International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1829-1842 www.ijprajournal.com ISSN: 2456-4494

Revolutionizing drug formulation: Advanced approaches for enhancing solubility

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Date of Submission: 15-06-2025 Date of Acceptance: 25-06-2025

ABSTRACT:
This article is done deliberately to easily understand the concepts of solubility enhancement techniques with their diagrammatic representation. Nowadays, newer potent drugs are facing solubility issues, which is a challenging aspect in the pharmaceutical industry. Many efficacious drugs are not able to reach the market due to their low solubilisation factor, and this creates a negative impact in the pharmaceutical field. Here, we have focused on the major techniques for solubility enhancement such as Particle size reduction, Lipophilicity of the drug,Cosolvency, Sonocrystallization, Nanonization, pH adjustment of the drug, hydrotrophy, salt formation which helps to improve rate of absorption, bioavailability, Dissolution rate and permeability of the newer poor water-soluble drugs.

I. INTRODUCTION:[1], [17]

In the present scenario, only 8% of new drugs have both solubility and permeability. On average, nearly 40% of newly discovered drugs are poorly water soluble, so thereisa higher risk of failure and innovation in drug development. Solubility is a prevalent issue with the newly discovered APIs as it has to be absorbed, distributed and should be present in aqueous form at the site of action; therefore,Solubility is essential to achieve an optimum quantity of drug in the bloodstream to get the desired therapeutic effect. Among all pharmaceutical dosage forms, oral dosage forms are highly conventional and preferable. And due to itsconvenience, 50% of pharmaceutical products are oral preparations. But a major issue behind oral dosage form is that they are poorly water soluble and to overcome this scenario, solubility enhancement techniques comeinto action.

Important definitions related to solubility: [16]
Solubility: Solubility means the maximum amount of the solute dissolved in the given solution.
Solute: Solute is a medium which is present in solution in small amount and it can be present in solid, liquid or gaseous form.
Solvent: Solvent is a substance in which solute dissolves to form a solution and solvents are generally present in liquid form.
Solution:A Solution is a homogeneous mixture that is a combination of solute and solvent.
Quantitative solubility:maximum concentration of solute dissolved in a given solvent at a specific temperature.
Qualitative solubility: the spontaneous interaction of two or more substances to form a homogenous molecular dispersion.
Bioavailability: The Amount of incorporated drug that reaches to systemic circulation of the body in a chemically unchanged form.

Need for solubility enhancement: [1]

- Drugstaken through the oral route have a low dissolution rate**.**
- The bioavailability of the drug is directly proportional to solubility, so to get an increased rate of bioavailability, the solubilization power of the drug should also be higher.
- The therapeutic action of the drug depends on the solubility, so for effective action of the drug,enhanced solubilityis required.
- If the optimum solubility of the drug is not accomplished, then it will lead to alteration in dose. that will increase the negative effect of drug.

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Process of solubilization:[13]

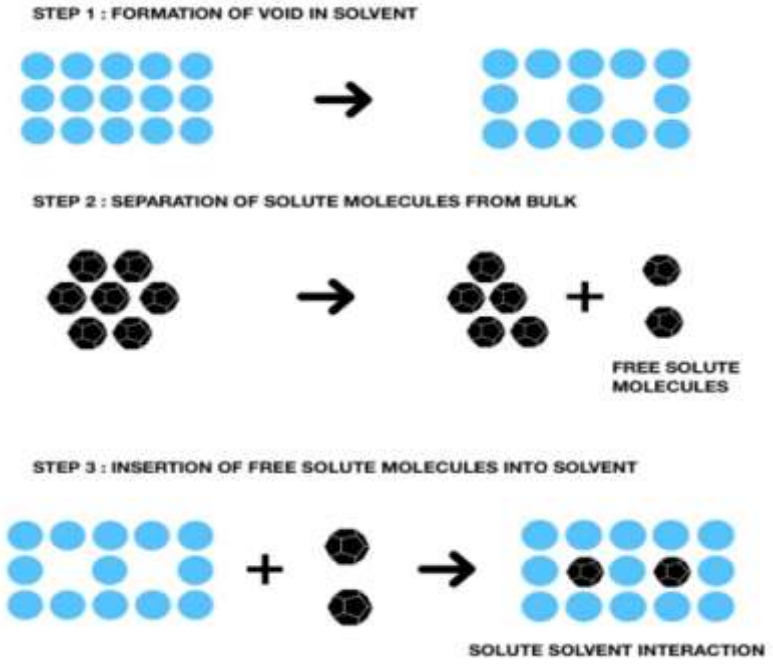

Fig. 1: Process of solubilization

Biopharmaceutical Classification System (BCS):[11]

This classification was first given by Amidon et al in 1995. Solubility, permeability, and dissolution are key components on which BSC classifies its drugs. This system can predict drugs the solubility and intestinal permeability. This classification is based on the United States Pharmacopoeia (USP). According to the BCS, drug substances are classified into four classes based on their solubility and permeability:

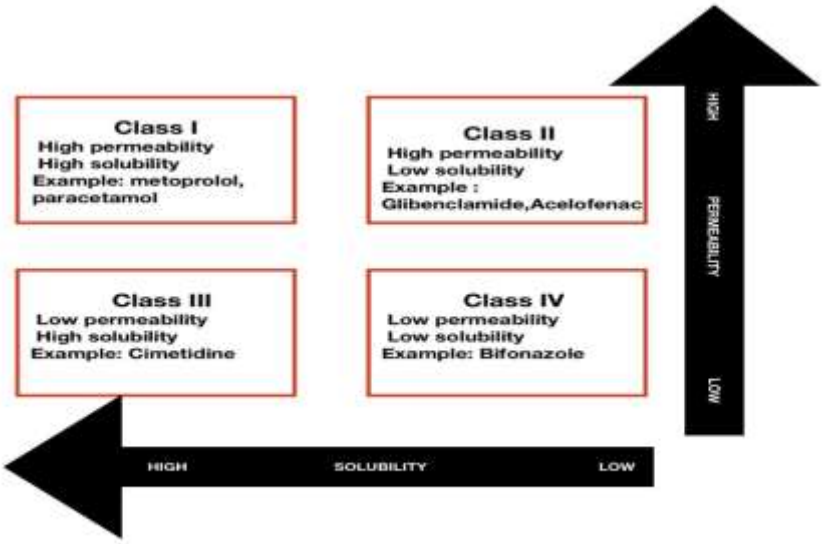

Fig. 2: BCS Classification

International Journal of Pharmaceutical Research and Applications
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Table 1: Descriptive terms [1]

Descriptive term	Part of the solvent required per part of the solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Factors affecting solubility:[16]

- Particle size
- Temperature
- Polarity
- Molecular size
- Pressure
- Polymorphs
- pH
- nature of solute and solvent
- rate of dissolution
- intermolecular forces

Table 2: Factors Affecting Solubility

Particle size	On reducing the particle size of drug particles, it leads to increase in the surface area results into increase in the dissolution rate of the solute particles in solvent.
Temperature	When heat is applied, it leads to increase in the kinetic energy, which allows the solute to break more effectively in the solvent which resultingin the intermolecular attraction, hence solubility is increased.
Polarity	In terms of solubility, polarity follows “like dissolves like” phenomenon. For example, nonpolar substances will have higher solubility in nonpolar solvents.
Molecular size	If the molecular size of a solute is high it requires more time to dissolve in a solvent so, its dissolution rate will be less.
Pressure	According to Henery’s law, the increase in Solubility is directly proportional to the increase in pressure.
Polymorphs	Polymorphs are capable of altering melting point of different substances. Polymorph means there are change in structure of substance. And due to that change, there is differ in solubility.
Dissolution rate	Dissolution Rate of drug means how quickly the drugs gets dissolved after entering in our body. Dissolvement is directly proportional to disintegration. So, if disintegration doesn’t take place, then there is no solubility.
Intermolecular forces	The stronger the intermolecular forces between the solute molecule and solvent, greater the solubility of the solute in the solvent.

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Methods to improve solubility:

As solubility and permeability are major factors for absorption of drugs in our body, and these can be changed or altered by techniques like,

As Solubility and Permeabilityarethe decidingfactors for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like,

Physical Modification Technique				
1. Reduction of particle size	**2. Drug dispersion in carrier**	**3. Modification of crystal habit**	**4. Complexation**	**5. Solubilisation by surfactant**
a. Micronization b. Nanosuspension c. Sono crystallization d. Supercritical fluid process e. Spray Drying	a. Solid solution b. Eutectic Mixture c. Solid dispersion	a. Polymorph	a. Use of complexing agent • Inorganic • Coordination • Chelates • Metal Olefin • Inclusion • Molecular complexes	a. Microemulsion b. Self emulsifying drug delivery system
Chemical Modification Technique				
a.Co-solvency	b.Co-crystallization	c.Salt formation	d.Solubalizing agent	e.Hydrotrophy
Other Technique				
a.Hot melt extrusion	b.Supercritical fluid method	c.Solvent evaporation	d.Lyophylization Technique	e.Polymeric alteration

Fig. 3: Methods to improve Solubility

- In this article we are reviewing some of the major methods like:

1. Particle size reduction
2. Sonocrystallization
3. Super critical fluid
4. Hydrotrophy
5. Cosolvency
6. Lipophilicity of the drug
7. pH adjustment of the drug
8. Salt formation
9. Prodrugdelivery system

1. Particle size reduction:[11], [12]

` Particle size is a crucial factor affecting the solubility. Every particle hasa different size and shape according to its nature, which causes the difference in the solubility of the drug. The main aim of the particle size reduction is to increase the surface area, and due to the increased surface area, the dissolution rate will also increase. The dissolution rate of a drug is directly proportional to its bioavailability and therapeutic action of the drug. With the help of the particle size reduction method,many techniques have been developed to enhance the solubility by reducing particle size.

Importance of particle size reduction in pharmacy:

- Enhanced dissolution rate
- Increased surface area
- Uniform distribution of the drug
- Higher stability of API
- Better controlled properties of powder(Suspension, dispersion, absorption)
- Increased rate of reaction
- Desired therapeutic effect
- Facilitates drying process

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Methods for particle size reduction is categorised into:-

a) Conventional method [10]

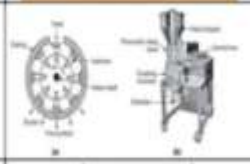
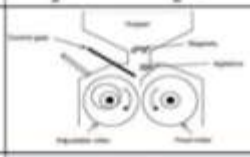
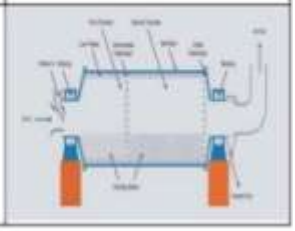
Sr No	Methods	Examples	Approx. particle size (µm)	Uses	Figure
1	Cutting	Scissors Shears Cutter Mill	100-80000	Size reduction of tough and fibrous materials. Medicinal plants, animal tissues are converted to small parts.	
2	Compression	Pestle-Mortar	50-10000	For extraction of botanical oil from the plants. Fragile material is best ruptured by the impact of the blunt hammers	
3	Impact	Hammer Mill , Disintegrator	50-8000	Fragile material is best ruptured by the blow of the blunt hammers. To mill all types of drugs including very complex drugs.	
4	Attrition	Roller Mill	1 - 50	For Extracting different type of highly viscous liquids Act as a homogenizer. Used in emulsifying and dispersing.	
5	Combined Impact and Attrition	Ball Mill , Fluid Energy Mill	1-2000	For Pulverizing and grinding of noxious substance. To pulverize heat sensitive materials.	

Table 3: Different conventional methods

b) Modern method:

1) Micronization [2]: -

In this technique, we convert normal drug particles into micro particles, whose range is less than 10 µ. And due to this micro form of particles dissolution rate of the drug is increased as the surface area of particles is increased. Conversion of normal drug particles into micro particles can be done with the help of some techniques like jet mill, rotor stator colloid mills, etc.

Advantages:

- Convenient process to reduce particle size.
- Bioavailability of the drug can be increased.
- Flowability of powder can be improved.
- Stability of powder is improved by reducing particle size

Disadvantages:

- This technique is not applicable for hydrophilic drugs as it leads to aggregation.
- The size of the particles can't be controlled
- Drugs having high doses are not preferred as the saturation solubility is not increased.

2) Nanonization [2]: -

Conversion of particles into nano constituents has been performed since 1970 in order to achieve higher dissolution rate and bioavailability. In this technique, we convert the particles into the nanoscale, which ranges between 1-100 nm. Nanoparticles have better site selectivity in comparison with normal particles,resultingin reduced adverse effects. Nanonization technique is mainly applicable for weakly water-soluble drugs, which face low bioavailability and reduced pharmacokinetic actions. As nanoparticles can expand the surface area due to which their

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dissolution rate is increased, which causes enhancement of bioavailability. Nanonization is a technique that can be applied to all classes of drugs, due to which nanodrugs are widely available. When a drug having 100 % efficacy reaches to damaged site in our body, its efficacy is reduced to 40 %. While in the case of nanodrug, its efficacy remains nearly unchanged.

Table 4: Different Particle Forms and their Solubility

Particle Form	Efficacy (%)	Onset of action	Solubility
Normal Particle	40%	Minimum	Poorly Soluble
Micro Particle	60%	Moderate	Soluble
Nano Particle	80%	Maximum	Highly Soluble

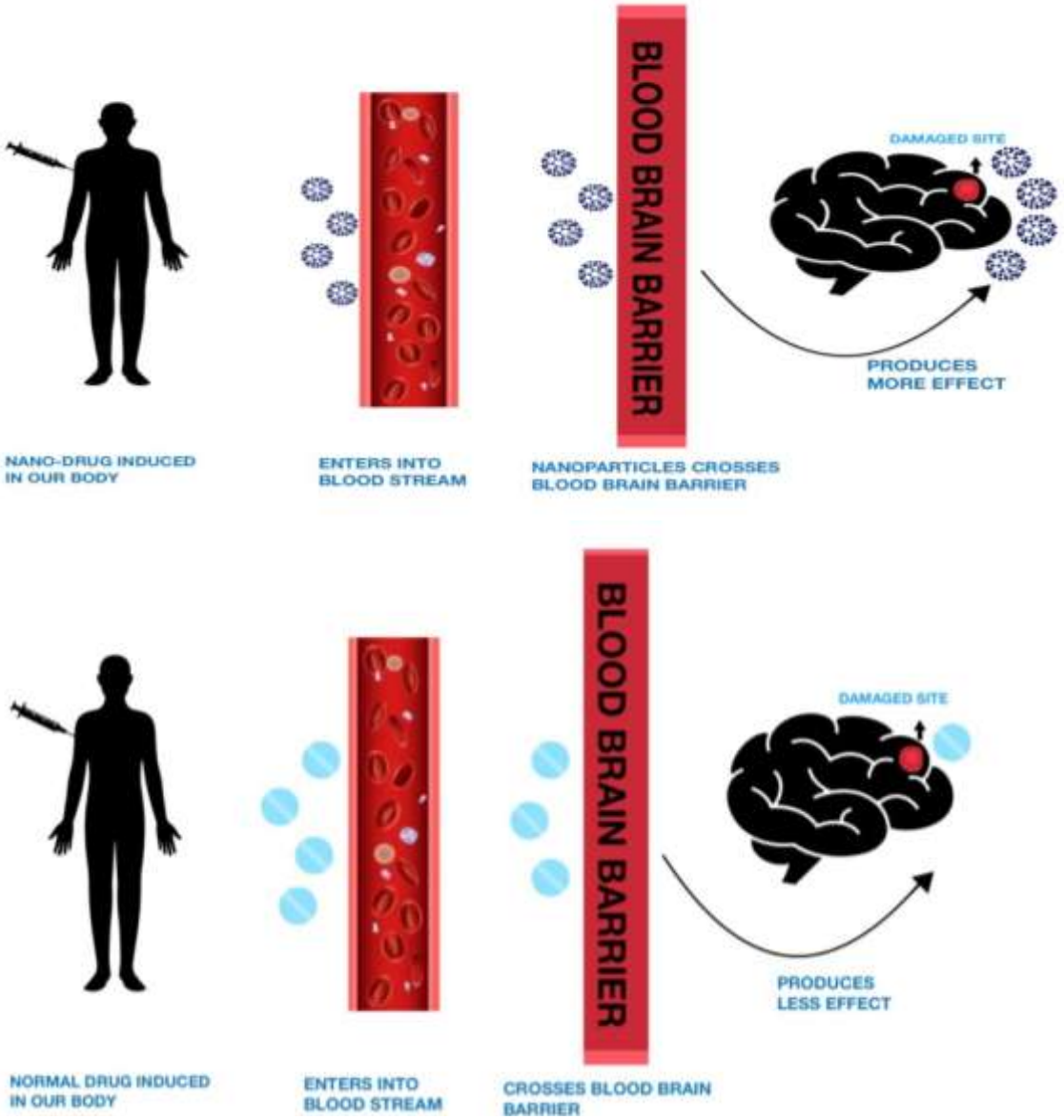

Fig.4: Effect comparison of Normal drug and Nano-drug in our body'

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2. Sonocrystallization: [13], [18]

Mainly, Sonocrystallization is done with the help of ultrasound. When a sound having a frequency less than 20kHz wavelength is imparted on drug particles will lead to an increase in the energy between particles. And it is increased due to frequent compression and refraction of the drug molecule, which leads to the formation, growth and collapse of the particle. And since the energy in increased particles will attract each other and form a group of molecules known as a cluster. This whole process is known as nucleation. It not only improves the nucleation rate but also helps in particle size reduction and controls the particle size distribution of the drug molecules, which results in enhanced solubility of the drug.

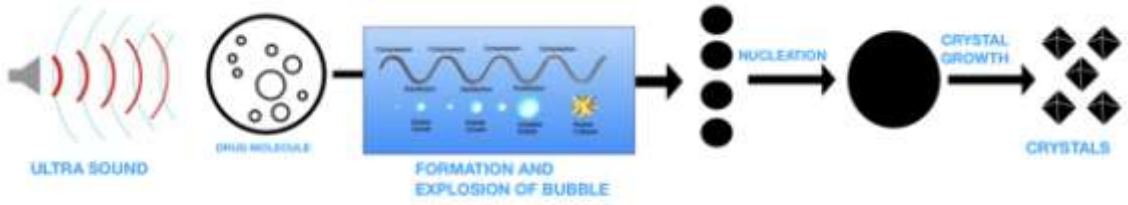

Fig.5: Process of Sonocrystallization

These are some following factors may affect Sonocrystallization:

1) Frequency of ultrasound
2) Intensity of ultrasound
3) Sonication time
4) Type of ultrasound generator

Advantages:

- Reduced agglomeration
- Increased crystal growth rate
- More stable and soluble drug crystals

Disadvantages:

- Inefficiency in ultrasound transmission
- Expensive method
- Knowledgeable staff is required

3. Super Critical Fluid:[6]

Super critical fluid technology was discovered around 1980 – 1990. This Technology is also referred to as an eco-friendly technique or green technology, as no organic solvents are used in this technique. SCF technology is mainly based on the principle of precipitation of the drug, micro particles, and nanoparticles by using pressurized supercritical fluid, such as [CO_2] to dissolve the solute in a solvent. The matter used in this technique is present in the super critical state, which can be attained when the temperature and pressure conditions are greater than the critical point; such substances are known as super critical fluid. And due to its super critical state, it will cause quicker expansion of the drug molecules and fasten the nucleation process of the drug which resultinginthe desired particle size distribution in a short duration of time. It leads to a decrease in the overall particle size,resultingin effective solubilization.

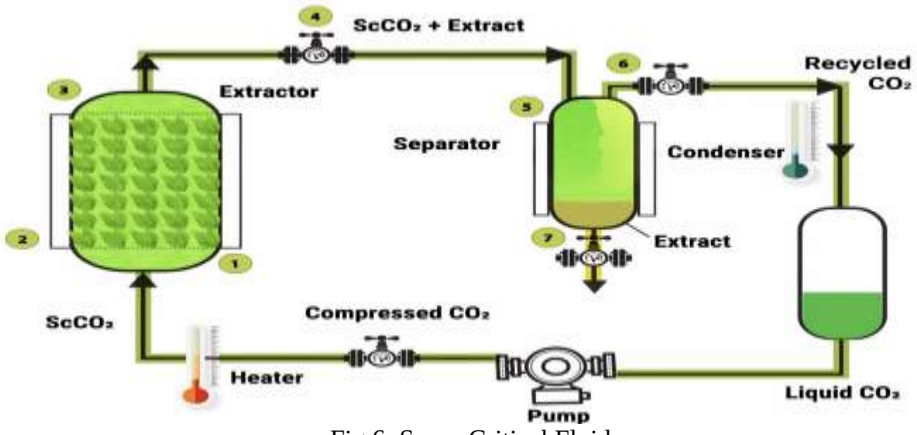

Fig.6: Super Critical Fluid

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Advantages:

- Rapid method for extracting oils.
- Highest purity can be achieved.
- Higher efficiency for botanical extraction.
- Environmentally friendly method.

Disadvantages:

- Expensive
- Complex method
- Polar substances cannot be extracted out
- Expertise is required

4. Hydrotropy:[7]

Solubility is theparameter that works on the interaction between solute and solvent. As solvent is the major vehicle for the dissolution of the solute.Hydrotropyis the concept which is used to enhance the solubilisation power of the poorlywater-soluble drugs. Hydrotropic agents are added because they are made up of different solutes, in which one solute drastically encourages thesolubility of another solute. Hydrotropic agents are ionic organic saltsthat have higher solubility in both polar solvents as well as non-polar solvents. As we all know, 40%-60% of drugs are poorly water soluble.Now let's take an example of the mechanism for hydrotropic agents.In this, we are using sodium benzoate asa hydrotropic agent, which consists of a benzene ring and sodium.Inwhichthe benzene ring acts as a non-polar solvent and as the drug is water insoluble, it will also have a non-polar nature. So, it will follow like dissolve like principle, due to which the solubility of poorly water-soluble or water-insolubledrugs is increased because of a hydrotropic agent.

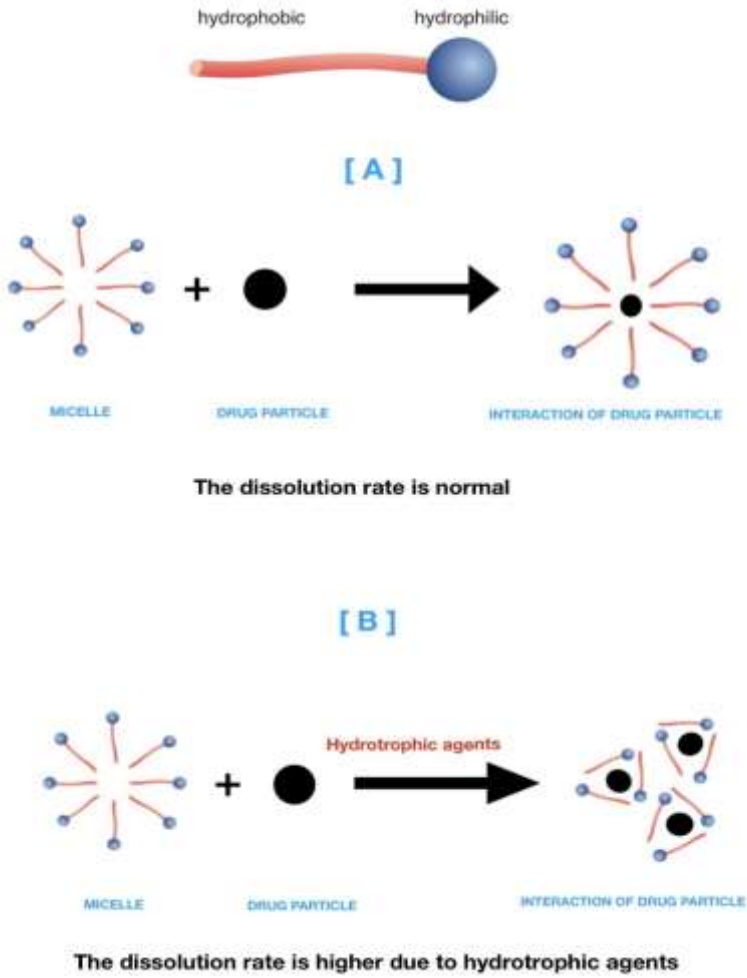

Fig. 7: Effect of Hydrotropic Agent on Solubility

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Advantages:
- Improve the solubility of lipophilic drugs in aqueous medium.
- It enhances thestability of microemulsions and suspensions.
- Hydrotropes are cheap and easy to handle.
- Non-toxic and environmentally friendly.

Disadvantages:
- Leads to precipitation.
- Unsuitable for IV preparation because of the high concentration of hydrotropic agents.
- Low stability.

5. Cosolvency: [4],[9]

Cosolvency is the most commonly used pharmaceutical method to increase the solubility of poorly aqueous soluble drugs. Cosolvency is a procedure in which cosolventsare added to two immiscible solvents to make them miscible.The main principle of this procedure is to reduce interfacial tension between two solvents to make them a miscible solution. The examples of widely used cosolvents are PEG-300, Etoricoxib, Propylene glycol or Ethanol, Glycerine, Dimethyl sulfoxide (DMSO), and Dimethylacetomide (DMA).

Characteristics of Cosolvents:
1. Cosolvents are mainly lipophilic in nature
2. They are toxic free in nature
3. It hasa better ability to solubilise the drug in the given solvents

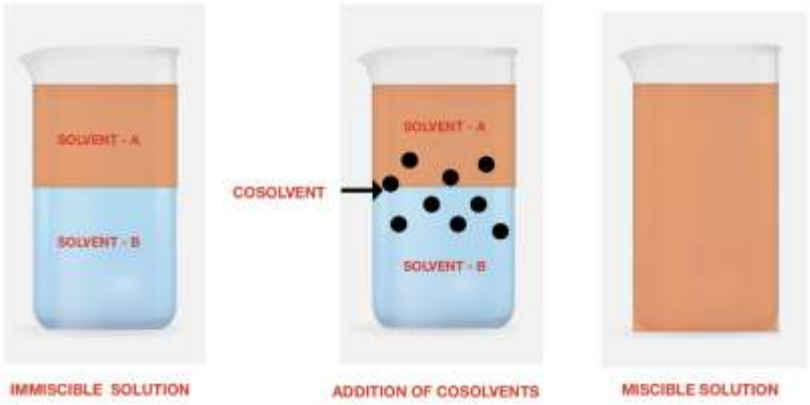

Fig. 8 Addition of Cosolvent

Advantages:
- Simple technique
- Rapid method
- To increase the dissolution rate of hydrophobic molecules

Disadvantages:
- Not applicable for solid particles

6. Lipophilicity of the drug:[3]

Lipophilicity refers to the ability ofdrug substances to dissolve in lipids, fats, oils and nonpolar solvents. The distribution of the drug in our brain and CNS is regulated by the blood brain barrier, which prevents the entry of foreign particles. Our cell membrane is mainly made up of lipoproteins. Thus, drugs having higher lipophilicity will have greater affinity towards lipid containing cell membranes. So, the lipophilicity of the drug is directly proportional to the rate of absorption. The drugs that are lipophilic in nature can easilycross the blood brain barrierdue to their greater affinity, whereas hydrophilic drugs cannot able to cross the blood-brain barrier.

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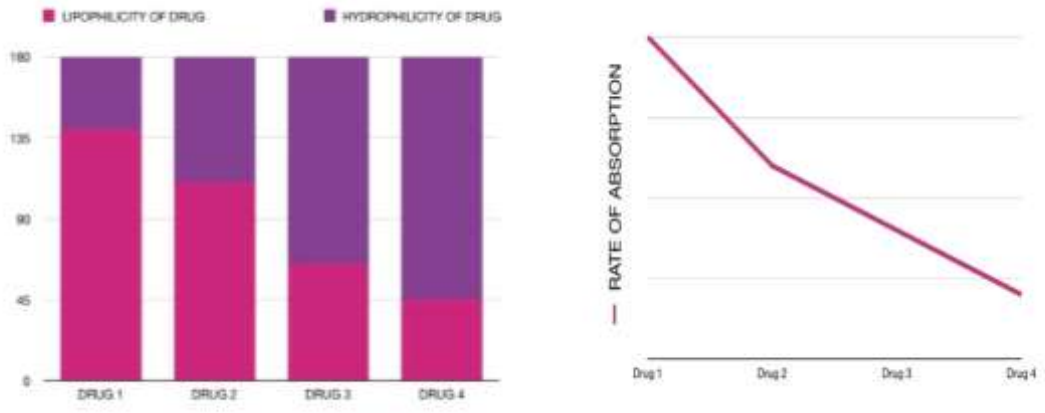

Fig. 9: Rate of Absorption of different drugs

According to this graph, the pink colour indicates the lipophilicity of the drug and the purple colour of the drug indicates the hydrophilicity of the drug. Here we have four drugs (Drug: 1,2,3,4)in which,

Drug: 1 - Highly lipophilic in nature. Thus, its rate of absorption is also high.

Drug: 4 -Highly hydrophilic in nature. Thus, its rate of absorption is low.

From the above graph, we can conclude that the drugs that are highly lipophilic in nature have a greater rate of absorption, which leads to increased drug solubility.

7. pHAdjustment:[11]

The pH adjustment technique is the universally applicable method. As pH plays an important role in the dissolution rate. For availing the desired solubility, the pH of the drug should be equivalent tothe standard pH of the body. Drugs having two types of nature, protonated(base) and deprotonated(acid). The solubility of a poorly water-soluble drug can be increased by changing itspH. Protonated(base) or Deprotonated(acid) drugs, which are poorly water soluble, can be dissolved in water. In this method, we have to observe mainly two things,which are buffer capacity and tolerability of the selected pH. According to the pH-partition hypothesis and the Henderson-Hasselbalch equation, the ionization of a compound depends on the pH of the media and the pKa of a drug.

- For weakly acidic drugs /salts,
  - o Lower pH → unionized form →insoluble/ precipitation
  - o Higher pH → ionized form →more solubility

- For weakly basic drugs/salts,
  - o Lower pH → ionized form →more solubility
  - o Higher pH → unionized form → insoluble/precipitation

This method can be used in oral and parenteral administration. In Intravenousadministration, due to a strong buffer like blood pH, ranging between 7.2-7.4, the drug may lead to precipitation. In the stomach, the pH is around 1 to 2 and in the duodenum, the pH is between 5-7.5, so upon oral administration, the degree of solubility is also likely to be influenced as the drug passes through the intestines. Ionisable compounds that are stable and soluble after pH adjustment are best suited. The change in the ionic milieu can also result in in situ salt formation. However,this salt formation is infeasible for unionized compounds. The formed salts may also convert to their respective acid or base forms in the gastrointestinal-tract.

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Table 5: Required pH of the drug

Drug dissolution path	Optimum pH for the drug
Stomach	1-3.5
duodenum	6-7.5
Blood	7-7.5
saliva	6.2-7.6
urine	4.5-8
liver	7
Lacrimal fluid	6.5-7.6

Advantages:

- Simple to formulate and analyse.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

- Risk for precipitation upon dilution with aqueous media having a pH at which thecompound is less soluble. Intravenously, this may lead to emboli, but orally, it may cause variability.
- Tolerability and toxicity (local and systemic) related to the use of a non-physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid formulation. The selected pH may accelerate hydrolysis or catalyse other degradation mechanisms.

8. SALT FORMATION:[8], [14]

Study shows that 50% of prepared pharmaceutical products are administered in the form of salts. **A drug present in the salt form is more stable and more soluble than its parent drug.** Salt formation is a basic technique that is applied toacidic or basic drugs. Salts are the ionic compounds thatare formed by reacting aparent drug with an acid(anion) or a base(cation). The principle of salt formation includes the ionic interaction of the counter ion and charged molecule, which results in the crystalline or salt form of the drug.

Now,let'sunderstand this with an example. Agomelatine is a poorly soluble "nonionizable" amide. Here, there are three salts of agomelatine: a) hydrogensulfate, b) mesylate, and c) besylate. In all of the structures, the agomelatine molecule was positively charged and it is being protonated bythe amide oxygen. So, by this sulfonate salt formation, there is 200 times faster dissolution of agomelatine, which proves that the formation of salt is better than the parent drug.

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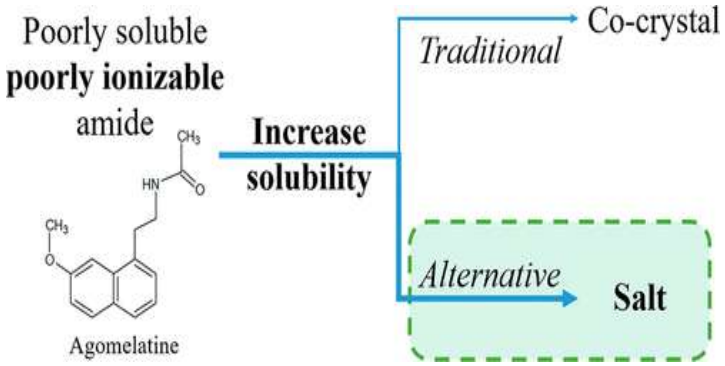

Fig. 10: Agomelatine

Advantages:
- Improved permeability
- Reduced hygroscopicity
- Altered solubility and dissolution rate
- Improved drug efficacy

Disadvantages:
- Not applicable for neutral compounds
- Risk of precipitation
- Corrosiveness of the salts

9. Prodrug delivery system:[5]

In the year 1958 term 'prodrug'was introduced by Albert. Prodrugs are medications that are present in inactive form, which are transformed or converted into an active form when theyreach the site of action to produce the desired therapeutic effect. Here, Molecules of the drug undergoa certain biotransformation process to exhibit their pharmacological effects, which are mainly done by certain enzymes present in our body such as CYP450, DT-diaphorase, carboxylesterase and β glucuronidase. Whenprodrugs are converted frominactive to active form,theydisintegrate at the site of action and resultinthe formation of macro molecules. These macro molecules will enhance permeation by increasing drug lipophilicity,which is followed by improved solubility and effective therapeutic action.

Prodrugs are developed in two different ways includes:

a) Carrier-linked prodrugs: These prodrugs are connected to an activemedication and this connection is disrupted when it enters the body.
b) Bio precursor prodrugs: These are chemically modified versions of medication. Different enzymes transform them into active medications.

Advantages
- Reduction in toxicity
- Prevention of presystemic metabolism
- Prolongation of drug action
- Achievement of site-specific activity

Disadvantages
- Numerous absorption barriers
- Consecutive sites of potential metabolism on the way to systemic circulation
- Activation of the prodrug before reaching the site of action
- Formation of toxic metabolites

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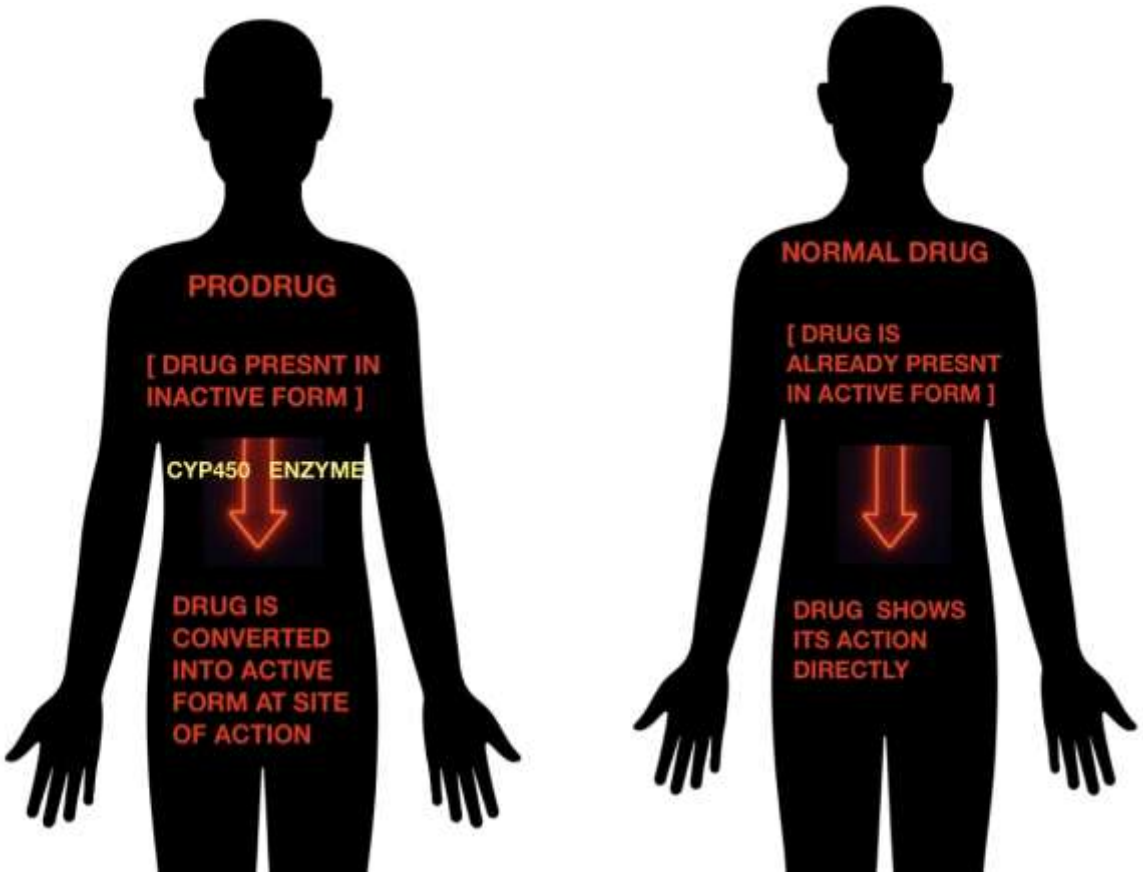

Fig. 11: Comparison of Normal and Prodrug

II. CONCLUSION:

Ultimately, we would like to conclude that the issue of poor aqueous solubility is one of the major challenges in the development of pharmaceutical medication, directly impacting the bioavailability and therapeutic efficacy of orally administered drugs. This article explores the strategies and methods that can enhance the solubility of oral drugs, as 40% of newly discovered drugs are poorly water soluble. So, to overcome this situation and improve bioavailability and therapeutic efficacy of the drug, various approaches to improve solubility become essential.

When it comes to the methods we have talked about, reducing particle size—using techniques like micronization and nanonization - shines as a great way to boost surface area and speed up dissolution rates. There are also innovative and eco-friendly options like sonocrystallization and supercritical fluids that can help improve solubility by carefully designing particles and controlling nucleation. Plus, formulation strategies such as CoSolvency, hydrotrophy, and salt formation have been shown to be quite effective in enhancing drug solubility, especially for compounds with challenging profiles.

When it comes to drug development, physicochemical properties such as lipophilicity and pH are crucial for influencing solubility and permeability. By identifying these factors, we can gain better control over how drugs are absorbed and distributed in the body. Additionally, employing prodrug strategies highlights the power of chemical modifications to transform drugs that are hard to dissolve or permeate into more effective forms with improved pharmacokinetics.

So, by reviewing and analysing, we can say that each API has different characteristics and we have to apply a technique according to those characteristics to improve the solubility of the drug.

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