Review Article

Solubility of Drugs, Their Enhancement, Factors Affecting and Their Limitations: A Review

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ABSTRACT

The solubility of drugs is a crucial factor in determining their efficacy and bioavailability. This review article provides an overview of the concept of drug solubility, including enhancement methods and factors that affect solubility. The limitations of current methods are also discussed, along with why we need to continue the improvement in drug solubility. The article highlights the importance of solubility in drug development and delivery, and provides insights into the future of solubility research and its potential impact on patient outcomes along with the examples of each method mentioned with advantages and disadvantages.

Keywords: Solubility, Physical, Chemical, Supercritical, Polymeric, Ph.

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INTRODUCTION

The International Union for Pure and Applied Chemistry defined, "Solubility is the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent[1]. Also stated as "Dexterity of one substance to entirely deliquescence in another substance under disciplined conditions such as Temperature and Pressure". It is expressed in Grams/Liter.

The solute is the minor component in a solution dissolved in a solvent, a dissolved agent is usually a less abundant part of the solution[2-5].

Why is the Solubility of Drugs important?

If the solubility of the drug is poor the amount of drug required by the system to act on the target area will be less as the amount of drug being administered is supposed 500mg in the body but the solubility is poor so the body will be supposed absorb less than 500mg, to tackle this the frequency of dose will be increased, Increasing the frequency of drug will have some adverse effect on the body as every drug has some side effect and the patient may start to suffer from any other disease.

*Around 92% of the drug in the market faces solubility issues and 8% of the drug in the market is soluble to a class 1 to class 2 level of BCS (table 1).

Class Boundaries

To consider the boundary in this Solubility and Permeability is taken in consideration. In all Class of BCS classification boundary can vary on source[3].

Solubility: The appropriate drug should have 1 gram per liter (g/L) solubility at 37 degrees Celsius in aqueous media. Table 2 represents the different solubility expression along with examples.

Permeability: The appropriate drug should have a permeability coefficient of 1×10^-6 cm/s in a Caco-2 cell monolayer or an intestinal epithelial cell model of human.

Drugs of Class 1 and 3 are believed to have a good bioavailability, and Drugs of Class 2 and 4 sometimes require special formulation to improve their absorption as they have poor bioavailability[4].

Drugs of Class 2 and Class 4 are modified using Micronization, Complexation, Pro-Drugs, Solid Dispersion and Lipid-base formulations.

Advantages and Disadvantages of High Solubility and Low Solubility[3-4]

High Solubility:

Advantages:

1. They have a faster onset of action as they are more like to be bioavailable.

Table 3 represents the examples of some drugs along with their bioavailability on the basis of route of administration.

2. Variety of dosage forms can be prepared.

3. Crystal formation is very less, which reduces the risk of poor dissolution and precipitation.

4. To reduce the risk of adverse effects they can be administered in lower doses.

Disadvantages:

1. Increased in risk of chemical degradation can cause them lower shelf life.

2. Increase the risk of toxicity as they have lower therapeutic window.

3. Absorption and Bioavailability can be affected as they are more prone to interactions with other drugs and food.

Low Solubility:

Advantages:

1. Chemical degradation is reduced which leads to increase in Shelf life.

2. Risk of toxicity is reduced as they have a wider therapeutic window.

3. Bioavailability and Effectiveness is improved as they are less prone to interactions with other drugs and food.

Disadvantages:

1. They may require higher doses and longer dosing intervals because of their poor bioavailability.

2. Onset of action is slow.

3. Effectiveness may be reduced as they are prone to precipitation and poor dissolution.

4. To improve their bioavailability, they may require special formulations.

BCS Classification

The British Pharmacopoeia (BP) classifies drugs into four categories, known as the BCS classification (figure 1). These categories are based on the solubility and permeability ofthe drug.

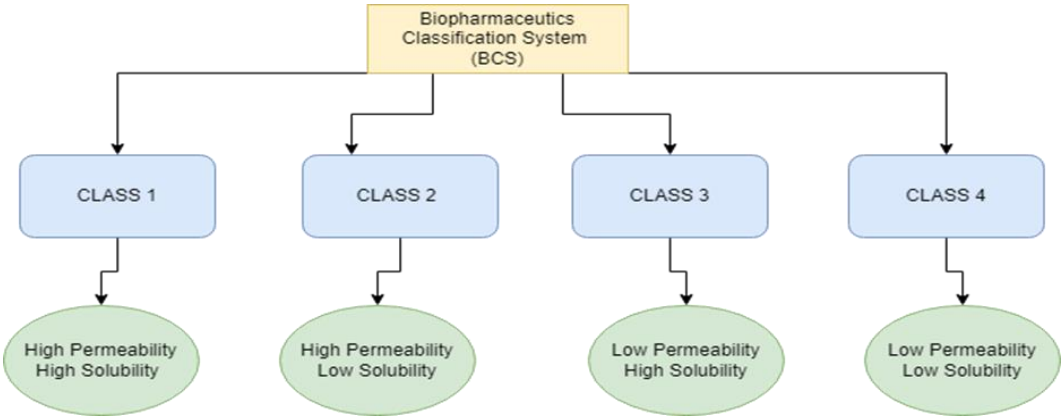

Figure 1: BCS Classification.

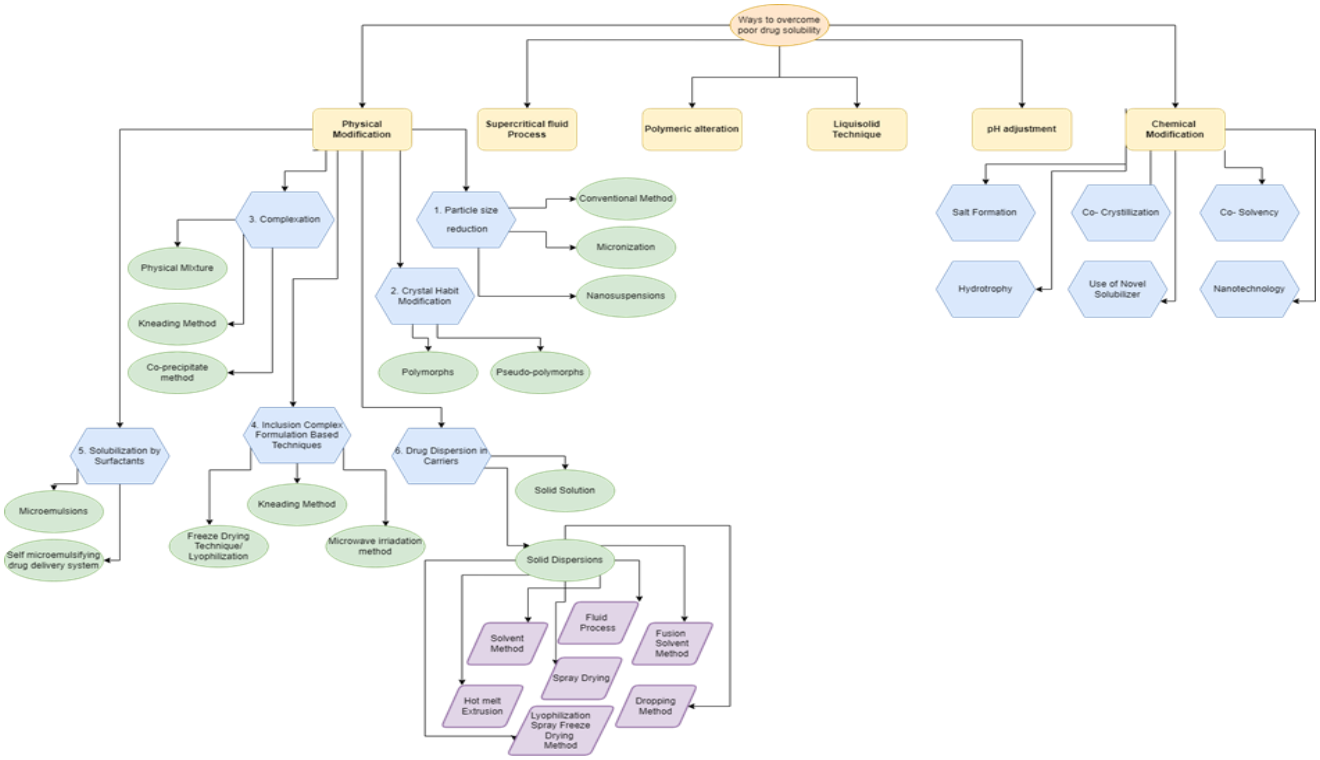

Figure 2: Ways to Overcome poor solubility of drug.

Table 1: Examples of BCS classes with some marketed preparations along with their dose and absorption time.

Class	Drug Name	Name in Market	Marketed Preparation	Company	Standard Dose	Absorption Time
1	Ibuprofen	Advil	Tablet	Pfizer	200-400mg every 4-6 hours (Not to exceed 3200mg in 24 hours)	20-30 minutes
2	Diltiazem Hydrochloride	Dilzem	Capsule/ Tablet	Torrent Pharmaceuticals Ltd.	30-120mg orally. T.D.S.	30 minutes to 2hours
3	Gliclazide	Glycinorm	Capsule/ Tablet	Ipca LaboratoriesLtd.	80mg O.D. daily before Breakfast	30 minutes to 2hours after oral administration, peak effect occur between 2-4 hours
4	Griseofulvin	Griseoful vinFP	Tablet/ Oral Suspension	GSK Pharmaceuticals Ltd.	200-500mg a day for 6-8 weeks	1-2 hours after oral administration,peak effect occurs between4-8 hours.

Table 2: Solubility Expressions and Examples

Terms	Parts of Solvents required for1 part of Solvent	Example
Very Soluble	Less than 1 part (**Quickly dissolve)**	Aspirin (acetylsalicylic acid) Paracetamol (acetaminophen) Ibuprofen
Freely Soluble	1-10 parts (**Dissolves**)	Sodium chloride (NaCl) Glucose, Sucrose
Soluble	10-30 parts (**Dissolve by mix bystirring**)	Sulfamethoxazole Diclofenac, Naproxen
Sparingly Soluble	30-100 parts (**Dissolve on heating**)	Silver nitrate ($AgNO_3$) Barium sulfate ($BaSO_4$) Calcium carbonate ($CaCO_3$)
Slightly Soluble	100-1000 parts (**Heating byStirring**)	Digoxin, Phenytoin Carbamazepine
Very Slightly Soluble	1000-10,000 parts (**Maximum efforts very low amount of solutedissolved**)	Silver NitrateLead Sulfate Calcium Phosphate
Practically Insoluble	More than 10,000 parts (**Does notdissolve**)	Paclitaxel, Tetracycline

Table 3: Examples of drugs with their bioavailability and route of administration.

Route	Bioavailability (%)	Characteristics	Examples of Drug
Transdermal	80 to less than 100	Very slow absorption, lack of first-pass effect, prolonged duration of action	Nicotine Patch Hormone Replacement Therapy Birth Control Patches
Inhalation	5 to less than 100	Often very rapid onset	Bronchodilators Steroids, Antibiotics
Rectal	30 to less than 100	Less first-pass effect than oral	Suppositories Enemas, Rectal Creams
Oral	5 to less than 100	Most convenient, first-pass effectpresent	Tablets, Capsule, Liquids
Sub-cutaneous	75 to less than 100	Smaller volumes than I.M. maybe painful	Insulin, Growth Hormone Epinephrine
Intramuscular	75 to less than 100	More Painful	Antibiotics, Hormonal Agents Vaccines
Intra- venous	100 by definition	Most rapid onset	Cancer, Chemotherapeutics Antifungals Antinociceptive drugs

Chemical Modifications (table 4)

1. Salt Formation:

Pure forms of Drugs (API) that is not able to be formulated in their original (pure) forms due to issues of instabilities5. To overcome this problem, the drug (API) is converted into solid forms: Salts, Co- Crystals, Solvates, Hydrates, and Polymorphs (table 4). Every method has its Physiochemical property which also affects the performance characteristics stability, production, amount of drug available to the system (bioavailability), and the purification of the drug in their ways (table 5). The ionization of compounds leads to the formation of Salt. The method is useful in the Parenteral, Liquid forms, and solid dosage forms. Drugs that were converted to salts have far better solubility than it was in their original form of the drug[6].

2. Co- Crystallization:

Revamping the molecular interaction is a contemplative assuring substitute to enhance drug properties. Co-Crystallization in the words can be said as "Formation of a multicomponent crystal between two compounds that are solid under ambient condition, where at least one component is an ion or molecule". Overcoming the various chemical, physical or physiological drawbacks of API has been made possible through the method of co-crystallization[7] (table 5).

Various methods through which Co- crystallization is achieved.

1. Solvent evaporation.
2. Grinding.
3. Slurry Co- Crystallization.
4. Solvent Drop grinding.
5. Hot Melt Extrusion
6. Son crystallization method.

3. Co- Solvency/ Solvent Blending:

Enhancement of poorly water-soluble drugs by adding a solvent (water miscible) the solubility of the drug is good and reduces the interfacial tension between the hydrophobic solute and aqueous solution8. These types of drugs are always in liquid form. It has low toxicity therefore used commonly in the parenteral dosage form. The lipophilic or highly crystalline compounds which are poorly soluble can be used in the Co-solvent approach method[9].

4. Hydrotrophy:

An increase in the aqueous solubility by adding an excess amount of the second solute increases the aqueous solubility of the preexisting solute[9].

5. Nanotechnology:

The previous technique of Micronization is not as much as useful because some drugs cannot be made soluble using the micronized method and bioavailability was not reached, so to overcome these problems the researchers took a step ahead and started using nanotechnology methods in the enhancement of the solubility of the drug[10].

Physical Modification (table 6)

1. Particle Size Reduction:

The particle size of any drug is directly related to the solubility of that particular drug and has a greater affinity towards it. As the size of the particle decreases the surface area to volume ratio increases thus enhancing the solubility of the drug (table 7). Inhalants are highly soluble as compared to Tablets or any other form of the drug[11].

a. Conventional Method:

Cutting, Compression, Impact, Attrition, Combined Impact, and Attrition are the various methods that are employed to reduce the particle size in the conventional method. Reducing the particle, it only does not have a positive effect on solubility but also has a positive effect on the economy and the pharmaceutical industry producing it as the very last of the drug is used and the wastage is reduced.

But the conventional method of size reduction cannot always be used as some drugs are poorly soluble and even this method alone will not help in increasing the solubility of the drug[12].

b. Micronization:

Conversion of high coarse particles into smaller fine particles of size less than 5 µ using high energy . It helps in the formation of uniform and narrow-size particles which is essential for developing a proper uniform dosage form[13]. A decrease in particle size increases the surface area thus increasing the solubility. The different techniques used in Micronization have a different impact on the micronized particle size. The most commonly used micronized techniques include Mechanical Communition, Spray drying, and supercritical fluid (SCF) technology[14].

Various methods employed in Micronization are[14]:

- Micro-crystallization and Microprecipitation
- Rotor stator colloids mills
- Fluid energy mills/ Jet milling or micronizer
- Spray freezing into liquid
- Supercritical fluid technology
- Controlled crystallization

c. Nanosuspensions

Drugs that are poorly soluble in both water and oil are made soluble using the nanosuspension method15. It is a biphasic system that contains drug particles of nano sizes in the aqueous vehicle stabilized using surfactants for the use of parenteral or oral form and pulmonary administration. In nanosuspension, the particle size is generally reduced to less than 1 micron with the average and approximate particle size ranging from 200 to 600 nm. Bottom-up technology and top-down technology are the two methods used in the formation of nanosuspension[16].

2. Crystal Habit Modification (table 8)

The ability of a compound to crystallize in more than one crystalline form is termed Polymorphism[17]. Polymorphs of drugs are chemically identical but they have different physiochemical properties which include melting point, solubility, texture, density, and stability. When comparing between crystalline form and the amorphous form is more favored as it has a larger surface area and higher energy associated with it[18-20] (table 9).

Table 4: Examples of Drug modified by chemical method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Salt Formation	Valsartan	Diovan	Novartis	Tablet	Oral	80-320mg	Hypertension and HeartFailure.
Co- Crystallization	Paracetamol	Tylenol	Johnson & Johnson	Tablet/Capsule/ Syrup/Suppository/ Oral Suspension	Oral or Rectal depending upon dosage form	325-1000mg every 4-6 hours (Not to exceed 4gm perday)	Mild to Moderate pain and inFever.
Co- Solvency	Itraconazole	Sporanox	Janssen Pharmaceuticals	Capsule	Oral	200mg once or twice daily	Fungal Infections.
Hydrotrophy	Aceclofenac	Acenac	Medley Pharmaceuticals	Injection	IV/IM	100mg twice daily	Pain and Inflammationin Osteoarthritis and Rheumatoid arthritis.
Nanotechnology	Paclitaxel	Abraxane	Celgene	Injection	IV	260mg/m2 every 3 weeks.	Breast and Non-smallcell lung cancer

Table 5: Advantages and disadvantages of chemical modification method.

Method	Advantages	Disadvantages
Salt Formation	Improvement of bioavailability and absorption of drug. Improve the safety of drug assome salt form of drug is less toxic than the parent drug.	Salt form of drug may be less potentthan parent drug so it requires high doses of drug to achieve its therapeutic effect. Few drugs can have bitter taste intheir salt forms so it can cause barrier for patient compliance
Co- Crystallization	It increases the solubility by forming the new crystal structure which is more watersoluble compared to parent drug. Increases the stability as the new crystal formed is more stable compared to the originalparent drug.	It is a complex process as it requiresidentification of suitable co-crystal partners and crystallization condition. Co-crystallization cannot be done with every drug which is available in market as there is limited suitablepartner available.
Co- Solvency	Increase in solubility by increase in the polarity ordielectric constant of the system. It reduces the interactions between the drug and solvent which may increase stability and prevent precipitation and degradation of drug.	Certain dosage forms are not compatible with Co-solvency method such as injectables, and some co-solvents may have toxic orother safety concerns. Viscosity of drug and other formulation properties can be affected by the addition of co-solvents which may not be suitable for certain dosage forms.
Hydrotrophy	Increase in solubility by increase in the polarity ordielectric constant of the system. It is inexpensive and generally easily available making it mostaffordable method of enhancing solubility.	Some hydrotropes are not approvedfor human uses so they may requireadditional regulatory approval. Viscosity and other properties of formulation can be affected whenadded hydrotropes so may not be suitable for certain dosage forms.
Nanotechnology	It increases the solubility ofhydrophobic drugs which increases the bioavailabilityand efficacy of drugs. It allows for targeted deliveryof drugs to the specific tissue or cells, and reducing off target effects improving efficacy and safety of drugs.	It increases the Surface area of drugsas they are reduced to nanoparticles which leads to increase in toxicity incase of poor biocompatible particles. It is a costly method and can increase the cost of final product of drug to a greater margin.

Table 6: Examples of Drug modified by physical method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	StandardDosage	Used In
Particle size reduction	Ibuprofen	Advil	Pfizer	Tablet	Oral	200-400mg every 4-6 hours (Notto exceed 1200mg in day)	Pain, Fever, Inflammation.
Conventional method	Amoxicillin	Amoxil	GSK	Capsule/ Oral Suspension Form	Oral	200-500mg every 8 hours for mild to moderate infection and 500- 875mg every 8 hours forsevere infection,	Pneumonia, Bronchitis, UTI and Skin Infection.
Micronization	Albuterol	Proair HFA	Teva Pharmaceuticals	Inhaler	Inhalation	Children above 4 years is 2 puffs every 4-6 hours maximum 12 puffsper day	Asthma, Bronchospasm, COPD
Nanosuspensions	Itraconazole	Sporanox	Janssen Pharmaceuticals	Capsule	Oral	200mg O.D., for mild to moderate infection and 200mg B.D., for severe infection	Fungal Infection such as Aspergillosis, Blastomycosis and Histoplasmosis

Table 7: Advantages and disadvantages of physical modification method.

Method	Advantages	Disadvantages
Particle size reduction	Reduction in particle size increases the surface area of drug increasing the solubility of drug providing greater bioavailability. It is simple method and is cost effective compared to nanotechnology method so can easily be produced.	Increasing in surface area increases the drug's susceptibility to oxidation or degradation which reduces the shelf life of drug and bioavailability. It has a poor reproducibility which may vary from batch to batch whichcan affect the drug's solubility, stability, and efficacy.
Conventional method	It is a well-established methodbeing used from decades which includes Salt formation,Solvates and Solid dispersion. It is more cost effective than other methods which includes nanotechnology and particle size reduction.	This method of improving solubilityof drug may not be as effective to variety of highly hydrophobic drugs. This method can cause stability issues, such as increase in susceptibility to oxidation or degradation or oxidation and change in drug's crystal form.
Micronization	Particle size reduced which increases surface area for absorption of drug in humanbody. It is cost effective method ascompared to other method which are used for the same purpose.	It is difficult to obtain same particlesize every time which can cause problem in consistency of reproduced particle size distribution which effects the drug's stability, solubility and efficacy. This method can cause stability issues, such as increase in susceptibility to oxidation or degradation or oxidation and change in drug's crystal form.
Nanosuspensions	It provides a targeted deliveryof drugs to specified tissue or cells increasing the bioavailability and efficacy ofdrugs and reducing off target effects also increasing safety of drugs. It increases the stability of drugs, saving them from oxidation or degradation.	It has regulatory challenges and regulatory approval is challenging because safety and efficacy of system needed to be demonstrated before the drug launches in market. It is a complex process which makes the formulation process challenging and increase in the cost of final product.

Table 8: Examples of Drug modified by crystal habit modification method along with their marketed formulation, dosage form and their applications.

Method	Example	Market Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Crystal habit Modification	Levothyroxine	Synthroid	AbbVie	Tablet	Oral	Depends upon Patient need	Hypothyroidism
Polymorphism	Carbamazepine	Tegretol	Novartis	Tablet	Oral	Seizure 200-1200mg/day Bipolar Disorder 400-1200mg/day	Seizures, Trigeminal neuralgia and bipolar disorder
Pseudo-polymorphism	Naproxen	Naprosyn	Bayer AG	Tablet/ Oral Suspension	Oral	250-500mg every 8-12 hours maximum daily dose of 1250mg	Rheumatoid Arthritis, Osteoarthritis, and gout

Table 9: Advantages and disadvantages of crystal habit modification method.

Method	Advantages	Disadvantages
Crystal habit Modification	It increases the stability of the drug compound by reduction intheir degradation or oxidation. It is less expensive method when compared with other methods like nanotechnology,Micronization or particle size reduction.	It has limited control which may leadto variability in the results and in some cases not achieving the level ofsolubility which is desired by the drug. It may cause changes in the physicalproperties of the drug like increasedhygroscopicity or changes in the dissolution rate which may lead to the incompatibility issue of the drug with other additives and excipients in the final product.
Polymorphism	It improves the solubility andbioavailability of drug and enhancing its stability. It improves processing and handling characteristic of drug.	It is a complex and time-consumingprocess and has difficulty in predicting and controlling the outcome of the modification. It has regulatory issues with regard toapproval of modified form and has risk of loss of crystalline identity andpotency.
Pseudo-polymorphism	It has better flow and handling properties. Use of excipients is reduced which helps lowering of manufacturing cost, making itcost effective.	Risk of loss of biological activity ofthe drug molecule. Unwanted impurities during thepreparation process.

3. Complexation (table 10)

The formation of a non-bonded entity with a well-defined stoichiometry by the association between two or more molecules is known as Complexation[19-20].

There are two types of complexes:

i. Stacking Complex:

It forms a clear solution by the association of the complexing agent and the non- polar area of the drug which results in the exclusion of the non-polar area from contact with water. The stacking can be homogenous or mixed20.

ii. Inclusion Complex:

Insertion of the non-polar molecule into the cavity of another molecule or group of molecules. Cyclodextrin (CDs) and their derivatives can be seen in commonly used in complexation20.

a. Physical Mixture:

Mixing the CDs or suitable polymer thoroughly by trituration in a mortar and passing through appropriate sieves to get the desired size of particle in the final product[21] (table 11).

b. Kneading Method:

The CDs are soaked with a minimum quantity of water or any hydro-alcoholic solution which converts it into a paste. When the paste is formed, the drug is added to it and for a specified time it is kneaded. Then after drying the paste, it is passed through sieves[21].

c. Co-precipitate Method:

A specific amount of the drug is added to Cyclodextrin solution or a suitable polymer. This mixture with controlled process parameters is kept under magnetic agitation and kept away from light. The formed precipitate is passed through vacuum filtration to separate it and is kept at room temperature for drying, to avoid the loss of water from the inclusion complex. This method is industry oriented[21-25].

4. Inclusion of Complex Formulation Based Techniques (table 12)

Formation of inclusion complex is achieved by lodging a non-polar region of one molecule or a non-polar molecule (also known as GUEST) into the gap or cavity of other groups of molecules or a single molecule[22]. Cyclodextrin is the most commonly used host molecule. The host must bear a cavity of a variable greater size to accommodate the guest and comparatively smaller so that water can be eliminated from it[23]. The formation of a Solid Inclusion complex can be done by a number of methods, which include, the Kneading Method, Co-precipitation Method, Neutralization, Co-grinding Method, Spray Drying Method, and Microwave Irradiation Method[24] (table 13).

a. Kneading Method:

The CDs are soaked with a minimum quantity of water or any hydro-alcoholic solution which converts it into a paste. When the paste is formed, the drug is added to it and for a specified time it is kneaded. Then after drying the paste, it is passed through sieves[25-27].

b. Lyophilization/Freeze-Drying Technique:

It is a process in which molecular mixing of drug and solvent takes place in a common solvent, which can also be referred to as an alternative for solvent evaporation26-29. Lyophilization is hugely dependent upon the unique property of water as water plays a vital role in being as Solvent, Gas, Diluent, Plasticizer, and Stabilizer. This method involves the removal of the solvent system from the solution by primary freezing and subsequent drying of the solution with contains both drug and Cyclodextrin at reduced pressure[28-31].

c. Microwave Irradiation Method:

As the name suggests this method employs the use of a Microwave oven, which causes a microwave irradiation reaction between the drug and the complex agent[30-34]. The Cyclodextrin and the drug are mixed in a solution of organic solvent and water in specified proportion in R.B.F in definite molar ratio. Then the reaction is initiated in a microwave for

1-2 minutes at a temperature of 60ºC[35-37]. When the reaction gets completed, the solution is added adequately so that the residual, uncomplexed free drug and Cyclodextrin are removed. Then using the Whatman filter paper, the precipitate is filtered, and using a vacuum oven it is dried for 48 hours at 40ºC[36-39].

5. Solubilization by Surfactants (table 14)

Molecules that contain both polar and non-polar regions are termed Surfactants. Generally, a surfactant consists of a segment of hydrocarbon connected to a polar group. The polar group to which the hydrocarbon segment is attached can be anionic, cationic, zwitterionic, or nonionic[40]. The addition of small polar molecules can create an accumulation in the hydrophobic core of the micelles. This is the most important process employed in industries for the solubilizing process. With the addition of surfactants, the solubilization of lyophilic drugs is increased in an aqueous medium, as it decreases the surface tension thus increase in solubility. Suspensions are stabilized using Surfactants[41]. When the Surfactants concentration is greater than the critical micelle concentration (CMC), the formation of micelle takes place, which traps the drug inside it this is known as Micellization, and by this, the solubility of the poorly soluble drug is achieved[42] (table 15).

a. Microemulsions

A Microemulsion is isotropic, Thermo dynamically stable, transparent, optically clear pre-concentrate, translucent system, which contains a mixture of hydrophilic surfactant and hydrophilic solvent, oil which dissolves drugs which is poorly soluble in water[42-46]. When the solution comes in contact with water self-emulsification of solvent takes place and it forms a clear emulsion of uniform and small oil droplets which enclose the solubilized poorly soluble drug. Criteria for the selection of surfactant are the non- toxicity and HLB. A huge number of drugs which is insoluble in water are made soluble using the method of micro-emulsion, along with the addition of proteins, for parenteral and oral. The most suitable emulsion which can be used is O/W which increases the solubility[45-50].

b. Self-emulsifying drug delivery systems (SEEDS)

This method uses the approach of In Situ emulsion formation in the GI tract. The combination of various entities which includes the mixture of oil, co-surfactant, surfactant, on or more than one hydrophilic solvent, co-solvent articulates an isotropic solution that is transparent in nature and is known as (SEEDS)[49]. SMEDDS (Self micro emulsifying drug delivery system) solution of surfactant and oil which is isotropic in nature and on mild agitation in presence of water from O/W microemulsions. On administering Orally these novel colloidal formulations act as O/W microemulsions[48-57].

c. Micellar Solubilization

The dissolution of poorly soluble drug products has been improved using the Surfactants. In aqueous medium the solubilization of lipophilic drug is improved by lowering the surface tension using the Surfactants[56]. Micelle formation occurs when the concentration of surfactant exceeds the CMC (Critical Micelle Concentration) and the micelle entraps the drug inside it. This is termed as Micellization and the enhancement of solubility of poorly soluble drugs takes place[58-61].

Non-Ionic Surfactants which are generally used includes: -

- Polyoxy Ethylated Castor Oil
- Polysorbates
- Polyoxyethylated glycerides
- Lauryl Macroglycerides

This method is widely used for the enhancement of poorly soluble drugs.

Table 10: Examples of Drug modified by complexation method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	StandardDosage	Used In
Physical Mixture	Amoxicillin and Clavulanicacid	Augmentin	GSK	Tablet, Capsule and Oral Suspension	Oral	Depend on Type and Severity of Infection butadministered Twice a day.	Respiratory Tract Infection and Urinary TractInfection
Kneading Method	Indomethacin kneaded with Hydrophilic Polymer (PEG)	Indocin	Merck	Capsule/ Tablets and Suppositories	Oral and Rectal	25-50mgT.D.S.	Relieve Pain and reduce Inflammation in Osteoarthritis, Rheumatoid Arthritis andGout.
Co-Precipitate Method	Carbamazepine	Tegretol	Novartis	Tablet/Capsule and Chewable Tablets	Oral	Seizures (100-200mg B.D.S. andcan be increased to 1200mg per day) Neuropathic pain (100mg B.D.S. andcan be increased to 800mg perday)	Seizures, Trigeminal Neuralgia andBipolar Disorder

Table 11: Advantages and disadvantages of complexation method.

Method	Advantages	Disadvantages
Physical Mixture	It is a simple and straight method in preparation process. It has ability to retain originalphysical and chemical properties of drug substance.	It has a limited improvement insolubility. The rate of flow of drug is poor as it forms lumps or agglomerates on mixing which also causes difficulty in handling of drug.
Kneading Method	It has good flow and handlingproperties. Stability of drug is enhanced.	Requires high energy consumptionduring kneading. Reduction in biological activity ofdrug molecule due to interactions with the excipients.
Co- Precipitate Method	Increase in the dissolution rateand bioavailability. Cost effective compared to other methods of solubilization.	Drug and excipients incompatibility may result in degradation or precipitation of the product formed. The process of preparation iscomplex.

Table 12: Examples of Drug modified by inclusion complex technique method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	StandardDosage	Used In
Kneading Method	Indomethacin kneaded with Hydrophilic Polymer (PEG)	Indocin	Merck	Capsule/ Tablets and Suppositories	Oral and Rectal	25-50mgT.D.S.	Relieve Pain and reduce Inflammation in Osteoarthritis, Rheumatoid Arthritis and Gout.
Lyophilization/ Freeze- Drying Technique	Zoledronicacid	Zometa	Novartis Pharmaceuticals	Injection	IV	4mg givenover 15 minutes infusion	Osteoporosis and Bone Cancer.
Microwave Irradiation Method	Curcumin	Curcumin C3 Complex	Sabinsa Corporation	Capsule/ Tablet/ Powder	Oral	Depends on the indication being treated.	Ayurvedic medicine for various health benefits.

Table 13: Advantages and disadvantages of inclusion complex technique method.

Method	Advantages	Disadvantages
Kneading Method	It has good flow andhandling properties. Stability of drug isenhanced.	Requires high energy consumption during kneading. Reduction in biological activity of drug molecule due to interactions with theexcipients.
Lyophilization/Freeze-Drying Technique	Moisture content is reduced so shelf life is enhanced. Solubility and the stability of the drug substance is improved.	It is expensive method as theequipment cost is high. Unwanted impurities can also be formed during preparationprocess.
Microwave Irradiation Method	It is a fast and efficientprocess. Stability is improved.	Thermal degradation of thedrug substance. Potential reduction in biological activity of the drug molecule due to interaction with excipients.

Table 14: Examples of Drug modified by solubilization by surfactant method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Microemulsions	Rsesveratrol	Age Less	Apex	Tablet	Oral	50-500mg per Day	Supplements To improve Cardiovascular Health
Self-emulsifying drug delivery system	Omega-3-acid ethyl esters	Lovaza	GSK	Capsule	Oral	4g/day	High Triglyceride Level
Micellar Solubilization	Doxorubicin	Adriamycin	Pfizer	Injection	IV	Depend upon type of cancer being treated.	Various type of cancer, including breast cancer, lung cancer, ovarian cancerand leukemia

Table 15: Advantages and disadvantages of solubilization by surfactant method.

Method	Advantages	Disadvantages
Microemulsions	It is easy to prepare	Unstable for IV administration ifhigh concentration of surfactant/cosurfactant is added.
Self- emulsifying drug deliverysystem	It promotes the lymphatic absorption of drug from the Gastrointestinal tract. It prevents the first pass metabolism of the drugs.	It has chemical instability due tohigh surfactant concentrations. It irritates the gastrointestinal tract.
Micellar Solubilization	It can solubilize hydrophobicdrugs, improving solubility and bioavailability. Micelles stabilizes drug, reducing degradation and improving shelf life.	It leads to variability in drug delivery as the micelles can be complex and difficult to control. It has limited uses in certain cases, as it may not be compatible with alldrugs.

6. **Drug dispersion in carriers (table 16)**

The absorption rate of drug and its therapeutic effectiveness gets hindered by solubility which is an important physiochemical factor. The formulation development process gets easily affected when the aqueous solubility of drug is poor60-65. The low solubility of drug in aqueous medium and decrease in dissolution rate is the most important reason behind the inadequate bioavailability of drug64-69. To overcome all this large number of carriers which are hydrophilic in nature are discovered which have shown promising result in the solubility enhancement of drug[70-74] (table 17).

a. Solid Solutions

Two crystalline solids when mixed forms a new crystalline solid. In one phase homogenous mixture when two components are crystallizing together formation of mixed crystal takes place. The crystal formed is expected to yield much more result than that of eutectic mixtures combined[75-79].

Amorphous Precipitation

Precipitation of drug in inert carrier as an amorphous form is known as amorphous precipitation. This state of system generally releases a higher energy state as compared to the corresponding crystalline forms of drug[78-82].

b. Solid Dispersions

The efficient and the most promising technique for the solubility enhancement of drug is solid dispersion formulation81-84. The solid dispersion can be defined as the (When one or more than one active ingredient in matrix or carrier (inert) at solid state made by the melting, solvent, or melting-solvent method. The matrix used is of hydrophilic nature and the drug used is of hydrophobic nature[85].

Applications of Solid Dispersion[86]

- Stabilization of unstabilized drug
- To obtain an equal distribution of little amount of drug in solid state
- Dispensing of Solid or Liquid Compounds in Solid Dosage
- Formulation of fast release of drug in Sustained release dosage form.

Methods by which preparation of Solid Dispersion takes place[87-90]

- Fusion Process
- Solvent Method
- Fusion Solvent Method
- Spray Drying
- Lyophilization
- Hot melt Extrusion
- Dropping Method

3. pH Adjustment (table 18)

A slight change in the pH of water can dissolve poorly water-soluble drug which were not able to dissolver earlier. If we have to gain solubility enhancement using this method firstly, we have to consider the buffer capacity and tolerability of the selected pH[91-94]. Excipients which already have been solubilized which increases the pH within a dosage form to a range higher than pKa of weekly acidic drugs. Alkalizing agents which are added as excipients have tendency to increase the solubility of weekly acidic drugs[92] (table 19).

4. **Supercritical Fluid Process (table 20)**

Non-Volatile solvents having critical point that of carbons can be dissolved using Supercritical Fluid (SCFs). It has benefit in major ways like it is environment friendly, economical, and is safe. Above critical temperature and pressure SCF exists in a single phase[93-94]. As SCF have an intermediate between pure liquid and gas it has a useful property. A small change in the operating temperature, pressure or both near about the critical point can bring about a considerable change in the density, transport properties and other physical properties. SCFs have a unique processing capability which were previously used in the food industry are now being recognized and used in the pharmaceutical applications[94] (table 21).

Commonly used Supercritical Solvents are: -

- Carbon Dioxide
- Nitrous Oxide
- Ethylene
- Propylene
- Propane
- N- pentane
- Ethanol
- Ammonia
- Water

Various methods of processing have been invented and developed to address individual aspects of these shortcomings such as[95-97]: -

- Precipitation with compressed antisolvents process (PCA)
- Rapid Expansion of Supercritical Solutions
- Gas Antisolvent Recrystallization
- Precipitation with impregnation or infusion of solution enhanced dispersion by SCF.
- Aerosol Supercritical Extraction system
- Supercritical antisolvents processes

5. **Liquisolid Technique (table 22)**

Absorption and Adsorption both of a drug take place when a drug which is dissolved in liquid medium is introduced in a carrier material having fibers and porous surface as cellulose in its interior surface, that is liquid initially gets absorbed[96]. In the interior of the particle is held captive by the internal structure, and when the process is saturated, adsorption of liquid on the external and internal surfaces of the porous carrier particles occurs. Then the material which is used for coating and having high property of adsorption and greater specific surface area will give the system (Liquisolid) with desired flow characteristics[97] (table 23).

Substance which can be used as coating materials are: -

- Microcrystalline cellulose
- Amorphous cellulose
- Silica powders

6. **Polymeric Alteration (table 24)**

Polymorphs also known as drug which is having different crystalline forms and may have different properties. They may differ in physiochemical properties such as[98]: -

- Chemical Stability
- Physical Stability
- Vapor Pressure
- Melting Point
- Shelf-life
- Morphology
- Dissolution rate
- Biological activities
- Density
- Intrinsic solubility
- Bioavailability

There are three types of polymorphs,

- Stable crystalline polymorphs
- Unstable crystalline polymorphs
- Metastable crystalline polymorphs

The polymorph amongst three which is related with higher energy, surface area, solubility, efficacy, and bioavailability is Metastable crystalline polymorphs. To ensure a longer shelf life of drug or bioavailability it is favored to change the form of drug into amorphous or metastable forms from crystal forms[99] (table 25).

Table 16: Examples of Drug modified by drug dispersion method along with their marketed formulation, dosage form and their applications

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Solid Solutions	Naproxen Sodium	Aleve	Bayer	Tablet	Orally	220mg B.D.	Relieve Painand Inflammation
Solid Dispersions	Fenofibrate	Tricor	AbbVie Inc.	Tablet	Orally	48mg O.D.	Lowering Cholesterol and Triglyceridelevel

Table 17: Advantages and disadvantages of drug dispersion method

Method	Advantages	Disadvantages
Solid Solutions	It is easily manufactured and scaled up for commercial use. It can reduce toxicity of drugs,which reduces side effects.	Some excipients used in this methodcan increase the hygroscopicity of drugs, reducing its stability. It can sometimes decrease the dissolution rate of drug, leading to reduction in their bioavailability.
Solid Dispersions	It reduces the toxicity of drugreducing it side effects. It increases the solubility ofdrugs, improving their bioavailability.	Not all drugs are compatible with thecarrier used in solid dispersion. It is subject to regulatory scrutiny,requiring extensive testing and approval before they are used in clinical practice.

Table 18: Examples of Drug modified by pH adjustment method along with their marketed formulation, dosage form and their applications

Method	Example	Market Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
pH Adjustment	Aspirin	Ecosprin	USV	Tablet	Oral	Depends upon Indication, Ageand weight of person	Relieve Pain, Reduce Fever, and Reduce Inflammation

Table 19: Advantages and disadvantages of pH adjustment method

Method	Advantages	Disadvantages
pH Adjustment	It is a simple and easy methodto formulate. It is simple to produce.	It is in risk of precipitation whendiluted with aqueous media. Use of extreme pH can lead totoxicity (local or systematic).

Table 20: Examples of Drug modified by supercritical fluid process method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Supercritical Fluid Process	Curcumin	Curcumin C3 Complex	Sabinsa Corporation	Capsule/Tablet/ Powder	Oral	Depends on the indicationbeing treated.	Ayurvedicmedicine for various health benefits.

Table 21: Advantages and disadvantages of supercritical fluid process method

Method	Advantages	Disadvantages
Supercritical Fluid Process	It can selectively extract the desired compounds, reducing the presence of impurities. It is environmentally friendly asit uses CO_2 as the solvent, which is non inflammable and non-toxic.	It is expensive method because it requires specialized equipment. This method requires high level of technical expertise and experience to operate effectively, therefore it is less accessible to small companies or individuals.

Table 22: Examples of Drug modified by liquisolid technique method along with their marketed formulation, dosage form and their applications.

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Liquisolid Technique	Theophylline	Theodur	GSK	Tablet	Oral	Depend upon thecondition being treated, the patient's age,weight and overall health	To treat Asthma, Chronic Obstructive Pulmonary Disease (COPD)

Table 23: Advantages and disadvantages of supercritical fluid process method

Method	Advantages	Disadvantages
Liquisolid Technique	It has a rapid release rate. Incorporating the drugs into liquid carriers and coating themwith solid carriers, their toxicity is reduced making them easier to use.	Difficulty in selection of nontoxic hydrophilic solvents, coating materials, carrier and the ratios according to which they are to be mixed. Some cases incorporating drugs into liquid carriers and coating them with solid carriers can reduce their efficacy by limiting access to target site inside body.

Table 24: Examples of Drug modified by polymeric alteration method along with their marketed formulation, dosage form and their applications

Method	Example	Marketed Preparation	Company Name	Dosage Form	R.O.A.	Standard Dosage	Used In
Polymeric Alteration	Diclofenac	Reactin 50	Cipla	Tablet	Oral	50-75mg B.D.S/T.D.S	Treatment of Pain, Inflammation and Fever

Table 25: Advantages and disadvantages of polymeric alteration method

Method	Advantages	Disadvantages
Polymeric Alteration	Encapsulating drugs in polymeric particles, their toxicity can be reduced, makingthem safer for us. It improves stability of drug, reducing the rate of degradation and increase in shelf life.	Not all drugs are suitable for this method and the process may not workon every drug. Particles used to encapsulate drug canthemselves be toxic, leading to adverse effect in body.

Factors Affecting Solubility[95-99]

1. *Chemical Nature of Substance:*

Chemical Structure, including molecular size, shape and functional groups influences the solubility factor of drugs.

2. *Temperature:*

Most of the substances dissolves easily in hot liquids as compared to cold liquids.

3. *Pressure:*

Pressure affects the solubility of gases in liquids, as the pressure is increased solubility is increased.

4. *pH:*

Solubility of substance sometimes increases or decreases depending upon the pH of the medium.

5. *Concentration:*

Increase in the concentration of substance leads to an increase in solubility.

6. *Polarity:*

Polar substances dissolve easily in polar solvents and non-polar dissolves easily in non-polar solvents, "like dissolves like".

7. *Presence of other substances:*

It can affect the solubility as they can compete for solute-solvent interactions or can form complex with the solute.

8. *Surface Area:*

Increase in surface area leads to an increase in solubility.

Table 26 represents the limitations of different methods used to increase the solubility.

Table 26: Limitations of methods used to increase solubility of poorly soluble drug.

Method	Limitations
Salt Formation	1. Chemical Compatibility. 2. Formation of unstable salts. 3. Formation of hydrates. 4. Loss of activity. 5. Limited solubility.
Co-Crystallization	1. Compatibility issues. 2. Limited solubility. 3. Yield issues. 4. Thermodynamic stability. 5. Complex synthesis.
Co- Solvency	1. Toxicity concerns 2. Flammability 3. Environmental impact. 4. Phase separation. 5. Cost.
Hydrotrophy	1. Stability issues. 2. Insufficient solubility improvement. 3. Toxic effects. 4. Cost. 5. Limited solubility.
Nanotechnology	1. Complexity. 2. Regulatory barriers. 3. Toxicity concerns. 4. Poor stability. 5. Limited drug compatibility.
Particle size reduction	1. Increased toxicity and limited efficacy for certain drugs. 2. Energy consumption. 3. Loss of active ingredients. 4. Effectiveness. 5. Time-consuming.
Conventional method	1. Limited to only certain types of compounds. 2. Complexity of the process. 3. High cost. 4. Quality degradation. 5. Environmental impact.
Micronization	1. Material loss. 2. Particle size distribution. 3. Difficulty in scaling up. 4. Heat sensitive. 5. Equipment cost.
Nanosuspensions	1. Complex preparation. 2. Scalability. 3. Stability. 4. Difficult to administer. Limited range of compounds.
Crystal habit Modification	1. Time consuming process. 2. Complexity. 3. Incompatibility with certain drugs. 4. Limitation in solubility improvement Effects on efficacy.
Polymorphism	1. Limited scope. 2. Challenges in isolation. 3. Regulatory challenges. 4. Stabilization issues. Limited knowledge.

Pseudo-polymorphism	1. Limited to water-soluble compounds. 2. Incompatible with certain excipients. 3. Inadequate control over drug release. 4. May result in aggregation of drug particles. Potential for interfering with drug stability.
Physical Mixture	1. Limited effectiveness. 2. Inconsistent results. 3. Incompatible excipients. 4. Limited drug loading capacity. Cost.
Kneading Method	1. High energy consumptions. 2. Limited to specific materials. 3. Limited solubility improvement. 4. Complex process. Possible degradation of product.
Co-Precipitate Method	1. Compatibility issue. 2. Particle size. 3. Process complexity. 4. Poor stability. Low yield.
Lyophilization/ Freeze-Drying Technique	1. High cost. 2. Time consuming. 3. Equipment limitation. 4. Unsuitable for heat sensitive drugs. Poor flowability.
Microwave Irradiation Method	1. Compatibility with drug molecule. 2. Energy input. 3. Inhomogeneous heating. 4. Inadequate solubilization. Limited scientific data.
Microemulsions	1. Stability. 2. Compatibility. 3. Preparation. 4. Dosage form. High cost.
Self-emulsifying drug delivery system	1. Low bioavailability. 2. Stabilization issue. 3. High manufacturing cost. 4. Complex dosage forms. Side effects.
Micellar Solubilization	1. Limited solubilization capacity. 2. Incompatibility. 3. pH sensitivity. 4. Insufficient drug transport. Toxicity.
Solid Solutions	1. Limited solubility. 2. Solubility variability. 3. Compatibility issues. 4. Limited shelf life. Regulatory approval.
Solid Dispersions	1. Limited compatibility. 2. Complex preparation process. 3. Poor stability. 4. Low drug loading. Difficulty in scaling up.
pH Adjustment	1. pH dependent solubility. 2. pH stability. 3. interaction with excipients. 4. Toxicity. Compatibility.
Supercritical FluidProcess	1. High cost. 2. Complexity. 3. Safety concerns. 4. Environmental impact. Limited applications.
Liquisolid Technique	1. Compatibility issues. 2. Complex preparations. 3. Limited scope. 4. Reduced drug loading. Potential toxicity.
Polymeric Alteration	1. High cost. 2. Time consuming. 3. Limited efficacy. 4. Complicated formulations. Limited drug class.

CONCLUSION

In conclusion, solubility is a crucial aspect of drug development and plays a significant role in the efficacy and bioavailability of drugs. There are various methods available to enhance the solubility of drugs, including Salt formation, Co-Crystallization, Solvency, Hydrotrophy, Nanotechnology, Particle size reduction, Conventional method, Micronization, Nanosuspensions, Crystal habit modifications, Polymorphism, Pseudo-polymorphism, Physical Mixture, Kneading mixture, Lyophilization/ Freeze-drying technique, Microwave irradiation method, Microemulsions, Self-emulsifying drug delivery system, Micellar solubilization, Solid solutions, Solid dispersions, pH adjustments, Supercritical fluid process, Liquisolid technique, Polymeric alteration, their examples and advantages and disadvantages

are mentioned along with them. However, these methods have limitations and may not be suitable for all drugs. The solubility of drugs is also influenced by various factors such as pH, temperature, and the presence of excipients.

It is essential to consider solubility when formulating drugs, as poor solubility can lead to reduced efficacy and bioavailability. Hence, understanding the factors affecting solubility and utilizing appropriate methods to enhance it is crucial for the success of drug development. Despite advancements in drug formulation techniques, solubility remains a challenging issue, and further research is needed to improve our understanding of this complex phenomenon.

In summary, solubility is a vital aspect of drug development and plays a significant role in determining the efficacy and bioavailability of drugs. The methods used to enhance solubility have limitations, and the solubility of drugs is influenced by various factors. Further research is necessary

to improve our understanding of solubility and develop more effective methods to enhance it.

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