased by solubilized excipients that raise the ambient pH in the dosage form to a range higher than pka; weekly basic drugs may be made more soluble by excipients that function as alkalizing agents.

Advantages

1. Easy to create and evaluate.
2. Uses little amounts of the drug, making it suitable for high throughput assessments.

Disadvantages

1. Precipitation risk when diluted with aqueous media whose pH makes the chemical less soluble. Orally, this may result in variability; intravenously, it may produce emboli.
2. When using a non-physiological pH or an excessive pH, tolerability and toxicity both local and systemic should be taken into account.
3. A dissolved medicine in an aqueous environment is often less chemically stable than crystalline solid formulations, as is the case with all solubilized and dissolved systems. The chosen pH may catalyze additional breakdown processes or speed up hydrolysis.[3][13]

2.3 CHEMICAL MODIFICATION

- **Salt formation**
- **Co-crystallization**
- **Co- solvency**
- **Hydrotrophy**
- **Use of novel solubilizer**

2.3.1 Salt Formation

For many years, salt production has been used to improve the solubility of weakly soluble therapeutic candidates (weak acids and bases). It works effectively for both solid dosage forms and parenteral and other liquid formulations. During the 12 years between 1995 and 2006, the FDA approved about 300 novel chemical entities for marketing, of which 120 were in salt form. Furthermore, hydrochloric acid was used to produce 54 of the 101 approved salts of basic medicines, suggesting that hydrochloride was the most common salt form.[14] Whether an acidic or basic medication will produce appropriate salts depends on its water solubility as a function of pH.[15] The interrelationships between pH and solubility also determine what counterions would be required to form salts, how easily the salts would dissociate into their free acid or base forms, how they would dissolve under various GI pH conditions, and whether common ions would affect the solubility and dissolution rate of salts.Numerous evaluations have described general methods and factors to take into account when choosing salt. Ionizable groups in the medication should promote the production of salt. The criteria used to select counter ion is as follows:

The medication and the counter ion should differ by at least 2 to 3 pKa units.

Crystal lattice forces should be reduced by counterions.

The choice of the counter ion should be supported by sufficient toxicological data or FDA approval.

Although this method can greatly increase the rate of dissolving, it has many drawbacks, such as the laborious process of approving salts and its inapplicability to neutral molecules.[12]

2.3.2 Co-crystallization

Co-crystallization is a viable method to optimize medication characteristics since it modifies molecular interactions. A co-crystal can be defined more precisely as a "multicomponent" crystal that forms between two materials in ambient conditions, at least one of which is an acceptable ion or molecule. Co-crystallization solves a number of an api's physiological, chemical, and physical problems. By reducing the interfacial tension, the co-solvency mechanism promotes the dissolving of a non-polar solute. Analytical methods and logical physicochemical research, including studies of solubility and stability, can be used to choose the best co-crystal. The physical state of the constituents is the only distinction between solvates and cocrystals. Solvates are defined as having one liquid component and one solid component; cocrystals, on the other hand, are defined as having both solid components. The api and the co-crystal former are the two main components of medicinal co-crystals.

Various methods for co-crystallization: 1) solvent evaporation 2) grinding 3) slurry co - crystallization 4) solvent drop grinding (modification of grinding) 5) high throughput co-crystallization 6) hot melt extrusion 7) sonocrystallization method.

Characterization parameters for co-crystals: 1) solubility 2) maximum wavelength 3) stability 4) intrinsic dissolution 5) bioavailability 6) melting point 7) melt (hot stage microscopy)8) scanning calorimetry (dsc) 9) xrd 10) vibrational spectroscopy.[17,18,19,13]

2.3.3 Co-solvency

Co-solvents, which are water miscible solvents in which a medicine has strong solubility, are widely used to augment the solubility of weakly water soluble drugs. These are combinations of water and one or more water-miscible solvents that are used to improve the solubility of chemicals that are weakly soluble in water. Due to its ease of production and evaluation, this has historically been one of the most popular methods. Co-solvency has been applied to both liquid and solid formulations. Examples of solvents used in co-solvent combinations include ethanol, propylene glycol, and PEG 300. To improve meloxicam's solubility and dissolution, different concentrations (5–40%) of the solid binary systems containing polyethylene glycol 6000 were used. Co-solvency methods have also been applied to the spray freezing of liquids, such as danazol in a micronized powder formulation with polyvinyl alcohol, poloxamer 407, and polyvinyl pyrrolidone K-15. Pharmaceuticals are always in liquid form. A co-solvent approach may be appropriate for poorly soluble lipophillic or highly crystalline compounds that are highly soluble in the solvent mixture. When compared to the drug's water solubility alone, co-solvents can make weakly soluble molecules several thousand times more soluble. Seedher and Bhatia (2003) found that introducing ethanol as a second solvent could greatly increase the aqueous solubility of celecoxib, rofecoxib, and nimusulide. Of the mixed solvent systems, PEG-400-ethanol had the best solubilization potentiality. However, because the poorly soluble medication would usually uncontrollably crash out upon dilution into a crystalline or amorphous precipitate, the bioavailability may not be significantly boosted.

Advantages

Easy to formulate and produce quickly.

Disadvantages

The toxicity and tolerability associated with the amount of solvent used must be taken into account, just like with any other excipient.[20-23]

2.3.4 Hydrotrophy

A solubilization phenomena known as hydrotrophy occurs when a significant amount of a second solute is added, increasing the solute's water solubility. The process by which it increases solubility is more closely associated with complexation, which is a weak interaction between the weakly soluble medications and hydrotropic agents such as urea, sodium alginate, sodium benzoate, and sodium acetate. Ionic organic salts are hydrotropic agents. The hydrotropic agent and solute interact weakly in hydrotropic solutions, which lack colloidal characteristics.[24]

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

Table 3: Classification Of Hydrotropes.[13]

Advantages of hydrotrophy

1. Because the solvent character is independent of pH, has good selectivity, and does not require emulsification, hydrotropy is thought to be superior to other solubilization methods such miscibility, micellar solubilization, co solvency, and salting in.
2. Emulsification is not necessary, hydrotrophy has great selectivity, and solvent character is independent of pH.
3. It doesn't require the fabrication of an emulsion system, the use of organic solvents, or the chemical modification of hydrophobic pharmaceuticals; it just requires mixing the medication with the hydrotrope in water.

4. Hydrotropic behavior has been described for a wide range of substances. Ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, b-naphthols, and salicylates, alkaloids like nicotine and caffeine, ionic surfactants like diacids, SDS (sodium dodecyl sulfate), and dodecylated oxidibenzene are a few examples.

2.3.4.1 Mixed Hydrotropy

It is a novel, easy, affordable, safe, precise, and accurate technology that uses hydrotropes in blends to increase the solubility of drugs that are poorly soluble in water.

Advantages of mixed hydrotropy

1. By using a combination of agents at lower concentrations, it may lessen the high total concentration of hydrotropic agents required to generate a slight increase in solubility.
2. The application of hydrotropic solubilizers to improve permeability.
3. The use of controlled precipitation in hydrotropic solubilization in nanotechnology.[25]

2.3.5 Use of novel solubilizer

Different solubilizing compounds can help increase the solubility of poorly soluble drugs. Examples of conventional solubilizers that increase the solubility of hydrophobic API include polysorbates, PEG 400 Sepitrap, Soluplus Povacoat, and dendrimers.

Sepitrap as a novel solubilizer Eighty percent of solubilizers are desorbed from SepitrapTM (Microencapsulated solubilizer for solid dosage application) in less than five minutes, making it possible to solubilize the therapeutic ingredient. In addition to improving the rate of dissolution, the 2:1 sepitrap to medication ratio has no effect on the properties of tablets and can be utilized without any formulation restrictions. [26-28]

Dendrimers are recognized for their three-dimensional, monodispersed, highly branching, macromolecular nanoscale architecture with a number of reactive end groups generated by repeating a series of processes. They serve as solubilizing agents to host both hydrophilic and hydrophobic medicines. Dendrimers are regarded as static unimolecular micelles, and even at greater solvent concentrations, their micellar structure is stable. Dendrimers' micelle-like properties led to their use in the solubilization of hydrophobic medications. Hydrophobic interactions, hydrogen bonding, and electrostatic interactions between the terminal functional groups of dendrimers and hydrophobes are likely the reasons why dendrimers increase the solubility of hydrophobes. Polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers are the most prevalent types. According to published research, PAMAM dendrimers are the most studied dendrimers in solubilization. The equally significant family of dendrimers known as poly (propylene)imine dendrimers (PPI) was initially identified by Brabander and Meijer. With the exception of repeating units, these dendrimers are quite similar to PAMAM dendrimers.[28]

2.3.6 Nanotechnology

refers, in general, to the investigation and application of materials and structures at the nanoscale level, which is roughly 100 nanometers (nm) or smaller. Because micronized products have very little effective surface area for dispersion, oral bioavailability improvement via micronization is insufficient for many new chemical entities with very low solubility. Nanonization is the next stage. It is possible to apply preparatory techniques such vacuum deposition, high temperature evaporation, high pressure homogenization, and grinding.

Advantages of nanotechnology

It increases the rate of dissolution and solubility by producing nano or microsized spherical particles with smooth surfaces, a narrow particle size distribution, and high specific surface areas.

Disadvantage of nanotechnology

The agglomeration issue is intrinsic and challenging to resolve. [29]

2.4 PHYSICAL MODIFICATION

- **Particle size reduction**
- **Modification of the crystal habit**
- **Momplexation**
- **Inclusion complex formulation based techniques**
- **Solubiization by surfactants**
- **Drug dispersion in carriers**

2.4.1 Particle size reduction

a. Conventional method

b. Micronization

c. Nanosuspension

Particle size reduction

One of the most promising methods for enhancing the bioavailability of lipophilic medications is micronization or nanonization, which increases surface area and saturation solubility by reducing the particle size to the sub-micron level.7 During the preformulation studies of any formulation, particle size is an important characteristic that needs to be closely regulated. Even though reducing the particle size is an effective method of improving solubility, if it is not managed and optimized, the drug may re-crystallize and re-aggregate during storage. Particle size and physical stability should therefore be thoroughly investigated.Conventional milling procedures cannot reduce size to the submicron range. The concepts of pearl milling high-pressure homogenization, solution enhanced dispersion by supercritical fluids (SEDS), rapid expansion from supercritical to aqueous solution (RESAS), spray freezing into liquid (SFL), and evaporative precipitation into aqueous solution (EPAS) have all led to the development of patented engineering processes.[30]

Advantages of particle size reduction

1. It is a cost-effective, repeatable, and efficient method of increasing solubility.
2. In the case of chemical compounds, enhance the rate of solution since a smaller particle size increases the solvent's surface area.
3. Enables quick solvent penetration.

Disadvantages of particle size reduction

1. There is a considerable tendency for particle agglomeration because discrete tiny particles have a high surface charge.
2. The active substance may degrade due to mechanical or physical stress.
3. When processing thermosensitive chemicals, thermal stress that arises during comminution may cause issues.
4. It is technically difficult to develop a solid dosage form with a high pay load without promoting agglomeration and sterile intravenous formulation..

2.4.1.1 Conventional method of particle size reduction

Cutting, compression, impact, attrition, and combined impact and attrition are some of the mechanisms used in the traditional way of reducing particle size. Traditional techniques for reducing particle size, such spray drying and comminution, rely on mechanical force to break down the active ingredient. Thus, a cost-effective, repeatable, and effective method of improving solubility is made possible by particle size reduction. However, the medicinal product is frequently subjected to considerable physical stress from the mechanical forces inherent in comminution, such as milling and grinding, which may cause deterioration. When processing

thermosensitive or unstable active substances, the potential thermal stress during comminution and spray drying is also taken into account. It is impossible to raise the solubility of poorly soluble medications to a desired level using only conventional solubility improvement techniques.[31-33]

2.4.1.2 Co-grinding/Co-micronization

Co-grinding a poorly water-soluble medication with water-soluble polymers, such as poly vinyl alcohol (PVA), hydroxyl propyl methyl cellulose (HPMC), etc., in the presence of a small amount of water is a very successful way to increase the drug's apparent solubility while maintaining some degree of drug crystallinity.34. Due to their larger surface area, small particles created by milling or micronization are predicted to dissolve more quickly. However, adding energy to lower particle size increases Van der Waals interactions and electrostatic attraction between particles, which reduces effective surface area through agglomeration and slows down the rate of dissolution.Cohesive and electrostatic forces can be lessened or eliminated by co-micronizing medications with excipients such microcrystalline cellulose. By forming an ordered mixture, which reduces particle-particle agglomeration or Van der Waals interactions, this method enhances the apparent surface area accessible for drug breakdown. Because of the microcrystalline cellulose-drug mixture's natural surface roughness and porosity, an increase in the ordered powdered mixture's real surface area is anticipated.[35]

Techniques for micronization

a) Jet milling /fluid energy mill or micronizer

b) Rotor stator colloids millsc) Microprecipitation & microcrystallization

d) Controlled crystallization

e) Supercritical fluid technology

f) Spray freezing in to liquid

Advantages of micronization

provides a homogeneous particle with a narrow particle size dispersion and an increase in surface area.

Disadvantages of micronization

The final product may contain disordered or amorphous regions as a result of high energy processes that break the drug crystal lattice.

Thermodynamically unstable, amorphous regions can recrystallize when stored, especially in hot and humid environments.[33]

2.5 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. Similarly, a drug's amorphous form is always preferable to its crystalline form because of its increased surface area and higher associated energy. Amorphous > Metastable polymorph > Stable polymorph is the order in which various solid drug forms dissolve.[33, 36]

2.6 COMPLEXATION

A class of cyclic oligosaccharides known as cyclodextrins is produced when starch is broken down by enzymes. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units.

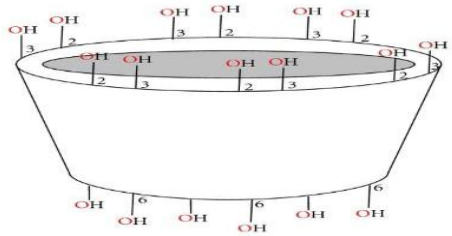
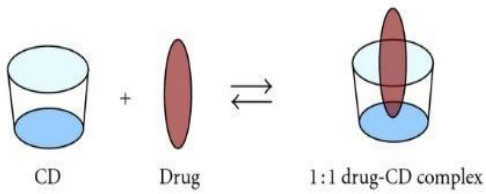


Fig 2: Representation Of Hydrophobic Cavity And Hydrophilic Outer Surface Of Cyclodextrin.

Primary and secondary hydroxyl groups are oriented outward in the torus-shaped structure of these drugs. As a result, cyclodextrins have a hydrophobic interior chamber and a hydrophilic outside. For oral or parenteral distribution, CD and its derivatives have been used as complexing agents to improve the water solubility, dissolution rate, and bioavailability of lipophilic medications. The percentage solubility enhancement achieved through cyclodextrin complexation increases with decreasing water solubility of the pure medication. Previous reviews have examined the pharmaceutical uses of cyclodextins in drug solubilization and stability, in vivo drug delivery, toxicological concerns, safety assessment, and processes of cyclodextrins altering drug release from polymeric drug delivery systems. Because of this cavity, cyclodextrins can combine guest drug molecules, changing the medications' solubility, stability, bioavailability, and toxicity characteristics.The factors causing complexation have been attributed to-

(i) the exclusion of high energy water from the cavity,
(ii) the release of ring strain particularly in t
(iii) he case of -CD,
(iv) Van der Wal's interactions,
(v) Hydrogen and hydrophobic bindings

The most popular natural cyclodextrins, ß-CD, have limited pharmaceutical applications due to their low water solubility (1.85 g/100 ml, 25°C), toxicity profile, and low aqueous solubility of the complexes they generate. In order to create more water-soluble and less hazardous compounds, derivatives like hydroxypropyl-ß-CD (HP-ß-CD) and sulphobutylether-ß-CD (SE-ß-CD) have been produced. One or two drug cyclodextrin complexes can be formed depending on the structure and characteristics of the drug molecule, as shown:



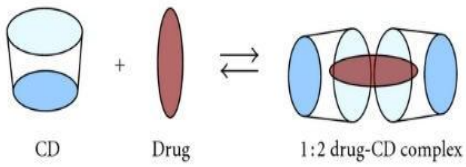


Fig 3: 1 : 1 Drug Cyclodextrin Complex **Fig 4: 1 : 2 Drug Cyclodextrin Complex**

This is the most popular technique for employing cyclodextrins to improve the stability and water solubility of hydrophobic medications. The following techniques can be used to create solid inclusion complexes.[37-42]

2.6.1 Physical mixture

To achieve the required particle size in the finished product, CDs or an acceptable polymer and medication are fully combined by trituration in a mortar and then passed through the proper sieve. It's a straightforward trituration technique. [3]

2.6.2 Kneading method

In order to turn the CDs into a paste, this process involves impregnating them with a little amount of water or hydroalcoholic solutions. After that, the medication is added to the paste mentioned above and kneaded for a predetermined amount of time. After kneading, the mixture is dried and, if necessary, sieved. A mortar and pestle can be used to accomplish kneading on a scientific scale. Extruders and other equipment can be used for large-scale kneading. This is the most popular, straightforward technique for creating inclusion complexes, and its production costs are extremely low.[42]

2.6.3 Co-precipitation

The necessary quantity of medication is added to the β-CD solution. The system is shielded from light and maintained under magnetic agitation with regulated process parameters. To prevent the structural water from the inclusion complex from being lost, the precipitate is separated by vacuum filtering and dried at room temperature. [43]

2.7 INCLUSION COMPLEX FORMULATION BASED TECHNIQUES

When a nonpolar molecule or nonpolar portion of one molecule (referred to as the guest) lodges into the cavity of another molecule or set of molecules (referred to as the host), inclusion complexes are created. Cyclodextrins are frequently utilized host molecules. Solid inclusion complexes are made using a variety of techniques, including kneading, co-precipitation, neutralization, co-grinding, spray drying, and microwave irradiation. The host's cavity must be both big enough to hold the guest and tiny enough to remove water.[33]

2.7.1 Kneading method discussed in complexation

2.7.2 Lyophilization/freeze-drying technique

This method involves first freezing the solution containing the medication and CDs or an appropriate polymer, then drying it at low pressure to remove the solvent system. The special qualities of water and its functions as a solvent, gas, diluent, plasticizer, and stabilizer greatly influence lyophilization. The medication and carrier are mixed molecularly in a common solvent as an alternative to solvent evaporation.

Advantages of lyophilization/freeze-drying technique

(i) To obtain a porous, amorphous powder with a high degree of contact between the medication and an appropriate polymer, the lyophilization/freeze drying process is deemed worthy.

(ii) This technique may effectively transform thermolabile materials into complex forms.

Disadvantages of lyophilization/freeze-drying technique

(i) Using specialist tools.

(ii) The procedure takes a long time and produces a powdered product that flows poorly.[44]

2.7.3 Microwave Irradiation Method

This method makes use of a microwave oven to facilitate the complexing agent and drug's microwave irradiation process.A round-bottom flask is filled with a mixture of water and organic solvent in a predetermined ratio to dissolve the medication and CD. The combination is heated to 60°C for a brief period of time—roughly one to two minutes—in the microwave oven. To eliminate any remaining uncomplexed free medication and CD, a sufficient amount of solvent mixture is added to the above solution or reaction mixture once the reaction is finished. The residual precipitate is then separated using Whatman filter paper and dried for 48 hours at 40°C in a vacuum oven.[45]

2.8 SOLUBILIZATION BY SURFACTANTS

Molecules containing polar and nonpolar sections are known as surfactants. The majority of surfactants are made up of a polar group joined to a hydrocarbon segment. Anionic, cationic, zwitterionic, or nonionic polar groups are all possible. Small polar molecules can build up in the micelles' hydrophobic center when they are added. In both natural and industrial systems, this solubilization process is crucial. By promoting the dissolving of lipophilic pharmaceuticals in aqueous media, the addition of surfactants lowers surface tension and improves drug solubility. Drug suspensions are also stabilized by the surfactants. Micelle formation, also known as micellization, happens when surfactant concentrations exceed their critical micelle concentration (CMC), which is typically between 0.05 and 0.10% for most surfactants. This process traps drugs inside the micelles and primarily increases the solubility of poorly soluble drugs.[42]

2.8.1 Micro emulsion

A Micro emulsion is an optically clear, isotropic, thermo dynamically stable translucent system which contains a mixture of oil, Hydrophilic surfactant and hydrophilic solvent in which the poorly water soluble drug dissolves. When comes in contact with water the formulation is spontaneously disperse or self emulsified to form a very clear emulsion of exceedingly small as well as uniform oil droplets containing the solubilized poorly soluble drug. These systems have been employed to increase the solubility of many temperature which are practically insoluble in water along with incorporation of proteins for oral, parentral as well as percutaneous or transdermal use. These homogeneous systems can be prepared by using a wide range of surfactant concentration and oil to water ratio are of fluids of low viscosity. So for improving the solubility of drugs formulated as a micro emulsion various parameter play an important role such as Surfactants, Surfactant Mixtures and co –surfactants.The surfactants like polyoxy ethylene surfactants for ex. Brij 35 or sugar esters like sorbitan monooleate (Span 80), cationic or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate or zwitter ionic such as phospholipids like lecithin because of it exhibits excellent bio-compatability.[46-50]

Advantages of microemulsions

Simplicity of preparation, clarity, ability to be filtered and incorporate a wide range of drugs of varying solubility.[51]

2.8.2 Self-emulsifying or self-micro emulsifying systems

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS), in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. The ease of emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. One of the advantages of SEDDS in relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Most self-emulsifying systems are limited to administration in lipid filled soft or hard shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. A Neoral-R is an example of self microemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine-α administered. A Neoral-R could be 174-239% of the bioavailability of cyclosporine-α from Sandimmune-R, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long term use due to the potential of causing diarrhea.[52-55]

2.9 DRUG DISPERSION IN CARRIERS

2.9.1 Solid solution

Solid solution is blend of two crystalline solids that exist as a new crystalline solid. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, it is expected to yield much higher rates of dissolution than simple eutectic systems.Amorphous precipitation: Amorphous precipitation occurs when drug precipitates as an amorphous form in inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.[56]

2.9.2 Applications of solid dispersions

It is possible that such a technique be used.

1. To obtain a homogeneous distribution of a minute amount of drug in solid state.

2. To stabilize the unstable drug.

3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

4. To formulate a fast release primary dose in a sustained released dosage form.

5. To reduce pre systemic inactivation of drugs like morphine and progesterone.

6. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

7. To convert polymorphs in a given system into isomorphous, solid.[57]

Advantages of solid dispersion

1. It has rapid dissolution rates.

2. Increase absorption rate of drugs.

3. Improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.

4. Decrease the crystalline structure of drug into amorphous form.

5. Prepare rapid disintegration oral tablets.

6. Mask the taste of the drug substance.

7. 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.)

8. Avoidance of polymorphic changes and there by bioavailability problems,

Disadvantages of solid dispersion

1. Instability of solid dispersion.

2. Moisture and temperature have deteriorating effect on solid dispersion.

3. It shows crystallinity and decrease in dissolution rate with aging.[58]

Limitations of solid dispersion system

1. Poor predictability of solid dispersion behavior due to a lack of a basic understanding of their material properties.
2. There is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also of a vital concern, because it may increase drug mobility and promote drug crystallization.
3. Most of the polymers used in solid dispersions have tendency to absorb moisture, which may result in the crystal growth, phase separation, or conversion from the amorphous to the crystalline state during storage which may result in decreased solubility and dissolution rate.

Methods of preparing solid dispersions

2.9.2.1 Fusion process

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Several mechanisms could operate during the process of dispersion. If the drug has a high degree of solubility in the carrier, the drug could remain "dissolved" in the solid state, yielding what is known as a solid solution. Particle size reduction under these conditions proceeds to the ultimate level leading to molecular dispersion of the drug in the carrier matrix. These systems show very high drug dissolution rates compared to control samples. If, on the other hand, the solubility of the drug in solid state is not so high, crystallites of the drug become dispersed in the matrix. Such systems show only moderate increases in dissolution rates. A third mechanism is the conversion of a drug to an amorphous form in the presence of the matrix, again exhibiting different dissolution rates and solubility. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties. An important limitation of the fusion method of preparation is the exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is heat-sensitive. [59]

2.9.2.2 Solvent method

In the solvent method of preparation, the carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum. As the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The coprecipitate is then dried under vacuum to drive out any solvent freely adhering to the particle surface. However, there is a possibility of the formation of a solvate within the crystal lattice. This presents a problem in terms of pharmaceutical acceptance since most of the solvents used are non-aqueous (organic) and toxic. Hence, removal of even trace amounts of the solvent is implied. Highly sensitive techniques such as differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetric analysis (TGA), and less sensitive procedures like gravimetry and spectroscopy can be used to demonstrate complete solvent removal.

2.9.2.3 Fusion-solvent method

In the fusion methods a 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. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drugs that have high melting points or that are thermolabile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000.[60]

2.9.2.4 Spray drying

In this type of preparation, the carrier and the active ingredient are dissolved or suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.[61]

2.9.2.5 Lyophilization (spray freeze drying method)

This method is used to avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD) has been successfully developed to prepare solid dispersions at ambient temperature, which was made significant development by the research work of William III. SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area.[62-64]

2.9.2.6 Hot melt extrusion:

This is method of choice in the polymer industry. But Speiser and Huttenrach were the first persons who use this technology for pharmaceutical purpose. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through heated screws, it is transformed into its "fluid like state". This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder.[27,65-67]

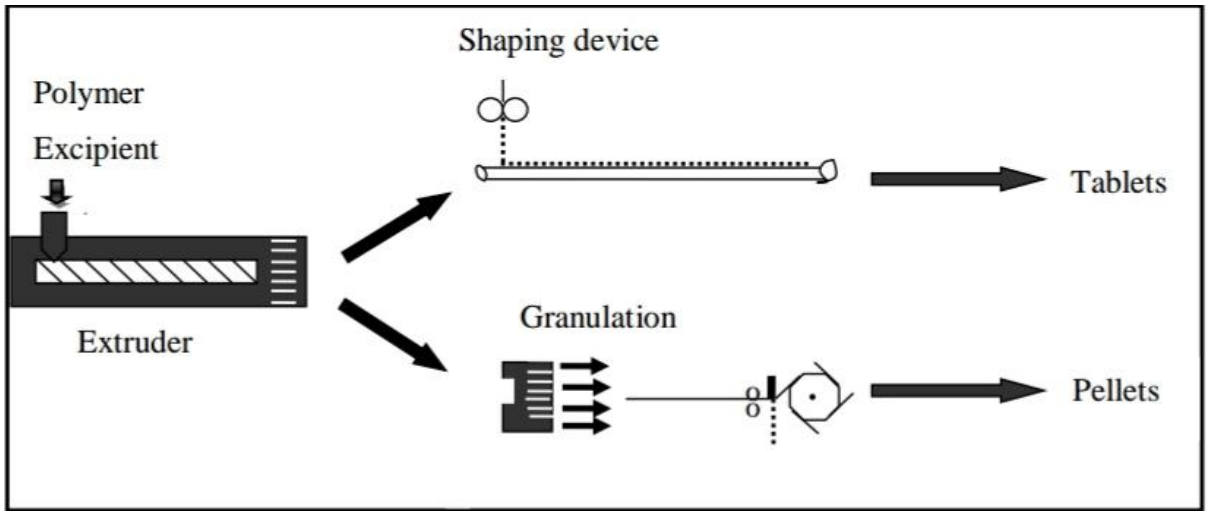


Fig 5: Scheme Of Hot Melt Extruder [69]

Advantage

Drug carrier mix is only subjected to an elevated temperature for about 1 minute which enables drug that are somewhat thermo labile to be processed.This method has already been used successfully to prepare Solid Dispersion of itraconazole and hydroxypropylmethylcellulose (HPMC), indomethacin, lacidipine, nefidipine, piroxicam, tobutamide and polyvinylpyrrolidone (PVP), itraconazole and HPMC, Eudragit E 100 or a mixture of Eudragit E 100-PVP vinyl acetate to improve solubility and dissolution rate of poor water soluble drugs.[68]

2.9.2.7 Dropping method

A solid dispersion of a melted drug-carrier mixture is pipetted then dropped onto a plate, where it solidifies into round particles. The size, shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped on the plate it solidifies to a spherical shape.[69]

2.10 SUPERCRITICAL FLUID (SCF) PROCESS

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs, are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid that largely determine its solvent power. Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5–2,000 nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle

size reduction and solubility enhancement. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions (RESS), gas anti solvent recrystallization (GAS), and aerosol supercritical extraction system (ASES).[70,71]

Advantages of supercritical fluid process

1. The low operating conditions (temperature and pressure) makes SCF attractive for pharmaceutical research.
2. Once the drug particles are solubilized within SCF, they maybe recrystallized at greatly reduced particle sizes. Current SCFprocesses have demonstrated the ability to create nanosuspensions of particles 5-2,000nm in diameter.
3. The flexibility and precision offered by SCF processesallows micronization of drug particles within narrow rangesof particle size, often to sub-micron levels.V.[51]

2.11 LIQUISOLID METHODS

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics. Liquisolid solid system is acceptably flowing and compressible powdered forms of liquid medications. In the concept of liquisolid system, liquid drugs having low aqueous solubility dissolved in suitable non-volatile solvents, converted in to free flowing and radially compressible powder by simple admixture with selected powdered excipients referred as carrier and coating materials. Microcrystalline and amorphous cellulose and silica powders may be used as coating materials.[72-78]

Advantages of liquisolid methods

1. Provides acceptably flowing and compressible powderedforms of liquid medications.
2. Method improves the solubility, bioavailability of orallyadministered water insoluble and is applicable in industry.
3. Useful for the formulation of oily drugs/liquid drugs.
4. Drug release drugs/liquid drugs.4. Drug release can be modified by using different carrier andadditives like PVP, PEG 60000, Hydroxy Propyl MethylCellulose and Eudragit etc.
5. A number of poorly soluble drugs can be formulated in tothe system.
6. This system is specifically for the powdered liquidmedications.
7. Production cost is low compared to that of preparation ofsoft gelatin capsules.

Disadvantages of liquisolid method

1. It requires recipients of high adsorption properties and high specific surface area.
2. It is not applicable to high dose insoluble drugs (>100 mg).[79]

2.12 POLYMERIC ALTERATION

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapor pressure, intrinsic solubility, dissolution rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most

thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.[80-82]

Nano-Suspension

A pharmaceutical Nano-suspension is a biphasic systems which consist of nano sized drug particles which is stabilized by using the surfactants for either oral or topical use or parenteral and for pulmonary administration. This technology has been developed as a promising candidate for the efficient delivery of hydrophobic drugs.This technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. Nanosuspension is produced by bottom up technology and top down technology. Top down technology involves various methods such as nano-edege, nano-jet technology, milling tech (Nano-crystals).[36 37]

Advantages of nanosuspension

1. In nanosuspension the particle size of drug is reduced which increases the surface area which in turn increases solubility, dissolution rate, and ultimately bioavailability.
2. Nanosuspension results in permeability enhancement.
3. Nanosuspension results in increases in bioadhesion and duration of action of residence.
4. Nanoformulation exerts advantage of high drug loading.
5. Avoidance of organic solvent.

Disadvantages of nanosuspension

Suffers from problem of instability due to agglomeration, crystal growth, Ostwald ripening.

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are biocompatible, lipid-based nanocarriers composed of a solid lipid core stabilized in an aqueous surfactant dispersion (typical size range ~50–1000 nm). SLNs solubilize poorly water-soluble drugs within a solid lipid matrix, protect labile payloads from degradation, enable controlled release, and can improve oral absorption via enhanced solubilization and lipid-mediated lymphatic transport. A broad palette of lipid excipients (triglycerides, glycerides, waxes) and surfactants allows tailoring of loading, stability, and release profiles, and numerous studies document improved bioavailability and pharmacodynamic outcomes with SLN/NLC systems

Advantages

- Improve oral bioavailability by solubilizing poorly water-soluble drugs within a lipid matrix and protecting labile drugs from degradation; lipid digestion and lymphatic transport can further enhance absorption for certain drugs
- Biocompatible and biodegradable; can be designed for controlled release and targeted delivery (e.g., lymph targeting) and protect peptide/protein drugs from proteolysis when appropriately formulated
- A wide range of lipid excipients (triglycerides, mono-/di-glycerides, waxes) and surfactants are available to tune solubilization, stability, and release properties

Polymeric micelles

Polymeric micelles are nanoscale self-assemblies of amphiphilic block copolymers formed above the CMC, featuring a hydrophobic core for drug encapsulation and a hydrophilic corona that imparts aqueous stability. They substantially increase the apparent solubility of lipophilic drugs, suppress precipitation in GI fluids, and can be molecularly engineered (block composition, molar

mass, end-groups) to optimize drug loading, stability, and release. Specialized polymeric excipients and block-copolymer designs have been shown to reduce recrystallization and enhance the oral performance of highly hydrophobic therapeutics

Advantages

- Increase aqueous solubility and maintain drug supersaturation by housing lipophilic drugs in their hydrophobic core while the hydrophilic shell stabilizes the micelle in biological fluids, reducing immediate precipitation in the GI tract
- Amphiphilic block copolymers can be precisely engineered (block composition, molecular weight, end-groups) to optimize drug loading, release, and stability; polymer chemistry (e.g., PNIPAM variants, PDMAm, PHEAm) influences performance [83]

Nanoemulsion

Nanoemulsion are kinetically stable dispersions of nanosized oil droplets (typically 20–200 nm) in water stabilized by surfactants/co-surfactants. Their large interfacial area enhances dissolution of hydrophobic drugs and can protect actives from enzymatic degradation. It increase apparent solubility by dissolving lipophilic drugs in the oil phase; small droplet size gives large surface area and faster mass transfer; surfactants/co-surfactants stabilize supersaturated states and can reduce intestinal enzymatic/lumenal degradation. Preparation methods include high-energy (ultrasonication, high-pressure homogenization) and low-energy techniques

Advantages

- High solubilization capacity for lipophilic drugs
- Provides rapid onset of action
- Suitable for multiple administration routes such as oral, topical, parenteral, and ophthalmic delivery
- Scalable manufacturing methods are available [84]

Limitations

- Possibility of thermodynamic instability
- May undergo Ostwald ripening
- Risk of droplet coalescence
- Requires careful selection of suitable surfactants and oils
- Surfactants may cause irritation or toxicity

Liposomes

Liposomes are self-assembled phospholipid bilayer vesicles (SUV, LUV, MLV, MVV) able to encapsulate hydrophilic drugs in the aqueous core and lipophilic drugs within the bilayer; composition and preparation determine size, encapsulation efficiency, and release. It solubilize hydrophobic drugs within bilayers and hydrophilic drugs in lumen; protect actives from degradation and control release via diffusion or collision-mediated transfer; can be modified (e.g., PEGylation, cyclodextrin inclusion) to improve stability, encapsulation and oral performance.

Advantages

- Can encapsulate both hydrophilic and lipophilic drugs
- Protects labile or sensitive drugs from degradation
- Allows controllable and sustained drug release
- Well studied for parenteral delivery systems
- Oral delivery potential can be improved using GI-stability modifications [84]

Limitations

- Conventional liposomes may show poor stability
- Rapid clearance from the body can occur
- Manufacturing process is complex
- Production cost is relatively high
- Oral liposomal systems may be destabilized by enzymes and bile salts

Electrospun nanofibres

Polymeric fibers produced by electrospinning, with high surface-area-to-volume ratio and porous structure; drugs can be molecularly dispersed (often amorphous) within fibers to improve dissolution and prevent recrystallization. Convert drugs to amorphous or finely dispersed states within polymers (e.g., PVP, PEO), increasing wettability and dissolution rate; fiber porosity and high surface area speed release; polymer selection and inclusion of excipients (cyclodextrins, surfactants) help prevent recrystallization and tune release profiles

Advantages

- Possess very large surface area
- Enhance rapid drug dissolution
- Can provide sustained release with suitable design modifications
- Help stabilize drugs in amorphous form
- Suitable for oromucosal, transdermal, and oral fast-dissolving systems [84]

Limitations

- Careful solvent selection is required
- Residual solvent toxicity may be a concern
- Scale-up and industrial production can be challenging
- Nanofiber mats may be mechanically fragile and difficult to handle

Spherical crystallization / spherical agglomeration:

A particle-engineering techniques that create spherical or agglomerated crystals combining crystallization, granulation and sometimes co-solvent steps to produce particles with improved flow, compressibility and dissolution. Produce spherical agglomerates that reduce crystallinity, increase surface area and improve wettability; improved micromeritics (flowability, compressibility) facilitates formulation into tablets or dispersible dosage forms and can accelerate dissolution compared to bulk crystals

Advantages

- Improves powder flow properties
- Enhances compressibility of drug particles
- Reduces downstream processing steps
- Can convert drugs into more amorphous forms
- Improves dissolution rate and tablet performance [84]
-

Limitations

- Highly sensitive to process parameters such as solvent system and agitation speed
- May require the use of organic solvents
- Drug-specific formulation optimization is necessary

Mesoporous Silica Particles

Drug delivery methods based on porous silica have shown great promise in enhancing the oral administration of medications that are insoluble in water. In particular, large amounts of drug molecules or amorphous forms can be adsorbed by micro and mesoporous silica carriers due to their high surface areas; these can then be released into an aqueous gastrointestinal environment through supersaturation, increasing absorption and bioavailability. Additionally, mesoporous silica particles improve solubility and permeability in transdermal medication administration.[85]

Deep eutectic solvents

Deep eutectic solvents (DESs) are liquid systems formed by mixing a hydrogen-bond acceptor (HBA) and a hydrogen-bond donor (HBD), resulting in strong intermolecular interactions that significantly lower the melting point of the mixture. DESs are considered important in solubility enhancement because they possess tunable polarity, low vapor pressure, non-flammability, and easy preparation methods. They improve drug solubility mainly through multiple mechanisms, including hydrogen-bond formation with drug molecules, disruption of drug–drug interactions, and weakening of the crystal lattice of poorly soluble drugs, which facilitates dissolution. Their composition can be adjusted to create suitable microenvironments for both hydrophilic and lipophilic drugs. In addition, solubility in DESs often increases with temperature due to improved molecular mobility and solute–solvent interactions. DESs can also be combined with other systems such as cyclodextrins, water, or polymers to produce synergistic co-solvency and inclusion effects, leading to greater solubility enhancement and improved formulation performance.

Advantages

- Experimental data show dramatic increases in solubility for multiple drugs
- Choice of HBA (e.g., choline chloride) and HBDs (citric acid, lactic acid, levulinic acid, sugars, polyols) and the water fraction enable optimization for specific APIs and target pH ranges

- DES-based systems (e.g., CycloDES, eutectogels) can also improve API stability and be formed into dosage-amenable systems (gels, emulsions, capsule-friendly liquids)
- DESs are often low-cost, biodegradable and simpler to prepare than many conventional solvents, supporting greener formulation approaches

Limitation:

- Solubility often decreases with increasing water fraction; ternary systems show more variability and require careful optimization
- While many DES components are biocompatible (NADES, choline chloride, organic acids), toxicity and regulatory acceptability must be assessed case-by-case for specific formulations
- Selection of optimal HBA/HBD ratios, control of viscosity, and ensuring physical/chemical stability over shelf life require formulation optimization; predictive tools (Hansen parameters, COSMOtherm) can assist solvent selection but experimental validation remains essential [86]

Polymeric nanoparticles:

Polymeric nanoparticles Polymeric nanoparticles—prepared using hydrophilic or biodegradable polymers such as HPMC, PVP, cellulose acetate, Eudragit and Soluplus—enhance the apparent solubility and oral bioavailability of poorly water-soluble drugs by nanosizing, converting crystalline drug to an amorphous or molecularly dispersed state, and stabilizing that state through polymer–drug interactions (e.g., hydrogen bonding and steric stabilization). Techniques such as sonoprecipitation, rapid precipitation, spray drying and hot-melt extrusion allow control of particle size and drug–polymer ratios; studies report multi-fold increases in dissolution (e.g., 10–20×) and improved pharmacokinetics for models like curcumin, ritonavir and efavirenz, with amorphization confirmed by XRD/DSC and enhanced in vivo exposure.[84]

Ionic liquids

Ionic liquids (ILs) Ionic liquids are designer, low-melting salts of organic cations and diverse anions that enhance solubility by forming strong ion–drug interactions (Coulombic forces, hydrogen bonds, and π–π interactions), disrupting crystal lattices, and creating a favorable microenvironment for dissolution. ILs can also promote drug permeation by fluidizing membranes, extracting lipids from barrier layers, or opening tight junctions, thereby improving absorption. The solubilization effect is highly dependent on ion selection (especially the anion), and choline-based ILs are preferred where lower toxicity and biodegradability are needed. Despite strong preclinical evidence of large solubility gains and improved permeability, ILs require careful toxicity evaluation and regulatory consideration before clinical translation[87

Comparative Analysis of Conventional and Advanced Solubility Enhancement Techniques Based on Dissolution Performance [88-92]

Drug	Technique category	Specific Technique	Formulation details	Preparation method	Dissolution / DE	Advantage	Limitation
Curcumin	Conventional	Solid dispersion — PVP (solvent evaporation)	Cur:PVP ratio 1:4 (solvent evaporation); amorphous solid dispersion	Dissolve Cur in ethanol with PVP; rotary evaporation under reduced pressure; dry and grind to powder (solvent evaporation)	Dissolution 94% at 90 min; DE = 87% (PVP solvent evaporation)	Produces amorphous dispersion; greatly increases wettability and dissolution rate	Amorphous form may recrystallize (stability concerns); storage/long-term stability not fully reported
Curcumin	Conventional	Solid dispersion — PEG 6000 (solvent evaporation / melting)	Cur:PEG 6000 ratio 1:4 reported for solvent evaporation and melting used as well	Solvent evaporation (ethanol) or melting (doping into molten PEG, rapid cooling and grinding)	DE = 75% (PEG 6000) ; dissolution improved vs raw	Easier melting method; hydrophilic carrier increases dissolution	Lower DE than PVP; limited amorphous stabilization vs PVP; possible phase separation
Curcumin	Conventional	Solid dispersion — Mannitol (melting/solvent evaporation)	Cur:Mannitol 1:4 in solvent evaporation; also melting method used	Melting (molten mannitol) or solvent evaporation then grind to powder	DE = 65%	Simple carrier; increased dissolution vs raw	Lower DE among carriers; limited storage capacity for amorphous drug
Curcumin	Conventional	Micronization	Micronized curcumin (reduced particle size)	High-energy ball milling (high-energy milling)	~80% dissolved at 90 min; DE = 80%	Increased surface area → faster dissolution	May not prevent recrystallization; less effective than methods changing molecular state; scalability/size distribution issues
Curcumin	Conventional	Surfactant systems (SLS, Pluronic F-127)	Curcumin dispersed in SLS or Pluronic F-127 solutions	Simple dispersion of Cur into surfactant solutions for dissolution tests	~88% dissolved at 90 min; DE = 88% (both SLS and Pluronic F-127)	Improves wettability and micelle formation → markedly better dissolution	Potential toxicity/safety issues of surfactants (SLS); may not prevent recrystallization long-term

Curcumin	Conventional	Co-solvent method (ethanol:water 1:1)	Curcumin solubilized in ethanol-water (1:1)	Dissolve Cur in ethanol:water and dilute for testing	~85% dissolution at 90 min; DE = 85%	Simple and immediate solubilization	Risk of precipitation upon solvent removal; not ideal as solid dosage without further processing
Curcumin	Conventional	pH adjustment	Dissolution medium adjusted to alkaline pH (~8.0)	Adjust dissolution medium to pH 8 for testing	~75% dissolution at 90 min; DE = 75%	Improves ionization and aqueous solubility	Not physiologically applicable for oral formulation (gastric pH); curcumin instability at high pH limits use
Curcumin	Conventional	Hydrophilic matrix (HPMC)	Curcumin in HPMC matrix (matrix tablets/dispersion)	HPMC hydrated and Cur dispersed for dissolution tests	~72% dissolution at 90 min; DE = 72%	Controlled/extended release options; simple polymer matrix	Moderate improvement only; lower DE vs advanced methods
Curcumin	Conventional	Cyclodextrin inclusion complex (β-CD)	Curcumin/β-cyclodextrin inclusion complex prepared by co-precipitation (Cur in ethanol, β-CD in water)	Combine ethanol (Cur) + β-CD aqueous solution, homogenize, stir, remove solvent, collect/dry/pulverize	Dissolution ~>90% at 90 min; DE = 92%	Inclusion complex increases apparent aqueous solubility by shielding hydrophobic moiety; high DE	Scale-up and cost; complexation efficiency and stability depend on conditions; limited in vivo data in RJPT
Curcumin	Advanced	Mesoporous silica adsorption (SBA-15) — conventional adsorptive approach	Cur loaded into SBA-15 (mesoporous silica) — physical confinement of drug	Adsorption/immersion, drying; carrier dissolved for analysis; dissolution in medium with SLS 0.1% used in some tests	Improved release vs raw curcumin in dissolution testing (exact % not explicitly given in RJPT; improvements described qualitatively)	Confinement reduces crystallinity and improves wettability; potential controlled release	Requires inorganic carrier (silica) — biocompatibility/clearance questions; precise quantitative numbers not provided in RJPT
Curcumin	Advanced	Nanoformulation — Lipid-based nanoparticles (SLNs/NLCs)	Curcumin encapsulated in solid lipid nanoparticles (Compritol as lipid)	Hot homogenization: melt lipid + disperse Cur; emulsify in hot water with surfactant using high-speed homogenizer; cool to form nanoparticles	Dissolution >90% within 90 min; DE = 94%	Excellent dissolution enhancement; likely improved bioavailability; scalable nano methods	Formulation complexity, surfactant/excipient safety, storage/stability issues

Curcumin	Advanced	Nanocrystals / Nanosuspension (Hot Melt Extrusion — HME Cur-NCs)	Cur-NCs employing Eudragit EPO (EEP) carrier; drug:carrier ratios 1:1, 2:1, 4:1; extrudate powders contained Cur nanocrystals (50–150 nm observed)	Twin-screw hot melt extrusion (Mini CTW), appropriate extrusion temp & speed; cool, crush strips, screen to 80 mesh to obtain powders; carrier dissolves in medium leaving dispersed nanocrystals	Dissolution: all three extrudates reached 80% in less than 2 minutes (very rapid). In vivo: AUC of metabolites in Cur-NC group ~4.07× higher than raw Cur group (improved oral exposure).	Very rapid dissolution and markedly improved oral exposure (AUC ~4×); continuous, scalable, solvent-free HME process; good for industrial scale	Requires HME equipment and careful thermal optimization; potential thermal degradation risk (authors tested stability via TGA/HPLC and reported acceptable stability); hydrophilicity of carrier affects dissolution at higher drug loads
Curcumin	Advanced	Nanocrystals / Nanosuspension (other nanosizing: top-down/bottom-up)	Nanosized curcumin stabilized in suspensions (general nanosuspension approaches cited in reviews)	Methods vary: high-pressure homogenization, solvent–antisolvent precipitation, milling; HME is also used to make nanocrystals			
Curcumin	Advanced	Amorphous solid dispersion (binary)	CUR + P(VP-co-VAc), 10% drug loading	Supercritical fluid technology (SCF) using CO_2-assisted amorphization	Significantly higher dissolution than crystalline CUR at pH 1.2 and 6.8; supersaturation maintained ~2 h in acidic medium and ~6 h in buffer	Markedly improves dissolution and apparent solubility; polymer stabilizes amorphous form	Reduced permeability compared with pure CUR; polymer alone showed limited permeability enhancement

3. CONCLUSION

Dissolution of drug is the rate determining factor for oral absorption of poorly water soluble drugs and solubility is the basic requirement for absorption of drug through GIT.The techniques describe above can use in combination or alone for enhancement of drug solubility. While selecting the techniques many things should consider like characteristics of drug, dosage form requirement, cost of production,etc. So by selecting proper accurate technique, solubility of poorly water soluble drug can be acheived and desired can be formed.

4. REFERENCES

1. Leon. L, Herbert A. L, and Joseph. L. K. The Theory And Practise of Industrial Pharmacy. 3rd ed. Bombay:Varghese Publishing House;1987. 197.
2. Yogesh S. T, Indrajeet D.G and Avinash H. H. Solubility Enhancement Techniques: A Review On Conventional And Novel Approaches. International Journal Of Pharmaceutical Sciences and Research 2011; 2(10): 2501-2513.
3. Sneha J, Chandrakant M, Dhandraj J and Rajesh J. Solubility Enhancement Technique: A Review. Journal Of Pharmaceutcal Sciences and Research 2018; 10(9): 2205-2211.
4. Vilas P. B, Vinayta R. A, Anirudha V. M, Arunadevi S. B, Sanjay B. Strategies To Enhance Solubility And Dissolution Of Poorly Water Soluble Drugs. Journal Of Innovations In Pharmaceutical And Biological Sciences 2015; 2(4): 482-494.
5. Ashwini P. G, Nilesh V. K And Saptarshi D, Review On Enhancement Of Solubilization Process, American Journal Of Drug Discovery and Development 2014; 4(2): 134-152.
6. Sinko P.J. Martin's Physical Pharmacy And Pharmaceutical Sciences. 6th ed. New Delhi; 2011. 182.
7. Nicholas B, Marcel de M, Gavan P.T, York P. Crystal Engineering Of Active Pharmaceutical Ingredients To Improve Solubility And Dissolution Rates. Advanced Drug Delivery Review 2007; 59(7): 617–630 .
8. C.V.S. Subrahmanyam. Textbook of physical pharmaceutics. 3rd ed. Delhi: Vallabh prakashan; 2015. 148.
9. Brahmankar D.M, Jaiswal S.B. Biopharmaceutics and Pharmacokinetics Treatise.Delhi: Vallaabh prakashan; 2009. 349-357.
10. Meyer M.C. Bioavailability Drugs And Bioequivalence In: swarbrick J. and J.C. Boylan.. Encyclopedia of pharmaceutical Technology. New york: Marcel Dekker Inc; 1998. 33-58.
11. Robert G. S. Solubilizing Excipients In Oral And Injectable Formulatons. Pharmaceutical Research 2004; 21(2): 201-230.
12. Michael H, Stephen T, Cathy F. Part 1: Oral Delivery of Poorly Soluble Drugs Pharmaceutical Manufacturing and Packing Sourcer. Summer Samedan Ltd 2003; 03.
13. Varun R. V, Venkateshwarlu L And Srikanth L . Solubility Enhancement Techniques. International Journal Pharmaceutical Science Review and Research 2010; 5(1): 41-51.
14. Abu T. M. S. Salt Formation To Improve Drug Solubility. Advanced Drug Delivery Review 2007; 59(7): 603–616.
15. Seshadri N. Strategies To Impact Solubility And Dissolution Rate During Drug Lead Optimization: Salt Selection And Prodrug Design Approaches. Small Molecule Pharmaceutics - Amgen Inc. Apr 2004; 7: 108-113.
16. Chawla R. C, Doura K. F, Mckay D. Effect Of Alcohol Cosolvents On The Aqueous Solubility Of Trichloroethylene. Proceedings Of The 2001 Conference On Environmental Research. 52-66.
17. Tanvee P, Ashwini D. Co-Crystallization-A Technique For Solubility Enhancement. International Journal of Pharmaceutical Science and Research 2014; 5(9): 3566-3576.
18. Michihiro S. A technique for throughput protein crystallization in ironically cross-linked polysaccharide gel beads for x-ray diffraction experiments. PLoS One 2014; 9(4): 1-8.
19. Amit C, Upendra N, Neha G, V. K Sharma, R. L Khosa. Enhancement Of Solubilization And Bioavailibility Of Poorly Soluble Drugs By Physical And Chemical Modification: A Recent Review. Journal Advanced Pharmacy Education & Research 2012; 2 (1): 32-67.
20. Keiji S, Noboru O. Studies On Absorption Of Eutectic Mixture-I: A Comparison Of The Behavior Of Eutectic Mixture Of Sulfathiazole And That Of Ordinary Sulfathiazole In Man. Chemical And Pharmaceutical Bulletin.1961; 9(11):866-872.

21. Ian R. Buxton And James M. Peach; John Wyeth And Brother Ltd, Assignee Process And Apparatus For Freezing A Liquid Medium. U.S. Patent: 4470202a. 1984 Sept 11.
22. Abikesh P.K.M, Vinod P And Ravindra P. Solubility Enhancement Of Poorly Soluble Soluble Drugs By Using Novel Techniques: A Comprehensive Review. International Journal Of Pharmtech Research 2020; 13(2): 80-93.
23. Letica S. K, Juliana B. B, Katia R. G, Clasrissa R. X, Roseli M, Paulo M, Teresa D. C and Valquiri L. B. Bioavailability Of Carbamazepine: Betacyclodextrin Complex In Beagle Dogs From Hydroxypropylmethylcellulose Matrix Tablets. European Journal Of Pharmaceutics 2004; 22(2-3):201-207.
24. Nidhi K, Indrajeet S, Mehta K, Karwani G, Dhrubo J. S, Hydrotrophy A Promising Tool For Solubility Enhancement: A Review. International Journal Of Drug Development And Research 2011; 3(2): 26-33.
25. Purwa J, Achhrih G, Shweta S And Meghal P. Solubility Enhancement Techniques With Special Emphasis On Hydrotrophy. International Journal Of Pharmaprofessional's Research 2010; 1(1): 34-45.
26. Doaa A. El-S, Emad B.B, Nevine S. A. Bioenhanced Sublingual Tablet Of Drug With Limited Permeability Using Novel Surfactant Binder And Microencapsulated Polysorbate: Invitro/Invivo Evaluation.European Journal Of Pharmaceutics And Biopharmaceutics 2015; 94: 386-392.
27. Naveen K. T, Alok R. Ray, Daniel B-S, Andre H E, Dipak K. M. Soluplus-Solubilized Citrated Camptothecin-A Potential Drug Delivery Strategy In Colon Cancer. AAPS Pharm Scitech 2012; 13(1):59-66.
28. Umesh G, Hrushikesh B. A, Narendra K. J.Polypropylene Imine Dendrimer Mediated Solubility Enhancement Eefect On pH and Functional Groups Of Hydrophobes. J Pharm Pharmaceut Sci 2007; 10(3): 358-67.
29. Mayank S, Rajesh S And Dinesh K. J. Nanotechnology Based Approaches For Enhancing Oral Bioavailibility Of Poorly Water Soluble Antihypertensive Drugs. Scientifica 2016. 2016.
30. Jiahui H, Dr.Keith P. J And Dr. Robert O. W. Nanoparticle Engineering Processes For Enhancing The Dissolution Rates Of Poorly Water Soluble Drugs, Drug Development And Industrial Pharmacy 2004; 30(3): 233-245.
31. Nikita N. C, Niraj V. P, Shakti J. S, Jayvadan K. P, Manish P. P. Micronization Of Bcs Class 2 Drugs By Various Approaches For Solubility Enhancement-A Review. Research Journal Of Pharmacy And Technology 2012; 5 (8) 999-1005.
32. Metkari V.B, Kulkarni L.V, Patil P.S, Jadhav P. A, Bhamane G.S, Kumbhar C. M. Microsphere – A New Drug Delivery System: A Review. Journal Of Current Pharma Research 2014; 4(2): 1128-1133.
33. Muller R. H, Peters K, Becker R, Kruss B. Nanosuspensions For The I.V. Administration Of Poorly Soluble Drugs – Stability During Sterilization And Long-Term Storage, 22nd International Symposium. Control Release Bioact. Mater, Seattle 1995; 22: 574-575.
34. Masaaki S, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement Of Dissolution Characteristics And Bioavailability Of Poorly Water Soluble Drug By Novel Co-Grinding Method Using Water-Soluble Polymer. International Journal Of Pharmaceutics 1998; 160: 11-19.
35. Spence J. K, Bhattachar S. N, Wesley J. A, Martin P. J, Babu S. R. Increased Dissolution Rate And Bioavailability Through Co-Micronization With Microcrystalline Cellulose. Drug Development And Industrial Pharmacy 2005; 10: 451-460 .
36. Patil J.S, Kadam D.V, Marapur S.C, Kamalapur M.V. Inclusion Complex System; A Novel Technique To Improve The Solubility And Bioavailibility Of Poorly Soluble Drugs: A Review. International Journal Of Pharmaceutical Science Review And Research 2010; 2(2): 29-34
37. Valentine J.S, Roger A. Rajewski. Cyclodextrins: Their Future In Drug Formulation And Delivery. Pharmaceutical Research 1997; 14: 556–567.
38. Rajeswari C, Alka A, Javed A, Khar R. K. Cyclodextrins In Drug Delivery: An Updated Review. AAPS Pharmscitech 2005; 6(2): E329-E357.
39. Roger A. R, Valentino J.S. Pharmaceutical Applications Of Cyclodextrins: In Vivo Drug Delivery. Journal Of Pharmaceutical Sciences 1996; 85(11): 1142-1169.
40. Diane O.T. Cyclodextrins- Enabling Excipients: Their Present And Future Use In Pharmaceuticals. Critical Review^{tm} in Therapeutics Drug Carrier Systems 1997; 14(1): 1-104.

41. James B, Stefan P. Some Important Considerations In The Use Of Cyclodextrins. Pharmaceutical Research 1999; 16(12): 1796-1798.
42. Rajesh K. P, Mansuri N. S, Mukesh C. G, And Moinuddin M. S. Dissolution Enhancement Of Nimesulide Using Complexation And Salt Formation Techniques. Indian Drugs 2005; 42(3): 149–154.
43. Jose R. M, Maria J. A. B, Ginesa J.M, Ferdinando G. Solid-State Characterization And Dissolution Characteristics Of Gliclazide-Beta-Cyclodextrin Inclusion Complexes. International Journal Of Pharmaceutics 1997; 148(2): 211- 217.
44. Mohini S. P, Sheetal Z. G, Saudagar, R. B. Solubility Enhancement By Various Techniques: An Overview. World Journal Of Pharmacy And Pharmaceutical Sciences 2013; 2(6): 4558 -4572.
45. Stelios C. T, Pavol R, Duc-Vinh P, William A. H, Jiri P, Scott D. R. Freeze Drying-Principles And Practice For Sucessful Scale Up To Manufacturing. International Journal Of Pharmaceutics 2004; 280(1-2):1-16.
46. Ahmed A, Sandra K, Karsten M. A New Self Emulsifying Drug Delivery System For Poorly Soluble Drugs: Characterization, Dissolution, In-Vitro Digestion And Incorporation Into Solid Pellets. European Journal Of Pharmaceutical Sciences 2008; 35(5):457-464.
47. Ingvar D, Bjorn L. The Definition Of Microemulsion. Colloids Surfaces 1981; 3(4): 391-392.
48. Jayne L, Gareth D. R. Micro-Emulsion-Based Media As Nvel Drug Delivery Systems. Advanced Drug Delivery Review 2000; 45(1):89-121.
49. Rene H, Christopher J H P, Glenn A E, Annette M, Henning G K, William N C. Examination Of Oral Absorption And Lymphatic Transport Of Halofantrine In A Triple Cannulated Canine Model After Administration In Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) Containing Structured Triglycerides. European Journal Of Pharmaceutical Sciences 2003; 20(1): 91-97.
50. Colin W. P. Lipid Formulation For Oral Administration Of Drugs, Non- Emulsifying, Self Emulsifying Drug Delivery Systems. European Journal Of Pharmaceutical Sciences 2000;11(2): S93-S98.
51. Sandeep K, Pritam S. Various Techniques For Solubility Enhancement: An Overview. The Pharma Innovation Journal 2016; 5(1): 23-28.
52. Mohanachandran P. S, Sindhumol P. G, Kiran T. S. Enhancement Of Solubility And Dissolution Rate: An Overview. Pharmacie Globale: International Journal Of Comprehensive Pharmacy 2010; 1(4):1-10.
53. Stijn K. M. J, Alwin H, Jan S, Beijnen J, Bastiaan N. Development Of An Oral Solid Dispersion Formulation For Use In Lowdosemetronomic Chemotherapy Of Paclitaxel. European Journal Of Pharmaceutics And Biopharmaceutics 2013; 83:87-94.
54. Prabhakar C. H, Bala Krishna K. A Review On Nanosuspensions In Drug Delivery, International Journal Pharma And Bio Sciences. 2011; 2(1):549- 558.
55. Mitesh P, Arpit S, Patel N.M, Patel M.R, Patel K.R. Nanosuspension: A Novel Approach For Drug Delivery System, Journal Of Pharmaceutical Science And Bioscientific Research 2011; 1(1):1-10.
56. Sudha R. V, Zeren W, Stefanie H, Steven L. K. Factors Affecting The Formation Of Eutectic Solid Dispersion And Their Dissolution Behaviour. Journal Pharmaceutical Science 2006; 96: 230- 294.
57. Kalyanwat R, Patel S. Solid Dispersion: A Method For Enhancing Drug Dissolution. International Journal Of Drug Formulation Research 2010; 1(3):1-14.
58. Surender V, Mahima K, Aruna R, Sapna S. Solid Dispersion: A Strategy For Solubility Enhancement. International Journal Of Pharmacy & Technology 2011; 3(2):1062-1099.
59. Praveen K, Chhater S. A Study On Solubility Enhancement Methods For Poorly Water Soluble Drugs. Americal Journal Of Pharmacological Sciencs 2013; 1(4):67-73.
60. Tetsuya H, Masaki I. Letter: Rapidly Dissolving Forms Of Digoxin: Hydroquinone Complex. Journal Of Pharmaceutical Sciences 1974; 63(5):809-811.
61. Teofilo V, Bruno S, Paulo C. Solid Dispersions As Strategy To Improve Oral Bioavailability Of Poor Water Soluble Drugs. Drug Discovery Today 2007; 12(23-24):1068-1075.

62. True L. R, Jiahui H, Zhongshui Y, Keith P. J, Robert O. W-III. A Novel Particle Engineering Technology: Spray-Freezing Into Liquid. International Journal Of Pharmaceutics 2002; 242(1-2):93-100.
63. True L. R, Andrew C. N, Jiahui H, Judith N. B, Marazban S, Timothy J. Y Et al. A Novel Particle Engineering Technology To Enhance Dissolution Of Poorly Water Soluble Drugs: Spray-Freezing Into Liquid. European Journal Of Pharmaceutics And Biopharmaceutics 2002; 54(3): 271-280.
64. Jiahui H, True L. R, Tim Y, Keith P. J And Robert O. W-III. Improvement Of Dissolution Rates Of Poorly Water Soluble Apis Using Novel Spray Freezing Into Liquid Technology. Pharmaceutical Research 2002; 19:1278-1284.
65. Ketan T. S, Anuradha K. G And Jignasa K. S. Drug Solubility: Importance And Enhancement Techniques. International Scholarly Research Notices 2012.
66. Enrico R, Lajos S, Jozsef S. Drug/Cyclodextrin/Hydroxy Acid Multicomponent Systems.Properties And Pharmaceutical Applications. Journal Of Pharmaceutical Sciences 2000; 89(1): 1–8.
67. Shan-Yang L, Hong-Liang L, Ying-Ting C, Ru-Ying H, Yu-Ting H, Chi-Yu K Et al Povacoat Affecting Solid-State Polymorphic Changes Of Indomethacin After Co-Evaporation From Different Types Of Solvents Via Conventional And Microwave Drying Techniques. Asian Journal Of Pharmaceutical Sciences 2016; 11(3): 376–384.
68. Avinash V.D, Gunesh N.D, Khalid U S, Irshad A S, Nandkishor B.B, Kulkarni A.S. Solubility Enhancement Techniques-A Review. Indo American Journal Of Pharmaceutical Sciences 2018; 05 (04): 2798-2810.
69. Pawar A. R, Choudhari P. D, Novel Techniques For Solubility, Dissolution Rate And Bioavailibility Enhancement Of Class 2 & 4 Drugs. Asian Journal Of Biomedical And Pharmaceutical Sciences 2012; 2(13): 9-14.
70. Gangadhar S, Uday B. K. Drug Delivery Applications Of Supercritical Fluid Technology. Drug Delivery Technology 2002; 2: 44–50.
71. Luigi M, Mauro B, Davide S, Ada F, Silvia R, Silvio S. Impregnation Of PVP Microparticles With Ketoprofen In The Presence Of Supercritical CO2. Journal Of Supercritical Fluids 2007; 42(3): 378–384.
72. Vijaykumar N, Ramarao T. R, Jayaveera K. N. Enhancement Of Dissolution Rate And Micromeritics Of Poorly Soluble Drug Ketoprofen By Liquisolid Technique. Journal Of Pharmaceutical And Biomedical Sciences 2011; 9(9):1-6.
73. El-Say M.K, Sammy M.A, Fetouh I.M. Formulation And Evaluation Of Rofecoxib Liquisolid Tablets, International Journal Of Pharmaceutical Sciences Review And Research 2010; 3(1):135-142.
74. Priya C, Raj K, Ankita K. Liquisolid Technique: An Approach For Enhancement Of Solubility. Journal Of Drug Delivery & Therapeutics 2013; 3(4):131-137.
75. Sahil M.G, Sharad S.P, Shirish V.S, Kisan R.J And Vilasrao J.K. Liquisolid Compact: A New Technique For Enhancement Of Drug Dissolution. International Journal Of Research In Pharmacy And Chemistry. 2011; 1(3):705-713.
76. Izhar A. S, Pavani E. The Liquisolid Technique: Based Drug Delivery System. International Journal Of Pharmaceutical Sciences And Drug Research 2012; 4(2):88-96.
77. Sandip V. Liquisolid Compact: A Novel Approach To Enhance Bioavailability Of Poorly Soluble Drug. International Journal Of Pharmacy 2012; 2(3):586-590.
78. Spiridon Spireas; Hygrosol Pharmaceutical Corp, Assignee. Liquisolids: Liquisolid System And Methods Of Preparing The Same. U.S. Patent: 6423339B1. 1998 Jul 23.
79. Dinesh P, Umesh S, Pravin S, Geetu C. Liquisolid Technique For Solubility Enhancement Of Poorly Water Soluble Drugs. Research Journal Of Pharmaceutical Dosage Forms And Technology 2010; 2(5): 314-322.
80. Masato O, Toshio O, Keiji Y. Evaluation Of Solubility Parameter To Predict Apparent Solubility Of Amorphous And Crystalline Cefditoren Pivoxil. Pharmaceutica Acta Helvetiae 1999; 74(1): 59–64.
81. Sudha R. V, Harry G. B, David J.W.G. Crystalline Solids. Advanced Drug Delivery Review 2001; 48(1): 3-26.
82. Elaine M-L, Garry G. L, Eugene R. C. Nanosizing: A Formulation Approach For Poorly-Water-Soluble Compounds. European Journal Of Pharmaceutical Science 2003; 18(2): 113-120.
83. Bhalani, D. V., Nutan, B., Kumar, A., & Singh Chandel, A. K. (2022). Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines, 2022 ; 10(9), 2055.

84. Bagade, P. V., Kulkarni, N. S., Chaudhari, P. D., Dhole, S. N., & Desai, U. S. (n.d.). Exploring modern techniques for solubility enhancement in drug formulations. 2025; 17(5).
85. Narmada I, Contemporary Review on Solubility Enhancement Techniques, Journal of Drug Delivery and Therapeutics. 2023; 13(2):110-120
86. Jignesh Parmar*1, Dr. Kashyap Thummar2,Krish Macwan, Preksha Patel, Soyodur Rahman5. (2025). Deep Eutectic Solvents as Solubility Enhancers: A Systematic Review. International Journal of Pharmaceutical Sciences.
87. Liu, C., Chen, B., Shi, W., Huang, W., & Qian, H. (2022). Ionic Liquids for Enhanced Drug Delivery: Recent Progress and Prevailing Challenges. Molecular Pharmaceutics, 19(4), 1033–1046.
88. Malkawi R, Tawalbeh J, Malkawi E, Jarwan B. Comprehensive Evaluation of Solubility Enhancement Techniques for Curcumin: A Comparative Study of 10 Methods. RJPT 2025:4126–32
89. Jignesh Parmar, Dr. Kashyap Thummar,Krish Macwan, Preksha Patel, Soyodur Rahman. Deep Eutectic Solvents as Solubility Enhancers: A Systematic Review. International Journal of Pharmaceutical Sciences 2025
90. Zhao, Y., Xu, X., Dai, A., Jia, Y., Wang,. (2024). Enhanced Dissolution and Bioavailability of Curcumin Nanocrystals Prepared by Hot Melt Extrusion Technology
91. Fitriani L, Azizah H, Hasanah U, Zaini E. ENHANCEMENT OF CURCUMIN SOLUBILITY AND DISSOLUTION BY ADSORPTION IN MESOPOROUS SBA-15 n.d
92. Shin GH, Li J, Cho JH, Kim JT, Park HJ. Enhancement of Curcumin Solubility by Phase Change from Crystalline to Amorphous in Cur-TPGS Nanosuspension. Journal of Food Science 2016;81.
93. Poeggeler B, Tagliazucchi D, Garbiec E, Rosiak N, Sip S, Zalewski P, et al. Curcumin Solubility and Bioactivity Enhancement Through Amorphization with Tryptophan via Supercritical Fluid Technology n.d.