"FROM INSOLUBLE TO BIOAVAILABLE: A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES"

A PROJECT WORK (BP812PW) SUBMITTED TO

NIRMA UNIVERSITY

In partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy

BY

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Semester VIII

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CERTIFICATE

This is to certify that Project Work (BP812PW) entitled ***"FROM INSOLUBLE TO BIOAVAILABLE: A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES"*** *is the bonafide work carried out by* ***MODI JAINIL (19BPH049), SURANI JINAL (19BPH055), PATIL SAMEER (19BPH093), PATEL SHREEDHAR (19BPH099), PATEL VASU (19BPH111)****, B.Pharm semester VIII under my guidance and supervision in the Institute of Pharmacy, Nirma University, Ahmedabad during the academic year 2022-2023. This work is up to my satisfaction.*

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CERTIFICATE OF SIMILARITY OF WORK

This is to undertake that the B.Pharm. Project work (BP812PW) entitled ***"FROM INSOLUBLE TO BIOAVAILABLE: A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES"*** *Submitted by* ***MODI JAINIL (19BPH049), SURANI JINAL (19BPH055), PATIL SAMEER (19BPH093), PATEL SHREEDHAR (19BPH099), PATEL VASU (19BPH111)****, B.Pharm. Semester VIII is a bonafide review/research work carried out by us at the Institute of Pharmacy, Nirma University under the guidance of Dr Mohit Shah. We are aware about the rules and regulations of Plagiarism policy of Nirma University, Ahmedabad. According to that, the review/research work carried out by us is not reported anywhere as per best of our Knowledge.*

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DECLARATION

We, ***MODI JAINIL (19BPH049), SURANI JINAL (19BPH055), PATIL SAMEER (19BPH093), PATEL SHREEDHAR (19BPH099), PATEL VASU (19BPH111),*** *students of VIIIth Semester of B.Pharm at Institute of Pharmacy, Nirma University, hereby declare that our project work (BP812PW) entitled* ***"FROM INSOLUBLE TO BIOAVAILABLE: A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES"*** *is a result of culmination of our sincere efforts. We declare that the submitted project is done solely by us and to the best of our knowledge, no such work is done by any other person for the award of degree or diploma or for any other means. We also declare that all the information was collected from various primary sources (journals, patents, etc.) has been duly acknowledged in this project report.*

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FROM INSOLUBLE TO BIOAVAILABLE: A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES

INDEX

1. ABSTRACT:

One of the most fundamental and significant characteristics to take into account in pharmaceutics is a medicine's solubility since it affects how a drug is formulated. Due to their complicated structural limitations that restrict their efficiency and bioavailability, many contemporary medications suffer from poor solubility, which can result in ineffective or inferior therapeutic effects. Drug solubility influences their physical, chemical, and environmental stability in the body, including when gastrin, blood, mucus, etc. are present. It has an impact on absorption and dissolution rates as well, both of which are critical for pharmacological response. This article reviews many strategies for solving solubility issues, including size reduction, complexation, co-crystallization, etc., and rates these approaches according to their benefits and drawbacks. Understanding these methods makes formulation creation simpler and more effective, which benefits patient therapy. Therefore, despite their potential for pharmacokinetic and therapeutic activity, drugs' poor aqueous solubility is a major barrier to their commercial success as a formulation.

2. INTRODUCTION:

The process of a solute dissolving in a solvent to produce a homogenous system is known as solubility. It is one of the most important factors in achieving the desired drug concentration in the systemic circulation for the pharmacological effect. It immediately impacts the drug's absorption and efficacy, which restricts the therapeutic effect. Numerous solubility enhancement methods have been created and are employed in pharmaceuticals to address these issues.

These solubility enhancement approaches allow us to increase absorption rate, solubility, dissolution rate, metabolism, and bioavailability, which enhances therapeutic effectiveness and effectively treats patients. The shelf life is also impacted by solubility because if a medicine is not entirely dispersed in its dosage form, it might separate or precipitate with time, resulting in variable dose and poor effectiveness.

2.1 Range of solubility:

Solubility can be measured by finding parts per solvent required for one part of solute.

Solubility	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 1000-10,0000
Insoluble	Greater than 10,000

Figure 1 Range of solubility

By these values we can determine how drug will get absorbed and how much of it will be absorbed

3. PROCESS OF SOLUBILIZATION

To make a homogenous mixture or solution, a solute must be solubilized, which is the process through which this happens.

The rate of drug solubilization has a direct bearing on a medication's bioavailability and pharmaceutical delivery properties, making solubilization an essential step during preformulation research. Solubilization, or the tendency of medication particles to dissolve in bodily fluids, can be characterised as this process. The bioavailability of the medicine will be greatly impacted by any changes in drug solubilization.

The general steps involved in solubilization are as follows:

1. Intermolecular interactions: When a solvent and a solute are together, the molecules of the solvent and the solute engage in interaction. Depending on how polar the solvent and solute are, these interactions can take different forms. Nonpolar solutes often react with nonpolar solvents via London dispersion forces, while polar solutes typically react with polar solvents via dipole-dipole forces and hydrogen bonding.

2. Intermolecular forces must be broken for the solute to dissolve into the solvent. Intermolecular forces are what hold the solute molecules together. The mixture can be heated or aggressively stirred to produce the necessary energy for this.

3. Solute particle dispersion: After the intermolecular interactions keeping the solute together are broken, the solute particles start to spread out throughout the solvent. The solvent molecules surround the solute particles, which aids in stabilising the particles and preventing re-aggregation.

4. Equilibrium: As the particles of solute dissolve in the solvent, a condition of equilibrium is established where the solute particles' rate of dissolution equals their rate of precipitation. The solution is referred to as saturated at this stage because the amount of solute in the mixture stays constant.

5. A substance's solubility is defined as the greatest quantity of solute that can dissolve in a specific amount of solvent at a specific temperature and pressure. A substance's solubility is influenced by a number of variables, including temperature, pressure, and solvent polarity, as well as its molecular make-up. (Kapoor et al., 2019)

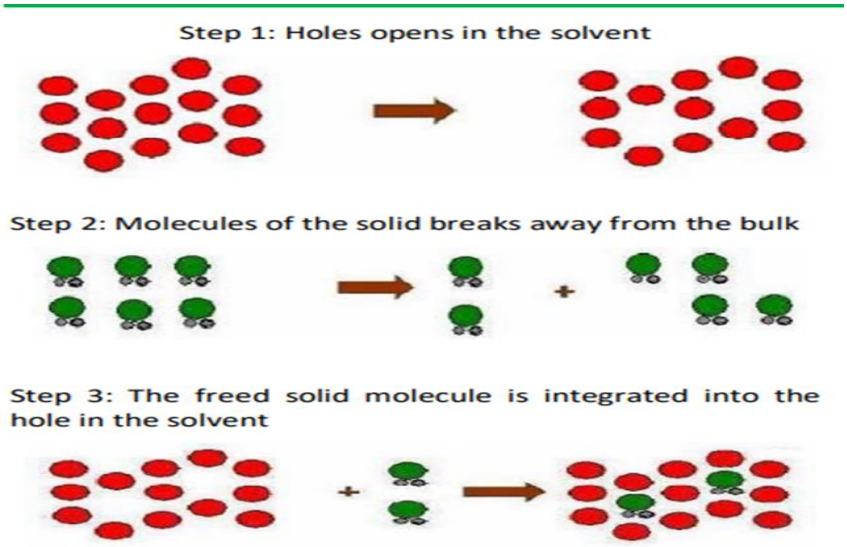

Figure 2 Solubilization process

The Solubilization of solute depends of various factor related to both solute and solvent

4. FACTORS AFFECTING SOLUBILITY OF DRUG:

1. Particle size: Smaller particles often dissolve more quickly than bigger particles in some solvents, hence the size of the particle may also have a substantial impact on solubility.

This is so because the amount of particle surface area that comes into contact with a solvent determines how quickly particles dissolve. In comparison to larger particles, smaller particles have a greater amount of surface area per unit mass, which allows them to dissolve more quickly and thoroughly.

Smaller particles can also assist weaken the intermolecular interactions between solute particles, increasing their solubility, as they have a higher kinetic energy because of their increased surface area.

The kind of the solute and solvent also affects how much of a substance is soluble when it comes to particle size. A further reduction in particle size, for instance, may not considerably boost a solute's solubility if it is already quite soluble in a particular solvent.

2. Temperature: As temperature rises, the solubilization process speeds up due to the molecules' increased kinetic energy, but if the solution process is releasing energy, solubility will fall as temperature rises.

Temperature-dependent decrease in solubility: If more heat is released during the dissolving process than is necessary to break up the material, the overall dissolving reaction is an exothermic one (emits energy). Since the dissolving reaction is already producing too much heat, adding more heat (raising temperature) prevents it from continuing. The circumstance when a rise in temperature results in a fall in solubility is uncommon.

Temperature-dependent increases in solubility: An endothermic reaction occurs when the heat produced by a dissolving process is more than the heat necessary to dissolve the material. By giving energy to break bonds in the material, additional heat is added, which speeds up the dissolving reaction. This is the most typical instance in which a rise in temperature results in a rise in the solubility of solids. (*Temperature Effects on Solubility - Chemistry LibreTexts*, n.d.)

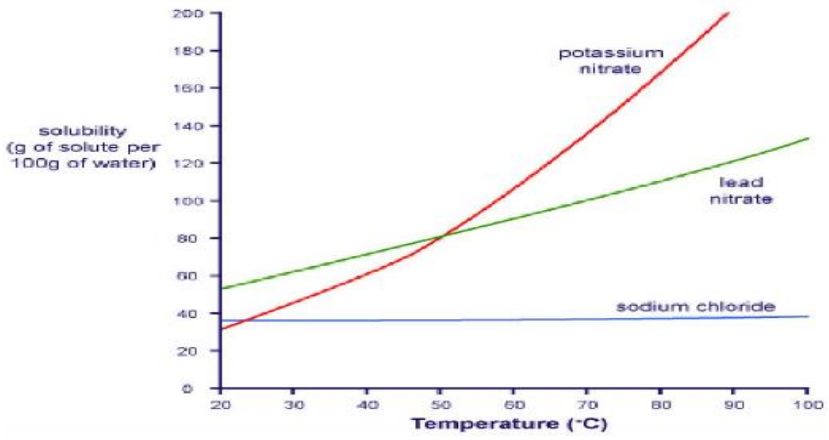

Figure 3 Effect of temperature on solubility

3. Molecule size: As a molecule's size increases, solubility declines because it is more difficult to surround the bigger molecules with molecules of solvent to form solutions.

This graph shows that solubility rises as molecule/particle size decreases, in contrast to the graph's observation that solubility decreases as particle radius increases.

Molecules with greater sizes have a tendency to be less soluble than those with smaller sizes in some solvents, which can have a substantial impact on solubility.

The intermolecular interactions existing between a substance's molecules and those of the solvent, in general, determine how soluble that substance is. Larger molecules often have stronger intermolecular interactions, such as van der Waals forces or hydrogen bonds, which might hinder their ability to dissolve in a particular solvent. In addition, the surface area-to-volume ratio of bigger molecules may be smaller, making it more challenging for the solvent to successfully dissolve the molecule by coming into touch with enough of its surface.

But the type of solvent also affects how well a molecular size is soluble. An enormous molecule, for instance, may be very soluble in ethanol or hexane but somewhat insoluble in water.

4. Nature of solute and solvent: The solubility is also influenced by the composition of the solute and solvent since differing concentrations and temperatures can make substances less soluble. A solvent is a molecule that can dissolve solutes, which are other molecules. A solvent may be either solid, liquid, or gaseous. The solute molecules eventually disperse equally across the solution. This flawlessly uniform homogeneous combination is impossible to physically separate.

Greater solubility is associated with strong solute-solvent attractions, whereas lesser solubility is associated with weak solute-solvent attractions. Conversely, non-polar solutes often dissolve better in non-polar solvents, whereas polar solutes typically dissolve best in polar solvents.

The composition of the solvent and the solute alone determines how soluble they are in each other. polar solvent and polar solute together. A non-polar solute is highly soluble in

a solvent. In a non polar solvent, a polar solute has a poor solubility or is insoluble. (*How Does the Nature of Solute and Solvent Affect Solubility? – Heimduo,* n.d.)

5. Polarity: A significant element that has a significant impact on a substance's solubility in a solvent is polarity. Nonpolar chemicals are soluble in nonpolar solvents, while polar substances are typically soluble in polar solvents.

This is due to the fact that partly positive and negatively charged molecules found in polar solvents may interact with partially charged molecules found in polar solutes via dipole-dipole forces and hydrogen bonding. For instance, water is a polar solvent that, because of its presence of its polar hydroxyl group (-OH), may dissolve polar compounds like sugar or salt.

Nonpolar solvents, on the other hand, have negligible partial charges and are consequently unable to interact with polar molecules in a useful manner. Hexane is an example of a nonpolar solvent that can dissolve nonpolar materials because they lack partial charges and are mostly made up of nonpolar hydrocarbon chains.

There are, however, a few exceptions to this general rule. Because of its tiny nonpolar hydrocarbon chain and polar hydroxyl group, ethanol is an example of a polar solvent that can dissolve nonpolar compounds like oils or fats.

6. Pressure: Since the solubility of a gas in a liquid often rises with increasing pressure, pressure may have a substantial impact on the solubility of gases in liquids.

This occurs because the higher pressure forces the gas molecules closer together, which facilitates their dissolution in the liquid. For instance, the liquid in a soda bottle has carbon dioxide gas dissolved in it, which causes carbonation. When the bottle is opened, the pressure is released, causing the liquid to bubble with carbon dioxide gas.

However, because solids and liquids are not compressible and do not significantly change in volume when exposed to pressure changes, pressure has little impact on their solubility in liquids.

It's important to remember that temperature has a role in how pressure affects solubility. The solubility of gases in liquids often decreases with increasing temperature. This occurs

as a result of the gas molecules' greater kinetic energy at greater temperatures, which makes it harder for them to dissolve in the liquid.

7. Polymorphism: The solubility of a material may be significantly impacted by polymorphism, which is the capacity of a substance to occur in several crystal structures or forms.

Physical and chemical characteristics, such as solubility, may vary among a substance's many polymorphs. Because of variations in crystal packing, surface area, or interaction between molecules, one polymorph of a material could be more soluble in a certain solvent than another polymorph. varied polymorphs may sometimes have highly varied solubilities. For instance, the medication sulfathiazole has many polymorphs, and one of them is much more soluble in water than the others. This might alter the medicine's bioavailability and therapeutic efficacy.

A substance's stability and shelf life might be impacted by polymorphism as well. To maintain constant bioavailability and efficacy of medications, for instance, the pharmaceutical industry rigorously regulates their polymorphic form. This helps to prevent stability problems that can occur as a result of changes in polymorph over the course of time.

Overall, the existence of polymorphism may have a substantial impact on the solubility and characteristics of a substance, making it a crucial factor to take into account in various disciplines, such as material science, the field of chemistry and medicines.

5. BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The US Food and Drug Administration (FDA), which divides drugs into four classifications based on their solubility and permeability, originated this notion. We may choose the best strategy for a drug's formulation procedure based on this categorization.

Pharmaceutical firms utilise the BCS while developing new drugs to identify the best medication composition and delivery strategy. Poorly soluble and permeable drugs are often challenging to manufacture and distribute to the target place. The BCS aids in the

early identification of these medications so that effective techniques to increase their solubility & permeability may be devised.

Class	Permeability	Solubility
1	High	High
2	High	Low
3	Low	High
4	Low	Low

Figure 4 BCS classification

Class 2 and 4 drugs have low solubility which is rate limiting step in absorption of drug.

The BCS aids in identifying medications that are challenging to create and administer, and it directs the creation of suitable drug delivery systems such , liposomes, microspheres or nanoparticles.

The BCS is a helpful tool for drug development and regulatory filings, assisting in the optimisation of medication formulations and delivery methods and enhancing patient outcomes.

BCS classes 2 and 4 medications provide particular potential and problems from a marketing standpoint.

Low solubility for BCS class 2 medications may lead to poor bioavailability, which indicates that the drug may not be efficiently absorbed by the body. Marketing initiatives may need to concentrate on methods to increase the drug's solubility or bioavailability. This can include marketing certain dosage forms or delivery systems, or highlighting the drug's special qualities or attributes that might help it overcome solubility problems.

The difficulties with BCS class 4 medications are distinct. The drug's ability to reach its intended target in the body may be hampered by limited solubility and permeability, which might restrict its efficacy. Marketing campaigns for BCS class 4 medications may need to concentrate on informing patients and healthcare professionals about the drug's special qualities and highlighting the advantages of the medication despite its solubility and

permeability restrictions. (*Percentage of Marketed Drug Molecules According to the BCS... | Download Scientific Diagram*, n.d.)

In general, BCS class 2 and class 4 medication marketing may call for a more focused strategy, with an emphasis on certain patient demographics and healthcare professionals who are most likely to profit from the medicine's special qualities. Healthcare professionals and patients may need effective communication and education tactics to assist them comprehend the advantages of these medications and to get over any possible fears or obstacles associated to solubility or permeability restrictions. (Poovi & Damodharan, 2018)

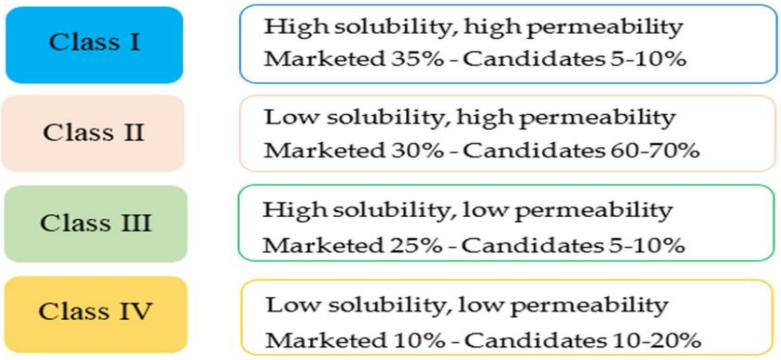

Figure 5 Market share of different class of drug

In recent years, 70%-90% of potential drugs and 40% of marketed drugs belong to biopharmaceutical classification system (BCS) class II or class IV

A total of 41.8% of BCS drug approvals in recent years were for Class I medications (based on in vivo bioequivalence and biowaiver studies), 20.9% were for Class II, and 37.3% were for Class III; there were no approvals for Class IV drugs. However, as seen in Figure, Class II now makes up the largest portion (60–70%) of drug molecules in development as well as a sizeable portion (30%) of the products that are currently on the market. This is due to the fact that the selection of possible therapeutic candidates is dependent on their capacity to attach to cell receptors, and because this binding necessitates hydrophobic interactions, lipophilic medications are typically chosen for development.

Drug permeability via the GI tract has demonstrated that the benefits of SEDDS could be used to BCS class IV medications with low solubility and low permeability with the proper component selection. Despite the fact that class IV drug approvals between the years of

2000 and 2011 were zero percent (Figure), in recent years these drugs have made up a sizable portion of the market—10% of marketed products and 10–20% of drug candidates in development. The ability of SEDDS to increase permeability through the gastrointestinal wall by affecting physiological and metabolic factors as well as the operation of protein transporters found in the cell membranes of the intestinal epithelium is the basis for the application of SEDDS to BCS class IV molecules.

Report Attribute	Details
Forecast Period	2022 – 2035
Drug Class	New Drug Approvals, Generics
BCS Classification	BCS II drugs, BCS IV drugs
Bioavailability Enhancement Approach	Solid dispersion, size reduction, lipid-based
Dosage Form	Liquids, solids, semi-solids, fine particles / powders
Key Geographical Regions	North America, Europe, Asia-Pacific, MENA, Latin America and Rest of the World

Figure 6 Data on methods use for solubility enhancement technique.

6. SOLUBILITY ENHANCEMENT TECHNIQUES:

6.1. CHEMICAL MODIFICATION

6.1.1. Salt Formation

A lot of the time, an API can't be created in its purest form due to various instability issues. They therefore undergo solidification, becoming salts, co-crystals, solvates, hydrates, and polymorphs, among others. Each one adds a distinct physiochemical characteristic and favourably affects the attributes of a drug's stability, bioavailability, purity, and manufactureability. Making salt from pharmaceutical candidates that aren't highly soluble has long been one way to increase solubility. Salts are created when a material ionises in solution. Along with parenteral and other liquid formulations, it functions well in solid dose forms as well. medications that are either acidic or basic are converted into salts that are more soluble than the original medications.

Advantages of Salt Formation to Increase Solubility:

1. Increased Solubility: The solubility of a medication or other chemical substance in water or other solvents may be greatly increased as a result of salt production. This is true because salts are ionic substances that, when dissolved in a solvent, may separate into ions, increasing the solute concentration in the solution. This improved bioavailability and more efficient delivery of the drug or compound in pharmaceutical and other uses can result from this increased solubility.
2. Improved Stability: By shielding a medicine or chemical from oxidation or hydrolysis, salt production may also improve stability. Under certain circumstances, such as being subjected to heat, moisture, or acidic or basic environments, some medications or chemicals are vulnerable to deterioration. They may often be made into salt to extend the stability and lifespan while maintaining their quality and effectiveness.
3. Simple Formulation and Processing: Due to their greater solubility and stability, salt versions of medications or substances are often simpler to synthesise into different dosage forms, such as tablets, capsules, or liquid formulations. This may streamline the manufacturing process and result in more productive, economical output.

Disadvantages of Salt Formation to Increase Solubility:

1. Physicochemical Properties: Salt production may change a drug's or compound's physicochemical characteristics, such as taste, colour, or melting point. This may have an impact on the formulation compatibility, processing requirements, or patient acceptance. For instance, the bitter or unpleasant flavour of certain salt formulations may make patients less likely to take their oral drugs as prescribed.
2. Complexity of the formulation process: While salt production might increase solubility, it can also make the formulation process more difficult. Some salt forms might need extra formulation considerations or steps, like pH adjustments, excipient selection, or handling potential ingredient incompatibilities. This may make the formulation process more expensive and difficult.

3. Considerations for Bioavailability: While salt production may enhance solubility, it may not necessarily result in better bioavailability. A medicine or compound's pharmacokinetics and pharmacodynamics may be impacted by a number of variables, including its salt form. A salt form's total bioavailability and effectiveness, for instance, may be impacted by the parent compound's different absorption, distribution, and metabolism. (Savjani et al., 1957)

6.1.2. Co-crystallization

Co-crystallization is a practical method for improving the properties of medications since it modifies the molecular connections. A co-crystal is a multicomponent crystal that forms between two substances that are solids under ambient circumstances, where at least a single element is an acceptable ion or molecule, according to a more precise definition. Co-crystallization may address a variety of an API's structural, chemical, or physiological issues. The cosolvency mechanism makes it easier for a non-polar solute to dissolve by lowering interfacial tension. To choose the optimal co-crystal, analytical techniques and logical physicochemical investigations, which include assessments of solubility and stability, may be applied. Solvates and cocrystals can only be distinguished by their components' physical state. Cocrystals are solids with two solid components as opposed to solvates, which are substances with one liquid component. Pharmaceutical co-crystals (s) primarily consist of the API and the cocrystal of the former.

6.1.2.1 Various methods of co crystallization:

A) **Solvent evaporation:** To co-crystallize a sample, a next to-saturated solution of the sample is prepared in a suitable solvent, and the solvent is then allowed to gently evaporate until co-crystals are formed. For air-stable samples, this is the easiest method. The sample may then be kept in a vial with a perforated top for storage. One experimental variable that is somewhat influenced by the sample's volatility is the size of the holes. It is preferable to tilt the tube in order to some crystals develop on its side. Delicate crystals may be removed more easily and damage-free thanks to this.

Advantages:

1. Simpleness: The solvent evaporation process is quite easy to follow and requires nothing in the way of special equipment. It may be used in most labs or research settings since it doesn't call for specialised tools or difficult methods.
2. The solvent evaporation technique enables control over the crystallisation parameters, including the rate of solvent evaporation, temperature, and humidity, which may affect the size, shape, and purity of the co-crystals created. This may make the co-crystal qualities more repeatable and manageable.
3. Versatility: The solvent evaporation approach is applicable to various solvents and co-crystall systems and may be used for the co-crystallization of a broad variety of components, including pharmaceuticals, small compounds, and polymers. Due to its adaptability, it can be used for many co-crystal research and development applications.
4. Scalability: The solvent evaporation process is excellent for use in industrial and commercial production since it is readily scaled up for the large-scale manufacturing of co-crystals.
5. Cost-effective: Since the solvent evaporation approach does not need costly equipment or chemicals, it is often a more affordable way for producing co-crystals.

Disadvantages of Solvent Evaporation Method for Co-crystallization:

1. Solvent evaporation is often a sluggish process since co-crystal formation requires the solvent to evaporate over time. Long processing durations might result from this, which would not be appropriate for applications that are time-sensitive or large-scale manufacturing.
2. Challenges with Solubility: The solvent evaporation process depends on the differing solubilities of the constituent parts, with the co-crystal being less soluble or insoluble than the constituent parts individually. Finding a suitable solvent or solvent combination that satisfies the solubility criteria for all components may be tricky, and it can be difficult to achieve the correct solubility behaviour for all components.

3. Polymorphism: The solvent evaporation process may cause the co-crystal to develop in a variety of polymorphic forms with varying physicochemical characteristics, such as stability, solubility, and bioavailability. The co-crystals that result from this may have variable characteristics that need to be properly characterised and managed.
4. Solvent molecules or other contaminants may be included in the co-crystal lattice as a consequence of the solvent evaporation process, which may influence the co-crystals' purity and quality. To get high-quality co-crystals and eliminate these contaminants, careful purification procedures would be needed. (Savjani et al., 1957)

B) Grinding: To create co-crystals, grinding is a common technique. Both plain and with drink assistance are acceptable methods. In a process known as neat grinding, no solvent is used while the two co-crystal components are combined. Through non-covalent interactions like hydrogen bonding, this brings the components very close to one another and leads to the formation of co-crystals.Liquid-assisted grinding involves adding a tiny or substoichiometric quantity of liquid (solvent) to the grinding slurry. By providing a platform for the constituents to communicate with one another, the solvent may aid in the development of co-crystals. Vibratory mills, ball mills, and mortar and pestles may all be used for the grinding. Co-crystal formation may be influenced by solvent selection and quantity. To prevent the development of co-crystals from being hampered, the solvent should be carefully selected.

Advantages of Grinding as a Method for Co-crystallization:

1. Co-crystallization may be accomplished by grinding, which is an easy process that doesn't need for specialised tools or laborious steps. It is readily accessible and practical for most labs or research settings since it requires physically grinding or milling the components together to promote co-crystallization.

2. High Success Rate: Grinding has been shown to be a reasonably successful approach for producing co-crystallization in many systems, with a high success rate. Co-crystals with desirable features, such as increased solubility, stability, and bioavailability, may often be formed as a consequence.
3. Process that Moves Quickly: Depending upon the system and parts being utilised, grinding may usually be finished in a matter of minutes to hours. When screening co-crystals quickly or for applications that must be completed in a short amount of time, this can be advantageous.
4. Versatility: Grinding is a versatile technique that can be used to a variety of co-crystallization systems and for the co-crystallization of a broad range of substances, including medicines, small molecules, and polymers. It may be used for many co-crystal research and development applications because of its flexibility.
5. Molecular-Level Mixing: Grinding enables close molecular mixing of the constituents, boosting molecular interactions and raising the possibility of co-crystal formation. As a consequence, co-crystals with clear shapes and characteristics may form.

Disadvantages of Grinding as a Method for Co-crystallization:

1. Variability: Because grinding conditions might change from batch to batch or depending on the operator, it can lead to variations in co-crystal attributes including size, shape, and purity. This may lead to problems with uniformity and repeatability in the manufacture of co-crystals.
2. Polymorphism: Grinding may cause the co-crystals to develop in various polymorphic forms that may have various physicochemical attributes. The co-crystals that result from this may have variable characteristics that need to be properly characterised and managed.
3. Contamination: Grinding requires physical contact between the components, and there is a chance that the grinding apparatus or other sources might be contaminated. This could have an impact on the purity and quality of the co-crystals

that are produced. To reduce contamination, careful purification and cleaning procedures can be needed.

4. Limited Scalability: Grinding is often a small-scale process, and it can be difficult to scale it up for co-crystal manufacture on an industrial scale. The procedure is manual, thus it may not be appropriate for high-throughput or industrial applications that call for larger production numbers. (*(PDF) SOLUBILITY ENHANCEMENT TECHNIQUES: AN OVERVIEW*, n.d.)

C) Slurry Co-Crystallization: Slurry co-crystallization is a technique for creating cocrystals that entails combining two components—the drug's active component and its coformer—that have been dissolved in a solvent. The solvent is chosen based on how well the active component and coformer dissolve in it. In this process, the heat energy produced by the friction between the particles and their crusher may lead to the formation of co-crystals. Through non-covalent interactions like hydrogen bonding, the components may come into close proximity to one another as a result of the heat energy and form co-crystals. The type of solvent and the quantity utilised may have an impact on co-crystal formation. To prevent interference with the production of co-crystals, the solvent of choice should be carefully selected.

Advantages of Slurry Co-crystallization Method:

1. Controlled Environment: The solvent content, temperature, and other factors may all be precisely managed during slurry co-crystallization in order to optimise co-crystal formation. Better consistency and reproducibility in the production of co-crystals may result from this.
2. Scalability makes slurry co-crystallization ideal for industrial applications or the manufacturing of co-crystals in bigger numbers. Slurry co-crystallization is simple to scale up for large-scale manufacturing of co-crystals.
3. Higher Purity: Slurry co-crystallization normally entails dissolving components in a solvent, followed by slow crystallisation, which may produce co-crystals that are

more pure than those produced by other procedures because impurities are more likely to be screened out during the crystallisation process.

4. Versatility: Slurry co-crystallization may be applied to a variety of co-crystal systems and can be utilised for a broad range of components, including medicines, small compounds, and polymers. Due to its adaptability, it can be used for many co-crystal study and development applications.
5. Application to Solubility Enhancement: Due to the lengthy crystallisation process, slurry co-crystallization is especially helpful for improving the solubility of weakly soluble components. These co-crystals have better solubility properties.

Disadvantages of Slurry Co-crystallization Method:

1. T Time-Consuming: Depending on the system and the parts being utilised, slurry co-crystallization may be a lengthy process that might take many hours or even days. When compared to other methods, this can result in longer production times, which might not be appropriate for applications with a deadline or when prompt results are required.
2. Slurry co-crystallization is a multi-step process that, when compared to other co-crystallization techniques, may be more difficult since it includes dissolving the component parts in a solvent, gradual crystallisation, and then isolating and drying the co-crystals. This can call for more advanced tools and further purification procedures.
3. Polymorphism: During slurry co-crystallization, many polymorphic forms of the co-crystals may occur. These forms may have various physicochemical features. The co-crystals that result from this may have variable characteristics that need to be properly characterised and managed.
4. Considerations for Solvents: Slurry co-crystallization necessitates the use of a solvent, and the choice of solvent has a big influence on the formation and characteristics of the co-crystals. For each co-crystal system, an adequate solvent must be chosen, which might be difficult and need optimisation.

D) Hot Melt Extrution: Extrusion of hot melt Co-crystals may be produced using a continuous, one-step, scalable, and commercially viable technique called hot melt extrusion (HME). It has gained popularity as a continuous, solvent-free method of producing co-crystals.

HME involves mixing the medication and co-former before feeding them through an extruder, where they get heated and melted. To create a solid product, the melted slurry is then pressed through a die. After cooling, the product may be cut into the required forms.

Compared to conventional techniques, HME provides a number of benefits for co-crystal formation. It is an ongoing procedure that is simple to scale up for commercial production. Additionally, it doesn't use any solvents, making it a sustainable method.

The co-crystal formation in HME may be influenced by the co-former used as well as the processing parameters. To guarantee that the co-former and the medicine form stable co-crystals, attention should be taken while selecting it. To guarantee the development of co-crystals, the processing parameters, such as temperature and screw speed, should also be optimised.

Advantages of Hot Melt Extrusion for Co-crystallization:

1. Hot melt extrusion (HME), a continuous technique that enables effective and continuous co-crystal formation, is appropriate for high throughput, large-scale manufacturing. Compared to batch procedures, this may lead to improved productivity and cost-effectiveness.
2. Solvent-Free: HME is a solvent-free approach that does not use any solvents to create co-crystals. This may make it a more environmentally friendly alternative by lowering the possibility of contaminants connected to solvents, streamlining the purification process, and reducing environmental issues raised by solvent consumption.
3. Homogeneous Mixing: HME entails melting and combining the constituent parts while they are in a molten state, which encourages homogeneous mixing of the co-formers and results in a uniform distribution of the constituent parts in the co-

crystals. Co-crystal characteristics may become more constant and repeatable as a consequence.

4. Flexibility: HME is a flexible technique that may be applied to a variety of co-crystal systems and employed for a broad range of components, include poorly soluble medicines, small compounds, and polymers. It is appropriate for a variety of co-crystal study and development applications because it provides for flexibility in the selection of parts, ratios, and processing conditions.
5. Enhanced Stability: Compared to other techniques, HME may facilitate the development of stable co-crystals by supplying carefully regulated heating and mixing conditions. This can increase the co-crystals' physical and chemical stability. Co-crystals with longer shelf lives and higher functionality in formulation applications may result from this.

Disadvantages of Hot Melt Extrusion for Co-crystallization:

1. Complexity of the Equipment: HME calls for specialised equipment, such as an extruder, which may be difficult to set up and maintain. This can need more money spent and equipment maintenance and operating knowledge.
2. Thermal Sensitivity: Some co-crystal systems or components may be susceptible to the high temperatures utilised in the HME process, which might cause deterioration or alteration of the co-crystals' characteristics. Processing conditions should be carefully chosen, and temperature-sensitive components should be watched over.
3. Polymorphism: HME may cause the co-crystals to develop in various polymorphic forms that may have various physicochemical features. Co-crystal performance and stability may be impacted by polymorphism, therefore careful characterization and management of polymorphic forms may be required.
4. Processing Difficulties: Due to the components' molten state during HME, certain co-crystal systems might have processing concerns such low solubility or viscosity. To address these issues, optimisation of processing parameters, formulation design, and characterisation may be necessary.

5. Product Yield: Compared to other processes, HME may provide lower product yields because certain co-crystals can get lost during the process of extrusion or because of difficulties in the subsequent steps of processing, such as gathering and storing of the extruded material. To attain desired product yields, careful process optimisation and control may be required. (Lang et al., 2014)

6.1.3. Co-solvency/solvent blending

By reducing the tension at the interface among the aqueous solution and hydrophobic solute, the addition of a water miscible solvent in which the medication is highly soluble enhances the solubility of a drug which is poorly soluble in water. Liquid is often the medicinal form. For weakly soluble compounds that are lipophilic or extremely crystalline with a high solubility in a solvent combination, a co-solvent method may be suitable. It has found its major use in parenteral dosage forms because to the low toxicity of numerous co-solvents and their relative superior ability to solubilize nonpolar medicines. Glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol are among the cosolvents that are often used.

Advantages of co-solvency/solvent blending:

A) offers a high solubilization capacity for medicines that are not readily soluble and is simple to develop, produce, and assess.
B) It may be used in concert with other solubilization techniques, such as pH adjustment, to further increase the solubility of poorly soluble compounds.

Disadvantages of co-solvency/solvent Blending:

a) The toxicity and tolerance of the solvent level must be taken into account provided.
b) Aqueous medium dilution may sometimes even cause uncontrolled precipitation. The precipitates may be either amorphous or crystalline and vary in size.
c) Many insoluble chemicals, particularly for intravenous use, are inappropriate co-solvents. injection. The drugs may increase the chance of embolism and cause

localised side effects at the if they are extremely soluble in water and do not quickly dissolve after injection precipitation caused by the co-solvent mixture.

d) The insoluble drug's chemical stability is poorer than when it is in a form that is crystalline because it with any form that is soluble. (Patel et al., 2012)

6.2. PHYSICAL MODIFICATION

6.2.1. Particle size reduction

Drug solubility is typically fundamentally correlated with drug particle size. to surface area As particle size is reduced, volume ratio increases. It is made feasible to increase contact with the solvent by increased solubility due to increased surface area. The relationship between medication particle size and the bioavailability of medications with low solubility. Surface area is increased through particle size reduction. which improves the dissolving properties and produces a wider range of formulations potential tactics and delivery methods.

Advantages of particle size reduction:

1. It is a successful, reproducible, and cost-effective technique for boosting solubility.
2. b) Increase the pace of solution when dealing with chemical compounds since the surface area as particle size decreases, more surface area becomes available for a solvent's action.
3. c) The potential for rapid solvent penetration

Disadvantages of particle size reduction:

1. A substantial potential exists because discrete tiny particles have a high surface charge. for the aggregation of particles.
2. Mechanical or physical stress may result in the active chemical degrading.
3. Because of temperature stress, processing of thermosensitive chemicals may be difficult. that grows during grinding.
4. Theoretically, it is challenging to produce solid forms of dosage with a significant payload without encouraging agglomeration. (Kanikkannan, 2018)

6.2.2. Complexation

A solute (such as a medication or other molecule with low solubility) and a complexing agent, often referred to as a ligand or host molecule, engage in a process called complexation in which a stable complex is produced. As a consequence of the complexing agent's interaction with the solute via intermolecular forces including hydrogen bonds, van der Waals forces, electrostatic interactions, and/or coordination bonds, a new chemical compound known as the complex is created.

One of the key benefits of complexation is that it may greatly improve the solubility of other molecules or medications that aren't very soluble in solutions. This is due to the fact that the complexing agent and the solute create a stable complex, which boosts the solute's concentration in solution and promotes faster dissolution rates. This may boost the drug's bioavailability since the body can absorb it more easily, and it can also provide poorly soluble medications additional alternatives for formulation.

Complexation is a flexible process that may be used with a variety of solutes and complexing agents, providing design freedom for formulations. In order to tailor complexation techniques to particular requirements, different complexing agents may be chosen based on their complexation characteristics and compatibility with the solute and the intended use.

Additionally, complexes with particular solutes or groups of compounds can be formed more preferentially through selective complexation. A great degree of control over the complexation process is possible by modifying the formulation parameters, including the kind and concentration of the complexing agent, pH, temperature, and other factors.

Because stable intermolecular interactions between the solute and the complexing agent are created, complexes formed by complexation can have greater stability than the original solute. As a consequence, the complex may have better physical, chemical, and thermal stability as well as defence against deterioration, precipitation, or other negative impacts.

As the complexing agent is easily incorporated into different dosage forms, including tablets, capsules, suspensions, emulsions, and other formulations, complexation also provides formulation flexibility. This enables the creation of varied and customised formulations to satisfy particular formulation demands and patient requirements.

Complexification may have certain drawbacks, however. The selection and optimisation of appropriate complexing agents, formulation parameters, and characterisation techniques may be necessary, which may add another layer of complexity to the formulation process. Comparing this to simpler formulation techniques may result in longer development times, more work, and more costs.

The physicochemical characteristics of the solute and the complexing agent, as well as how effectively they mix with other excipients in the formulation, may be impacted by intermolecular interactions involved in complexation. These interactions could affect the formulation's stability, bioavailability, or other qualities, necessitating careful evaluation and characterization.

The safety and toxicity of the complexing agent employed in the formulation should also be carefully assessed since it may have an impact on the complex's overall safety profile. According to regulatory regulations and standards, the use of certain complexing agents should be assessed for possible toxicity, allergenicity, and other negative consequences.

Additionally, complexation may be influenced by a number of variables, including pH, temperature, and concentration, which may have an impact on the process's success and repeatability. To get the appropriate complexation result, these parameters should be carefully managed and optimised. (*(PDF) SOLUBILITY ENHANCEMENT TECHNIQUES: AN OVERVIEW,* n.d.)

6.2.3. Inclusion Complex Formulation Based Technique

By creating inclusion complexes with host molecules, most often cyclodextrins, inclusion complex formulation-based approaches are ways to improve the solubility of medications or compounds that aren't very soluble. Cyclodextrins are cyclic oligosaccharides made up

of glucose units organised in a torus-like form with a hydrophobic cavity in the middle and a hydrophilic outside. Through host-guest interactions, cyclodextrins' special structure enables them to form inclusion complexes with a variety of guest molecules, including drugs that aren't very soluble.

Inclusion complexes are created when a guest molecule is enclosed inside the hydrophobic cavity of cyclodextrin, creating a stable compound. Improved bioavailability, dissolving rate, and formulation possibilities may result from this encapsulation's capacity to make the guest molecule more soluble in aqueous or other appropriate solvents.

The solubility of poorly soluble pharmaceuticals or other compounds in solution may be greatly improved by inclusion complex formulation-based approaches, which is one of their key benefits. The guest molecule is insulated from the solvent by the cyclodextrin cavity, preventing it from aggregating or precipitating. This enhances the guest molecule's apparent solubility in the solution as inclusion complexes develop. In turn, the drug's bioavailability may be raised and dissolving rates may be improved.

Utilising complex formulation-based techniques has the additional benefit of being adaptable. Cyclodextrins may form inclusion complexes with a variety of guest molecules, including medications with various physicochemical features, making them appropriate for a number of poorly soluble pharmaceuticals or compounds. The inclusion complex formation may be tailored to certain guest molecules by using several kinds of cyclodextrins with different cavity sizes, such as alpha-, beta-, and gamma-cyclodextrin. This versatility in formulation design is provided by these cyclodextrins.

With the ability to quickly insert inclusion complexes into a variety of dosage forms, including tablets, capsules, suspensions, emulsions, and other formulations, inclusion complex formulation-based approaches also provide formulation flexibility. In order to satisfy particular formulation demands and patient requirements, this enables the production of different and customised formulations.

An additional benefit of this method is the stability of inclusion complexes. Improvements in the complex's physical, chemical, and thermal stability may be achieved by encapsulating the guest molecule inside the cyclodextrin cavity to shield it from

deterioration, oxidation, or other negative consequences. In turn, formulation stability and shelf life may be improved.

The use of complicated formulation-based approaches, however, may have certain drawbacks as well. The possibility of inadequate inclusion complex formation, which would lead to a lesser solubility enhancement than anticipated, is one possible source of worry. The kind and concentration of cyclodextrin, temperature, pH, and other formulation parameters all have a role in how inclusion complexes are formed; these variables must all be carefully optimised to guarantee effective complex formation.

The possibility of interactions between the excipients in the formulation, such as cyclodextrin, the guest molecule, and other excipients, is still another area of possible worry. It may be necessary to carefully investigate and characterise interactions between the inclusion complex formulation's components as they may have an impact on the drug's physicochemical characteristics or other formulation qualities.

Because they have the potential to change the inclusion complex's overall safety profile, the cyclodextrins used in the formulation should also be assessed for safety and toxicity. Despite the fact that cyclodextrins are generally regarded as safe, it is still advisable to use them under strict regulatory oversight.(*(PDF) INCLUSION COMPLEX SYSTEM; A NOVEL TECHNIQUE TO IMPROVE THE SOLUBILITY AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS: A REVIEW*, n.d.)

6.2.4. Solubilization by surfactants Drug dispersion in carriers

To make poorly soluble medications or molecules more soluble for better formulation and drug administration, two approaches are used: solubilization by surfactants and drug dispersion in carriers. Surfactant solubilization is the process of making medications that aren't very soluble in a solvent more soluble by using molecules of surfactant, which are amphiphilic substances with both hydrophilic and hydrophobic sections. Surfactants may interact with drug molecules at the molecular level, generating micelles or other aggregates that solubilize the drug, when introduced to a solution or formulation containing a medication that is not readily soluble. A solubilized drug-surfactant complex that is more

soluble in the surrounding media is produced when the hydrophobic sections of the surfactant molecules surround the drug molecules and the hydrophilic areas of the molecules face outward. As a consequence, the drug's solubility and rate of dissolution increase, and its bioavailability may even be enhanced.

Drugs or molecules that are not well soluble are added to carriers to make them more soluble. This process is known as drug dispersion in carriers. In addition to liquid carriers like emulsions or microemulsions, carrier materials may also be solid carriers like nanoparticles, microparticles, liposomes, or solid dispersions. Because the drug molecules are dispersed throughout the carrier system, there is a greater surface area and a chance for improved solubility and dissolution. In addition to serving as a physical barrier to prevent precipitation or aggregation, carrier materials may also encourage solubilization and dispersion of the drug molecules in the media in which they are being administered.

There are benefits and drawbacks to both medication solubilization by surfactants and drug dispersion in carriers. The capacity to greatly enhance the solubility and dissolution rate of poorly soluble medicines or compounds, resulting in higher bioavailability and possible therapeutic effectiveness, is one of their key benefits. These methods may also provide formulation flexibility by allowing for the incorporation of multiple dosage forms, such as tablets, capsules, or liquid formulations, as well as a variety of surfactants or carrier materials to customise the formulation to particular medications or compounds.

There are a few possible drawbacks to take into account, however. One possible issue with solubilization by surfactants is the possibility of surfactant-induced toxicity or negative consequences. Some surfactants could be dangerous due to irritation, cytotoxicity, or unfavourable interactions with other formulation ingredients or physiological systems. Surfactants must be carefully chosen and assessed in order to guarantee their security and compatibility with the medication and formulation.

One possible issue with medication dispersion in carriers is the chance that the carrier may alter the characteristics or stability of the drug. Drug molecules may interact with carrier materials, which may change their physical, chemical, or thermal stability or other formulation characteristics. For the therapeutic molecules to remain stable and intact, the carrier system has to be optimised and characterised. (Malik, 2022)

6.3. pH ADJUSTMENT AS SOLUBILITY ENHANCEMENT TECHNIQUES

Increasing the solubility of medicines and other substances in aqueous solutions is a frequent practise that involves adjusting pH. Due to its effect on the ionisation state of the solute, the pH of a solution may have a significant impact on a solute's solubility. Lower pH values indicate more acidity and higher hydrogen ion (H+) concentrations in a solution, which is measured by pH. Higher pH levels and lower amounts of H+ are characteristics of basic solutions. Changes in the pH of the solution may either make a solute more or less soluble, depending on how the solute reacts with ions.

The fact that they only partly ionise in solution indicates that many medicines and other active substances are weak acids or weak bases. A weak base will only partly take hydrogen ions, for instance, whereas a weak acid will only partially contribute hydrogen ions to the solution. Depending on whether the medication is a weak acid or weak base, the pH of the solution affects how much the drug molecule is ionised, with greater ionisation happening at higher or lower pH levels.

The degree of ionisation of the drug molecule may be altered by changing the pH of the solution, which in turn has an impact on the drug's solubility. A weak acid medication, for instance, will be most soluble in a solution with a pH equal to its pKa (the pH at which the molecule is 50% ionised). Because the molecule is becoming more and more ionised at pH levels that are either higher or lower than the pKa, the solubility will decrease. It is possible to raise the solubility of a medicine, making it more soluble and hence more readily accessible for absorption or other uses, by changing the pH to the drug's pKa.

Buffering agents, which are substances that withstand pH changes when tiny quantities of acid or base are introduced to the solution, may be used to modify pH in a number of ways. Acetate, citrate, and phosphate are some examples of buffering substances. Together with the drug, the buffering agent is dissolved in the solution. The pH is then titrated with an acid or base until the desired pH is reached. Following that, the resulting solution can be applied to a variety of tasks, including in vivo administration and in vitro research.

Increasing the solubility of pharmaceuticals and other substances in aqueous solutions may be accomplished by adjusting pH, which is a potent solubility augmentation approach. The drug's solubility may be improved, making it more soluble and hence more soluble for absorption or other uses, by adjusting the pH level and adjusting the drug's degree of ionisation. In order to successfully utilise this procedure, buffering agents should be used, as should cautious titration.

Advantages:

1. Increased solubility: The degree of ionisation of the medication may be changed by altering the pH of the solution, which increases the drug's solubility and bioavailability.
2. Easy implementation in a range of contexts because to the relative simplicity and clarity of the pH adjustment approach.
3. Versatility: Regardless of a compound's chemical structure, pH modification may be utilised to improve the solubility of a broad variety of medications and other substances.
4. Cost-effectiveness: pH modification is often less expensive and needs less specialised equipment than other solubility improvement methods like particle size reduction or complexation.
5. pH modification is compatible with many different medication delivery methods, such as topical, parenteral, and oral formulations.
6. Flexibility: To raise solubility and bioavailability even further, pH modification may be used in conjunction with other solubility enhancement strategies.

Disadvantages:

Although pH adjustment is a common and successful solubility enhancement technique, there are some potential drawbacks to take into account, such as:

1. pH sensitivity: Small pH changes may have a big influence on a drug's solubility since pH adjustments can be quite sensitive to pH changes.
2. Chemical stability: At certain pH values, certain medications may get degraded and lose their effectiveness due to their chemical instability.

3. Complexity of formulation: The use of buffering agents and titration techniques may make the formulation process more difficult and time- and resource-intensive.
4. varied absorption: Changes in pH may also affect how well the medicine is absorbed and bioavailable, which might have unexpected or varied effects.
5. Limited impact on poorly soluble medications: Increasing the solubility of very insoluble pharmaceuticals may not be possible with pH modification; such drugs may need more aggressive solubilization methods.
6. Regulatory obstacles: pH changes may affect a drug's safety and effectiveness and may need further regulatory review and approval. (*(PDF) REVIEW ON: SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG*, n.d.)

6.4.HYDROTROPHY:

The increase in solubility is referred to as hydrotrophy. because the water contains a high quantity of pollutants. How it enhances solubility is more closely related to complexation, which includes a minimal contact between the hydrotropic chemical (sodium benzoate, sodium acetate, sodium alginate, urea).

They are substances that contain both a hydrophobic aromatic ring system and an anionic group. The ring structure interacts with the solute to be dissolved, and the anionic group improves the hydrophilicity. Complexation, which includes interactions between lipophilic drugs and hydrotropic chemicals, is the process behind hydrotropy.

Types of hydrotrophy:

1. Aromatic anionics
2. Aromatic cation
3. Aliphatic and linear anionics

Figure 7 Hydrotrophy

The following benefits of the hydrotropy method:

1. The solvent characteristic is very selective, pH independent, and emulsification is not necessary.

2. Just mix the drug and the hydrotropes with water for this operation.

3. Hydrophobic medications do not need chemical modification, organic solvent usage, or the creation of an emulsification system.

4. Application of hydrotropy: 1. Making dry syrups of medications with poor water solubility.

5. In the absence of organic solvents, quantitative evaluations of medications with low water solubility employing UV-Visible spectrophotometric analysis.

6. Titrimetric methods of analysis for numerical evaluations of drugs with limited water solubility. Two examples are ibuprofen and flurbiprofen. (*HYDROTROPHY: NOVEL SOLUBILITY ENHANCEMENT TECHNIQUE: A REVIEW | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH*, n.d.)

DRUGS	HYDROTROPIC AGENTS	DEGREE OF SOLUBILITY
Nevirapine	Urea, lactose, citric acid, mannitol	27,11,42,10 fold

lurasidone	Nicotinamide, urea, sodium citrate, sodium benzoate	12 – 61 fold
riboflavin	Nicotinamide, urea	20 fold
furosemide	Nicotinamide, urea, sodium citrate, sodium benzoate	16 – 296 fold

6.5. LIQUIDSOLID TECHNIQUE

Liquid may be transformed into a free-flowing, readily compressible, and apparently dry powder using the liquisolid method by mixing it with the right substances.

The coating ingredient as well as the carrier. The liquid component, which may be a liquid medication, drug suspension, or liquid drug solution in a suitable non volatile liquid vehicle, can be transformed into acceptable flowing and compressible powders by mixing with certain powder excipients. The powder version of liquid medication known as "Liquisolid Compact" is suitable for flowing and compressing.

The liquisolid formulation is a newer and more effective method because of its straightforward manufacturing procedure, cheap production costs, and industrial application because of its superior flow and compact features. Both absorption and adsorption take place when a drug dissolved in a liquid vehicle is added to a carrier substance like cellulose with a surface that is porous and closely matted fibres in its interior. The liquid is initially absorbed in the interior of the particles and is captured by its internal structure, and after this process reaches saturation, adsorption of the liquid onto both the interior and exterior surfaces of the porous carrier particles takes place. After that, the coating material gives the liquisolid system the appropriate flow properties by having a high capacity for adsorptive action and a large specific surface area.

The compacts' wettability is eroding as a result. Media Liquisolid condenses have been proposed as one of the causes for the increasing pace of media disintegration. The addition of a nonvolatile solvent in the liquisolid system improves the wetting of drug particles by reducing the interfacial tension that exists between the dissolving medium and the tablet surface.

Liquisolid compacts, which offer improved wettability due to a smaller contact angle than conventional tablets, are seen in Figure 2.

Classification of liquisolid system:

A. Depend on the type of liquid medication:

1. drug solution in powder form

2. drug solution in suspension form

3. powdered drug in liquid form

B. Depend on the technique of the formulation:

1. solid liquid compact
2. solid liquid microsystems

Components of liquisolid techniques: nonvolatile liquids ,carrier materials ,coating material, disintegrant, glidant ,lubricant, retardant material

The following benefits of the liquisolid approach:

1. Increases the oral bioavailability and solubility of medications that are poorly or completely insoluble in water.

2. The approach has applications in business.

3. Successful in the preparation of liquid or greasy medications.

4. Various carriers and additives, including PVP, PEG 60000, Hydroxypropyl Methyl Cellulose, and Eudragit, among others, may be used to modify drug release.

5. A number of poorly soluble drugs may be manufactured into the body.

6. Production costs are low in comparison to the price of making soft gelatin capsules.

7. Only powdered liquid medications are intended for use with this apparatus.

The following drawbacks of the liquisolid approach:

1. Increased bioavailability and dissolving rate due to high drug solubility in non-volatile liquid medicines.

2. It requires receivers with high levels of specific surface area and adsorption.

3. It does not apply to insoluble drugs used at large doses (more than 100 mg).

4. When a tablet is compressed, liquid medications may be forced out, giving the pill an inappropriate hardness (Namdev et al., 2022)

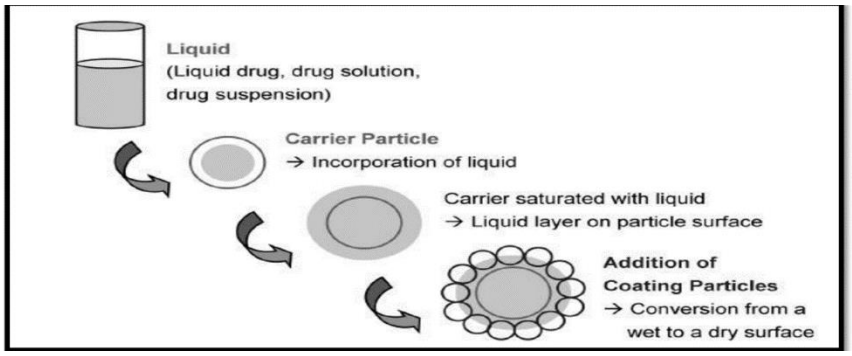

Figure 8 Liquisolid technique

6.6. MICELLES FORMATION

Amphiphilic compounds called surfactants have a hydrophilic or polar head and a hydrophobic or nonpolar tail. There are many surfactant heads available, including charged (anionic or cationic), dipolar (zwitterionic), and non-charged (nonionic). Among the anionic, cationic, nonionic, and zwitterionic surfactants are sodium dodecyl sulphate (SDS), dodecyl trimethylammonium bromide (DTAB), n-dodecyl tetra (ethylene oxide) (C 12 E 4), and decanoyl phosphatidylcholine (C 8 -lecithin). Halogenated, oxygenated, or siloxane chains are less common in surfactant tails, which are often long-chain hydrocarbon residues.

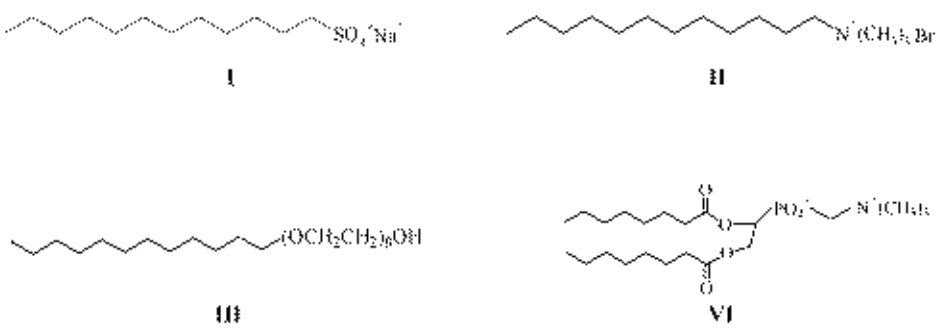

Figure 9 Different types of surfactants

I-anionic (SDS)

II-cationic (CTAB)

III- nonionic (C12 E4)

VI-zwitterionic (C8 -lecithin) surfactants.

A surfactant absorbs onto surfaces or interfaces when it is present in a system at low quantities, substantially changing the free energy of the surface or contact. Surfactants may be used to increase interfacial free energy, although they often act to reduce it. Surfactant molecules form micelles in water when their concentration exceeds the critical micelle concentration (cmc). The hydrophilic heads stay on the exterior surface of a micelle while the hydrophobic tails go to the inside to maximise water interaction.

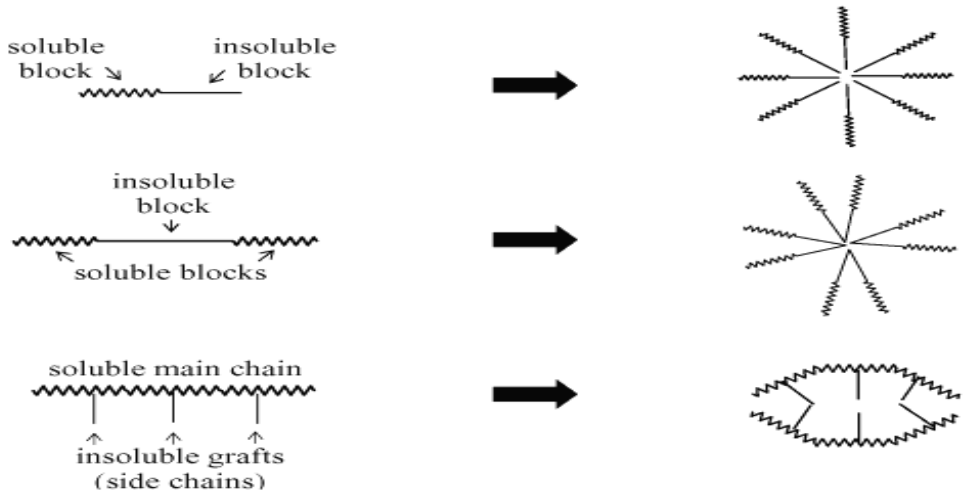

Figure 10 Different type of micelle chain formations

Hydrophobic, steric, electrostatic, hydrogen-bonding, and van der Waals interactions are only a few of the intermolecular factors that result in micelleization in water. The primary repellent force is produced by the electrostatic and steric interactions between the polar heads of the surfactant, while the primary attractive force is produced by the hydrophobic effect of the nonpolar surfactant tails. Micellarization can happen or not, and if it does, at what concentration of monomeric surfactant depends on the balance of forces favouring and opposing it.

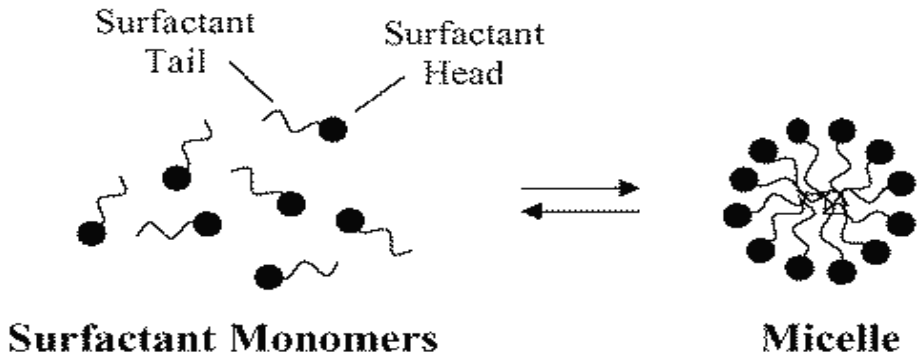

Figure 11 Micelle formation

Surfactant monomers aggregate noncovalently to form micelles, which are labile structures. They are hence capable of having spherical, cylindrical, or planar forms (such as discs or bilayers). Micelle shape and size may be altered by altering the chemical structure of the surfactant as well as factors in the solution such as pH, ionic strength, temperature, and total surfactant concentration. Depending on the surfactant type and solution conditions, spherical micelles may develop in one or two dimensions, becoming cylindrical, bilayer, or discoidal micelles. Since the curvature of the micelle surface and the available area per surfactant molecule at the micelle surface are both reduced during one-dimensional and two-dimensional growth by moving the surfactant heads closer to one another, the surfactant heads primarily regulate micelle growth.

$V_H/l_c a_o$	Micellar Structure
0 – 1/3	Spherical in aqueous media
1/3 – 1/2	Cylindrical in aqueous media
1/2 – 1	Lamellar in aqueous media
> 1	Reversed micelles in nonpolar media

Figure 12 Micelle structures

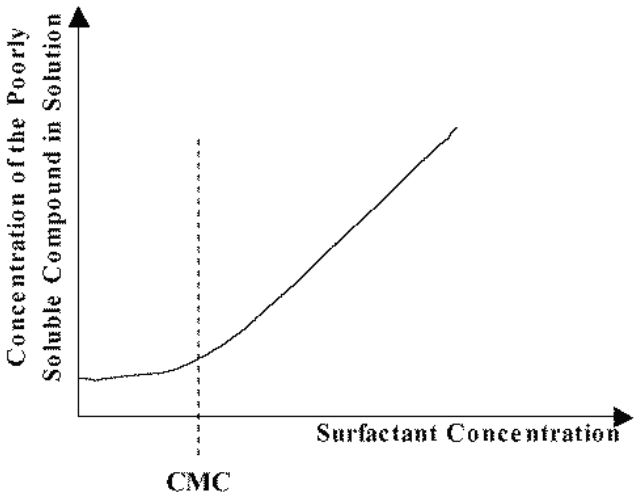

Figure 13 Surfactant concentration vs Drug concentration

Advantages of using wetting agents for solubility enhancement:

1. Improved bioavailability: Because poorly soluble medications sometimes have low bioavailability, only a tiny portion of the drug reaches the intended target location. Wetting agents may boost a drug's bioavailability and therapeutic effectiveness by making it more soluble.

2. Wetting agents enable for greater homogeneity and dispersion of the medication inside the dosage form, which may help increase drug delivery. More reliable medication release and absorption may result from this.
3. Wetting agents are a cost-effective way to increase solubility since they are often affordable and easily accessible.
4. Wetting agents are a flexible technique for improving solubility since they work with a variety of compounds and solvents.
5. Wetting agents are a good option for producing a range of dosage forms since they are often compatible with other excipients used in pharmaceutical and agrochemical formulations.

Limitations of wetting agents used to increase solubility

1. While wetting agents have a number of benefits for improving solubility, there are also some drawbacks to their use:
2. Because some wetting agents can be toxic at high concentrations, their use in some applications may be constrained. It is crucial to choose a wetting agent that is secure and appropriate for the application.
3. Stability: The use of certain wetting agents may be restricted in some formulations because they may become unstable in specific environments, such as high temperatures or acidic pH levels.
4. Drug activity interference: Using wetting agents may sometimes cause the drug's action to be disrupted. This is especially true for medications that are very sensitive to environmental changes.
5. Effects that are dose-dependent: Depending on the material and the solvent employed, the ideal concentration of the wetting agent may change. This is because wetting agents' effects on solubility may be dose-dependent.

Applications of wetting agents for improving solubility

1. The pharmaceutical and agrochemical industries make extensive use of wetting compounds to improve solubility. Wetting agents are used in various sectors in the following examples:
2. Oral dosage forms: To increase the solubility and bioavailability of poorly soluble medications, wetting agents are often employed in oral dosage forms, such as tablets, capsules, and solutions.
3. Topical formulations: Wetting agents may also be used to increase the solubility and penetration of active compounds in topical formulations like creams and gels
4. Wetting agents are often employed in the formulation of agrochemicals, such as insecticides and herbicides, to increase the solubility and effectiveness of the active component.
5. Coatings: To enhance the spreading and wetting qualities of coatings like paints and varnishes, wetting agents are also added to them. (Kanikkannan, 2018; Namdev et al., 2022)

6.7. SELF EMULSIFYING DRUG DELIVERY SYSTEMS:

When an aqueous medium, such as gastrointestinal fluids, is in touch with a self-emulsifying drug delivery system (SEDDS), it creates a fine oil-in-water emulsion using a combination of oils, surfactants, and co-surfactants.

SEDDS may increase the therapeutic effectiveness, bioavailability, and solubility of weakly water-soluble medicines. They may also increase the permeability of medicines across biological membranes and shield them from enzymatic destruction.

SEDDS are often produced in the form of liquid or semi-solid dosage forms including capsules, pills, or emulsions. They may be used for topical, transdermal, parenteral, or topical drug administration in addition to oral drug delivery, which they often perform.

SEDDS has the potential to minimise doses of medication while also improving drug absorption and pharmacokinetic parameter variability. SEDDS do have several drawbacks, however, including the possibility of drug precipitation, variation in drug absorption, and the need for rigorous formulation optimisation to guarantee stability and effectiveness.

Self emulsifying Drug Delivery System types:

Based on the ingredients in its formulation, self-emulsifying drug delivery systems (SEDDS) may be divided into many categories. Some of the SEDDS kinds that are often utilised include the following:

1. Oil-based SEDDS: These SEDDS have an oil phase as their main component, and they may be further divided into groups depending on the kind of oil that was utilised. For instance, they may be made using synthetic oils like medium-chain triglycerides (MCTs), caprylic/capric acid triglycerides, or propylene glycol esters of fatty acids or vegetable oils like maize, soybean, or sunflower oil.
2. Surfactant-based SEDDS: These SEDDS are made using a surfactant or a combination of surfactants as the main ingredient. To increase their emulsification effectiveness, they may additionally incorporate a co-surfactant.
3. Co-solvent-based SEDDS: These SEDDS have as their main ingredient one or more co-solvents, such as ethanol, propylene glycol, or polyethylene glycol.

SEDDS made of a polymer, such as polyethylene glycol or polyvinylpyrrolidone, serve as the main ingredient in these SEDDS.

The physicochemical characteristics of the medication, the planned route of administration, and the desired pharmacokinetic profile all play a role in the decision of which SEDDS type to choose. When choosing the best SEDDS type and perfecting its formulation for maximum efficacy and safety, formulators must carefully take these factors into account.

Importance of Self emulsifying Drug Delivery System:

Self-emulsifying drug delivery systems (SEDDS), which increase the solubility, bioavailability, and therapeutic effectiveness of poorly water-soluble medicines, are becoming more and more significant in drug delivery. SEDDS are crucial for the following reasons:

SEDDS may increase the solubility and dissolution rate of weakly water-soluble medicines, which increases medication absorption and bioavailability. This may have a more controlled and dependable therapeutic impact.

SEDDS may minimise the variability in pharmacokinetic parameters like Cmax (peak plasma concentration) and Tmax (time to reach peak concentration), which leads to more reliable drug administration and better therapeutic results.

SEDDS has the potential to increase a drug's bioavailability, allowing for lower dosages to have the same therapeutic impact. This may boost patient compliance and lower the chance of adverse consequences.

Versatility: SEDDS may be created for a variety of modes of administration, including oral, topical, and parenteral, and can be utilised for a broad range of medicines, including lipophilic, hydrophilic, and amphiphilic chemicals.

Improved stability: SEDDS may make medications more stable and prevent them from degrading, which extends their shelf life and improves storage conditions.

Overall, SEDDS are a potential drug delivery technique that may overcome the difficulties posed by medications that are not well soluble in water and enhance patient outcomes.

Self emulsifying Drug Delivery System examples:

Self-emulsifying drug delivery systems (SEDDS) are a formulation style used for a number of medications. Some examples are as follows:

Immunosuppressive medication known as cyclosporine is used to treat organ rejection and autoimmune illnesses. It is only marginally water soluble. Its self-emulsifying drug delivery system (SEDDS) formulation increases its solubility and bioavailability.

Drugs used to treat hyperlipidemia include fenofibrate, a lipid-lowering agent. To increase its dissolving rate and bioavailability, it is designed as a self-emulsifying drug delivery system (SEDDS).

Docetaxel: Docetaxel is a chemotherapy medicine used to treat malignancies such as breast, lung, and prostate. Its self-emulsifying drug delivery system (SEDDS) formulation increases its solubility and bioavailability.

Coenzyme Q10: A substance that boosts energy and acts as an antioxidant, coenzyme Q10 is used to treat a variety of ailments, including cardiovascular disease. Its self-emulsifying drug delivery system (SEDDS) formulation increases its solubility and bioavailability.

Immunosuppressive medication called tacrolimus is used to treat organ transplant rejection because of its limited water solubility. Its self-emulsifying drug delivery system (SEDDS) formulation increases its solubility and bioavailability.

These examples show the adaptability of SEDDS and their potential to enhance the therapeutic effects of medications that are not very water-soluble.

Self emulsifying Drug Delivery System benefits:

Compared to conventional drug delivery methods, self-emulsifying drug delivery systems (SEDDS) provide a number of advantages. Some of the main advantages of SEDDS include:

SEDDS may increase the solubility and bioavailability of medications that are weakly water-soluble, resulting in greater drug absorption and a more controlled therapeutic impact.

Improved medication stability: SEDDS may make pharmaceuticals more stable by preventing their deterioration and extending their shelf life.

Less variation in the dose: SEDDS may lessen the variation in pharmacokinetic parameters like Cmax and Tmax, resulting in more reliable drug administration and better clinical results.

Lower pharmacological dosages may be used with SEDDS, which lowers the risk of toxicity and adverse effects.

SEDDS may make medication delivery more user-friendly and easy, increasing patient compliance and adherence to treatment.

Versatility: SEDDS may be created for a broad variety of medications and can be utilised for oral, topical, and parenteral delivery.

SEDDS have the potential to increase the effectiveness and safety of medication treatment while providing considerable benefits over conventional drug delivery systems. This might enhance patient outcomes and quality of life. (Salawi, 2022)

Self emulsifying Drug Delivery System disadvantages:

Limitations and drawbacks of self-emulsifying drug delivery systems (SEDDS) must be considered. The following are some possible drawbacks of SEDDS:

SEDDS are complicated formulations that need careful excipient selection and formulation parameter optimisation to obtain the required drug release profile and stability.

Variability across patients: The gastrointestinal transit time, food consumption, and patient-specific characteristics may all have an impact on how well SEDDS are absorbed, resulting in interpatient variability.

Limited drug loading: SEDDS's high excipient content limits their ability to load pharmaceuticals, which may make them ineffective for medications needing large dosages.

SEDDS have the potential to interact with other medications or dietary substances, changing the pharmacokinetics and absorption of such medications.

SEDDS are more costly to produce than traditional medication formulations, which may restrict their availability and utilisation.

Regulatory obstacles: SEDDS must undergo extensive validation and testing in order to satisfy regulatory standards, which may be expensive and time-consuming.

When creating SEDDS and choosing them for medication delivery applications, it is crucial to take these potential limitations into account. Despite these drawbacks, SEDDS have

demonstrated significant potential for enhancing the effectiveness and safety of medication. (Singh et al., 2009)

6.8. MICROEMULSION:

A microemulsion is a dispersion of two incompatible liquids (often oil and water) that is stabilised by a third substance, such as a surfactant or a co-surfactant, and is thermodynamically stable. Small droplets with a size range of 10 to 100 nanometers are dispersed throughout the other liquid as droplets of the first liquid.

A large interfacial area between the two liquids, optical clarity, and thermodynamic stability are only a few of the distinctive qualities of microemulsions. Microemulsions may be used for a number of purposes, such as the administration of drugs, food processing, and personal care items.

According to the components of the system, there are three different kinds of microemulsions: bicontinuous, water-in-oil, and oil-in-water (O/W). While in a W/O microemulsion the water droplets are dispersed in the oil phase, oil droplets are dispersed in the water phase in an O/W microemulsion. Both the oil and the water phases are continuous in a bicontinuous microemulsion, generating a web of interconnecting channels.

The adsorption of the surfactant or co-surfactant at the interface and the interfacial tension between the two liquids must be carefully balanced in order for a microemulsion to occur. To create a stable and effective system, much consideration must go into choosing the surfactant, co-surfactant, and the two immiscible liquids. (Mariyate & Bera, 2022)

5.8.1 Based on their makeup and properties, microemulsions come in a variety of forms. Here are a few examples of the most well-known types:

1. Oil-in-water (O/W) microemulsions: These are emulsions in which a continuous water phase contains scattered oil droplets. O/W microemulsions are often used in the creation of pharmaceutical and personal care goods.

2. Water-in-oil (W/O) microemulsions: These are emulsions in which a continuous oil phase is mixed with small droplets of water. Topical creams and lotions are often made using W/O microemulsions.
3. Bicontinuous microemulsions: These have continuous water and oil phases that link to create a network of channels. In the creation of food items and medicine delivery systems, bicontinuous microemulsions are often utilised.
4. Droplet sizes for nanoemulsions, a subtype of microemulsion, vary from 20 to 200 nanometers. Pharmaceuticals, personal care items, and food goods all often incorporate nanoemulsions in their composition.
5. Multiple emulsions: Multiple emulsions can have several phases and more than two immiscible liquids. In the creation of food goods, cosmetics, and medicine delivery systems, several emulsions are often employed.

The required qualities and the intended application determine the kind of microemulsion that should be utilised. Each kind has distinct qualities that make it appropriate for certain purposes.

Benefits of using microemulsions:

1. Enhanced stability: Microemulsions do not disintegrate into their component phases over time because they are thermodynamically stable. The tiny droplet size and the presence of surfactants, which stabilise the droplets, are credited with this stability.
2. Improved solubility: Microemulsions are helpful in chemical and pharmaceutical applications because they may make poorly soluble medicines and other compounds more soluble.
3. Increased absorption and distribution in the body: Microemulsions may increase a drug's bioavailability by boosting its absorption and dispersion.
4. Enhanced productivity: Microemulsions may improve the productivity of procedures including food processing, cleaning, and oil recovery.
5. Better sensory qualities: When compared to conventional emulsions, microemulsions have better sensory qualities, including a smoother texture and increased transparency.

Disadvantages of microemulsions:

1. Complexity: Creating microemulsions may be challenging, and it takes careful consideration when choosing the ingredients to create a system that is both stable and effective.
2. Price: When compared to conventional emulsions, the expense of the surfactants as well as other ingredients used in microemulsions may be greater.
3. Limited scope of application: Microemulsions may not work well in all situations and might not work well with some substances or environmental factors.
4. Health and safety issues: Some of the ingredients employed in microemulsions might be poisonous or have an adverse effect on the environment, which call for cautious monitoring.

Overall, microemulsions offer a number of benefits that make them helpful in a number of applications; nevertheless, while creating and using them, care must be taken to take into account both their special characteristics and possible drawbacks.(Spernath & Aserin, 2006)

Microemulsions have a variety of roles and applications in different fields, including:

1. Pharmaceutical industry: Microemulsions are utilised in the creation of drug delivery systems to enhance the solubility and bioavailability of medicines that are not readily soluble. For applications on the skin and eyes, they are also used as topical medication delivery methods.
2. Industry of food: Flavourings, colours, and nutrients are delivered by microemulsions, which are also utilised as food additives and emulsifiers. For enhancing effectiveness and quality, they are also utilised in the preparation of food.
3. Industry of cosmetics and personal care: Due to microemulsions' enhanced sensory qualities, stability, and skin penetration capabilities, lotions, creams, and other cosmetic goods are made using them.
4. Industrial uses: Due to their increased efficacy and efficiency, microemulsions are employed in cleaning, lubrication, and oil recovery.

5. Applications in the environment: Microemulsions are used to remove toxins and pollutants from soil and water during environmental restoration.

Microemulsions play a variety of roles depending on the particular application and desired attributes, but because of their special qualities, they are helpful in a variety of industries and contexts.

To sum up, microemulsions are thermodynamically stable systems made up of tiny droplets of one immiscible liquid distributed in another liquid phase, stabilized by surfactants and co-surfactants. They are beneficial for a variety of applications, including medicines, food, cosmetics, and environmental remediation, thanks to their many benefits, including enhanced stability, solubility, bioavailability, efficiency, and sensory qualities. However, due consideration must be given to their formulation and use in order to account for both their special qualities and any potential drawbacks, such as complexity, expense, a narrow range of applications, and potential risks to human health.

7. CONCLUSION:

In conclusion, the solubility enhancement techniques discussed in this article are crucial in the pharmaceutical industry to improve the bioavailability and efficacy of drugs. Each technique has its advantages and limitations, and the choice of technique depends on various factors such as the physicochemical properties of the drug, the desired dosage form, and the intended route of administration. The use of these techniques has the potential to transform poorly soluble drugs into effective therapeutic agents, thereby improving patient outcomes. However, further research is needed to fully understand the mechanisms underlying these techniques and to develop novel approaches for solubility enhancement.

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