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# AN OVERVIEW ON DIFFERENT APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUGS

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**ABSTRACT**

Solubility is one of the major parameter to obtain desired concentration of drug in systemic circulation for pharmacological response to be displayed. Drug efficiency is directly proportional to the solubility of a drug. Poor solubility of a drug leads to low dissolution rate and is followed by low absorption of the drug in the gastro intestinal tract when administered orally. Around 40% of all new chemical entity shows poor bioavailability. Enhancing the bioavailability of poorly soluble drugs can be one of the biggest challenges for formulation scientists in the upcoming years. Molecules that would have highly beneficial effect on their physiological target would not be further developed if their bioavailability is limited by their solubility in water. Aqueous solubility of drug also affects physical, chemical properties of the drug, dose, stability in gastrointestinal track, severs as standard for test of purity, the rate of dissolution of solid, rate and extent of absorption, achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. Thus solubility is a most important concept presenting itself as valuable contributor in the formulation of pharmaceuticals. The purpose of this review is to discuss the various solubility enhancement technique like chemical modification which includes salt formation, co-crystallization, co-solvency, hydrotrophy, nanotechnology etc and physical modification includes particle size reduction, complexation, surfactants, solid dispersions etc and pH adjustment, supercritical fluid process, liquisolid technique, polymeric alteration. These technologies enhance the solubility of the drugs and thus allows to make the formulations in different dosage forms efficiently and thus enhances the dissolution and bioavailability of the drug.

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## INTRODUCTION

Orally administered drugs are only completely absorbed when they have a good solubility in the gastric medium and have a high bioavailability. More than 40% of new chemical entities (NCEs) developed in the pharmaceutical industry are practically water insoluble. These drugs' poor water solubility, combined with their slow absorption, result in insufficient and variable bioavailability, as well as gastrointestinal mucosal toxicity.[1]

As a result, improving drug solubility and thus oral bioavailability remains one of the most difficult aspects of the drug development process, particularly for oral drug delivery systems. There are a variety of methods for improving the solubility of poorly water soluble drugs that have been reported in the literature. The techniques are chosen based on factors such as the properties of the drug under consideration , the nature of the excipients to be used, and the nature of the intended dosage form.[2]

Solubility refers to a substance's ability to dissolve in a saturated solution at a given temperature. In terms of quality, it refers to the continuous interaction of two or more compounds to form a single phase with clear homogeneous molecular dispersion. It is defined as the maximum amount of solute that can be dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution.[3]

Solubility equilibrium is a dynamic equilibrium that occurs when a chemical compound in its solid state achieves chemical equilibrium with its solution. In pharmaceuticals, solubility equilibrium is important. Dissolution-related absorption issues are present in drugs with poor aqueous solubility (in other words, Class II or even Class IV BCS compounds).[4]

The purpose of this review discuss about the solubility enhancement of poorly water soluble drugs buy various methods because if the drug is poorly water soluble that affect dissolution, bioavailability and thus also have a poor pharmacological action as well as gastro intestinal musocal toxicity will be increases thus solubility enhancement of poorly water soluble drug is very important role for the formulation industry in order to get good pharmacological action.

**Quantitative solubility:**

Is defined as the number of milligram's of solute particles required to form a saturated solution.

**Qualitative solubility:**

When the two phases are combined to form a homogeneous mixture, it is possible to define qualitative solubility. The properties of the newly developed active compound will shift towards higher molecular weight and the lipophilicity of the compounds will get increase, resulting in a decrease in the drug's aqueous solubility, according to the introduction of combinatorial chemistry.[5,6.]

**Definitions of solubility:-**

**Table No: 01 Solubility expression:[7]**

| Definition | Parts of solvent required for one 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 | From1000-10,000 |
| Insoluble | Greater than 10,000 |

**Possible Causes for Poor Oral Absorption:** [8] any drug is said to be poorly soluble when:

1.Aqueous solubility <100µg/ml.
2.Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm2/min,
3.High molecular weight: (>500), Self association and aggregation.
4.High crystal energy.

## METHOD OF SOLUBILIZATION:

**Process of Solubilization**:

Solubilization is a process that requires the breaking of intermolecular or interionic solute's bond. Separation of the solvent molecules to provide space for the solute in the solvent, the interaction between the molecule and ion of the solute and the solvent.[9,10,11.]

**Process 1:**

The process of solubilization involves the breakage of interionic or bond form intermolecular in the solute parting molecule in solvent which provide space in the solvent for interaction of solute among the solute particle for ion and solvent.

**Process 2:**

The particle of solid which break the particles which is away from the bulk substances.

**Process 3:**
And solid molecules is combined with the solvents.[12,13.]

**Bio pharmaceutical classification system (BCS):**

Amidon et al., first developed BCS in1995. The US Food and Drug Administration (FDA) introduced it and it classify the drug in to four classes according to its permeability and solubility. solubility problems are mostly faced in class 2 and class 4 of the system facing dissolution as the rate limiting step for the absorption of drug due to low solubility.[14,15.]

**Table No: 02 BCS Classification:**

| Class | Permeability | Solubility |
|---|---|---|
| **I** | High | High |
| **II** | High | Low |
| **III** | Low | High |
| **IV** | Low | Low |

**Factors Affecting Solubility:**

**1) Particle size:**

Particle size affects solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases it causes greater interaction with solvent.[16]

**2) Temperature:**

Temperature has an impact on the solubility of drugs. If the energy is being absorbed by the solution process, the solubility will increase as the temperature rises. If the energy is released during the solution process, the solubility will decrease as the temperature rises.

**3) Molecular size:**

When molecules have a higher molecular weight and a larger molecular size, the solubility of the substance is reduced because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

**4) Solute and solvent nature:**

Solute and solvent nature is determined by the concentration of solute in a specific amount of solvent at a specific temperature. At room temperature, only 1 gm of lead (II) chloride can be dissolved in 100 gm of water, whereas 200 gm of zinc chloride can be dissolved.

**5) Pressure:**

While pressure has no effect on the solubility of liquids and solids, it does affect the solubility of gaseous solutes, which increases as pressure rises and decreases as pressure falls.[17]

**6) Polarity:**

Polarity of both solute and solvent molecules affects the solubility. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.[18]

**7) Polymorphs:**

The ability of a substance to crystallize in more than one crystalline form is polymorphism. Polymorph is an agent having ability to crystallize in more than one crystalline form. It is possible that solid can crystallize in different forms or polymorphs. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility.

**8) PH**:

Maximum of drugs is weak electrolytes and the weak bases and weak acids undertake ionization in the solution. The drugs which have more soluble in water when they are in ionised form. Poorly water soluble drug is Unionised drug.[19]

**TRADITIONAL SOLUBILITY ENCHANCEMENT TECHNIQUES:**

The solubility enhancement technique is listed below:[20,21]

1. Surfactant.
2. PH adjustment.
3. Co-solvency.
4. Co-crystallization.
5. Solubilizing agents.
6. Formation of salt.
7. Polymeric alteration.
8. Size reduction of particle.
9. Co-grinding and Co-micronization.
10. Micro emulsion.
11. Solvent evaporation.
12. Sonocrystalization.
13. Inclusion Complexation.

**ADVANCE TECHNIQUES FOR SOLUBILITY ENHANCEMENT:**

The advance techniques are given below: [22]

1. Micronization.
2. Homogenization.
3. Nano suspension.
4. Super critical fluid process.
5. Spray drying.
6. Hydrotrophy .

**TECHNIQUES TO OVERCOME POOR SOLUBILITY:**

**I. Chemical Modifications:**

1) Salt Formation.
2) Co-crystallization.
3) Co-solvency.
4) Hydrotrophy.
5) Use of novel solubilizer.
6) Nanotechnology.

**II. Physical Modifications:**

**1. Particle size reduction**

a) Conventional method.
b) Micronization.
c) Nanosuspension.

**2. Modification of the crystal habit**

a) Polymorphs.
b) Pseudopolymorphs.

**3. Complexation**

a) Physical mixture.
b) Kneading method.
c) Co-precipitate method.

**4. Inclusion Complex Formulation Based Techniques**

a) Kneading method.
b) Lyophilization/ Freeze- drying Technique.
c) Microwave irradiation method.

**5. Solubilization by surfactants**

a) Microemulsions.
b) Self microemulsifying drug delivery system.

**6. Drug dispersion in carriers**
a) Solid solutions.
b) Solid dispersions
i. Fusion Process.
ii. Solvent Method.
iii. Fusion solvent method.
iv. Spray drying.
v. Lyophilization (Spray Freeze Drying Method).
vi. Hot melt Extrusion.
vii. Dropping Method.

**III. pH adjustment.**
**IV. Supercritical fluid process.**
**V. Liquisolid technique.**
**VI. Polymeric alteration.**[23-27.]

**CHEMICAL MODIFICATIONS:**
**1) SALT FORMATION:**

Due to various issues of instability, an API is frequently unable to be formulated in its purest form. Salts, co-crystals, solvates, hydrates, and polymorphs are formed as a result of this conversion. Each one imparts a unique physiochemical property that improves the drug's performance characteristics such as stability, bioavailability, purification, and manufacturability. For decades, salt formation of poorly soluble drug candidates (weak acids and bases) has been used to improve solubility. When a compound is ionised in solution, salts are formed. It works well in both parenteral and other liquid formulations as well as solid dosage forms. A salt is formed when an acidic or basic drug is converted into a salt with a higher solubility than the original drug. Between 1995 and 2006, the FDA approved approximately 300 new chemical entities for marketing, 120 of which were salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form 12 For the salt formation drug should have ionisable groups that will assist salt formation.[28] The criteria used to select counter ion is as follows:

- There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
- Counter ion should decrease crystal lattice forces.
- It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.

This technique has tremendous capability to enhance dissolution rate but it is grasped with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.

**Advantages:** Best method to increase the solubility and dissolution rate of acidic nature substances and all basic drugs.

**Disadvantages:**

It is the high reaction with atmospheric $co_2$ and water high is resultant in the precipitation in low water soluble drug and displays in the epigastric stress due to alkalinity.

**2) CO-CRYSTALLIZATION:**

Co-crystallization modifies molecular interactions and is seen as a promising way to improve drug properties. Multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule," according to a more refined definition of a co-crystal.

Co-crystallization helps an API overcome its physical, chemical, and physiological flaws. The physical state of the components is the only difference between solvates and co-crystals. Solvates are formed when one of the components is liquid and the other is solid; on the other hand, co-crystals are formed when both components are solid. The API and the co-crystal former are the two main components of pharmaceutical co-crystals(s).[29]

**Different techniques for co crystallization**

1) Solvent evaporation 2) Grinding 3) Slurry Co - Crystallization 4) Solvent drop grinding 5) High throughput co-crystallization 6 ) Hot melt extrusion 7) Sono-crystallization Method.

**Co-Crystals Characterization Parameters:**

1) Solubility 2) Maximum wavelength 3) Stability 4) Intrinsic dissolution 5) Bioavailability 6) Melting Point 7) Melt (Hot stage microscopy) 8) Scanning Calorimetry 9) XRD 10) Vibrational spectroscopy.

**3) CO-SOLVENCY:**

Co-solvents, which are water miscible solvents in which the drug has good solubility, can be used to increase the solubility of a poorly water soluble drug. When compared to the aqueous solubility of the drug alone, co-solvents can increase the solubility of poorly soluble compounds by thousands of times. Co-solvents are solutions made up of water and one or more water miscible solvents that improve the solubility of poorly soluble compounds. Because it is simple to produce and evaluate, this has been one of the most widely used techniques in the past. PEG 300, propylene glycol, and ethanol are examples of solvents used in co-solvent mixtures. Poorly soluble drugs can be given orally or parenterally in co-solvent formulations. To lower the solvent concentration before administration, parenteral formulations may require the addition of water or a dilution step with an aqueous media. A co-solvent approach may be appropriate for poorly soluble compounds that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. To increase the solubility of poorly soluble compounds, co-solvents can be combined with other solubilization techniques and pH adjustments. The use of co-solvents to improve the solubility of poorly soluble drugs is a highly effective technique. Propylene glycol, ethanol, glycerine, and polyethylene glycol are the most commonly used low-toxicity co solvents for parenteral use. Because of their large solubilization capacity for poorly soluble drugs and low toxicity, dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA) have been widely used as cosolvents.[30,31.32.]

**Advantages:**

- Simple and rapid to formulate and produce.
- Has large solubilization capacity for poorly soluble drugs, simple and rapid to formulate, produce and evaluate.
- It can be combined with other solubilization techniques and pH adjustment to further increases solubility of poorly soluble compounds.

**Disadvantages:**

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size.
- Many of the insoluble compounds Phases works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily re dissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.
- As with all solubilised forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

**4) HYDROTROPHY:**

Hydrotrophy is a solubilisation process in which a large amount of a second solute is added, resulting in an increase in the aqueous solubility of the first solute. Alkali metal salts of various organic acids make up the solute. Ionic organic salts are hydrotropic agents. Salts that increase the solubility of a solute in a given solvent are said to "salt in," while salts that decrease solubility are said to "salt out." The "salting in" of non-electrolytes called hydrotropic salts is caused by several salts with large anions or cations that are themselves very soluble in water, a phenomenon known as hydrotropism. Hydrotropic solutions are non-colloid and have a weak interaction between the hydrotropic agent and the solute. The term hydrotrophy refers to the increase in water solubility caused by the presence of a large amount of additives. Its mechanism for increasing solubility is more closely related to complexation, which involves a weak interaction between the hydrotrophy agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.[33,34.]

**Table No : 03 Hydrotropic agents classification:**

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

**Advantages of hydrotrophy:**

- Hydrotrophy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.
- Wide variety of compounds has been reported to exhibit hydrotropic behavior. Examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene .

**Disadvantages:**

Hydrotrophy exhibit effects on the surfactant combination important to micelle formation, and stage display of more than one systems with the position towards the Nano dispersions and it conduct percolation, clouding nature of the polymer and surfactants etc.

**Mixed Hydrotrophy:**

It is a new, simple, cost-effective, safe, precise, and accurate method that uses hydrotrope blends to give a synergistic effect on the solubility of poorly water soluble drugs.[35]

**Advantages of mixed hydrotrophy:**

- It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.
- The use of hydrotropic solubilizers as permeation enhancers.
- Application of hydrotropic solubilisation in nanotechnology (by controlled precipitation).

**5) USE OF NOVEL SOLUBILIZER:**

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap, Soluplus, Povacoat, dendrimers is improve the solubility of hydrophobic API.[36,37.]

**6) NANOTECHNOLOGY:**

Oral bioavailability enhancement by micronization is insufficient for many new chemical entities with low solubility because micronized products have a small effective surface area for dissolution, so the next step was nanonization . Milling, high-pressure homogenization, vacuum deposition, and high-temperature evaporation are some of the preparation methods that can be used.[38]

**Advantages of nanotechnology:**

It results in production of the nano or micro sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

**Disadvantage of nanotechnology:**

The agglomeration problem is inherent and difficult to overcome.

**II. PHYSICAL MODIFICATIONS:**

**1. PARTICLE SIZE REDUCTION:**

The surface area to volume ratio of a particle decreases as it gets smaller, resulting in a higher surface area to volume ratio. Because of the larger surface area, there is more interaction with the solvent, resulting in an increase in solubility. Particle size is a critical parameter that should be closely monitored during any formulation's preformulation studies. Although particle size reduction is a successful way to increase solubility, if it is not controlled and optimised, it can result in re-crystallization and re-aggregation of the drug during storage.[39]

**Advantages:**

- Liquid forms can be developed quickly for preclinical testing and then converted to solids for later clinical development.
- Low excipient to drug ratios are usually required.
- If no strong surfactants are required for stabilisation, formulations are generally well tolerated.
- Crystal forms are generally more chemically and physically stable than amorphous particles.
- A method to consider for stubborn compounds that have failed to increase solubility in the past.
- In the case of chemical substances, increase the rate of solution because particle size reduction increases the surface area available for solvent action.

**Disadvantages:**

- There is a strong tendency for particle agglomeration due to the high surface charge on discrete small particles.
- It may be technically difficult to develop a solid dosage form with a high payload without encouraging agglomeration.
- Developing sterile intravenous formulations is even more difficult from a technical standpoint.
- Physical and mechanical stress can cause the active compound to degrade.
- Thermal stress caused by comminution can cause issues with the processing of thermo sensitive agents.
- There is a strong trend for element gathering because of the increased surface control on distinct lesser elements.

**Conventional method of particle size reduction** :

Cutting, compression, impact, attrition, and combined impact and attrition are some of the mechanisms used in traditional particle size reduction methods. Mechanical stress is used in traditional particle size reduction methods like comminution and spray drying to disaggregate the active compound. As a result, particle size reduction allows for a cost-effective, repeatable, and efficient method of increasing solubility. However, the mechanical forces that occur naturally during comminution, such as milling and grinding, can cause significant physical stress on the drug product, which can lead to degradation. When processing thermo sensitive or unstable active agents, the thermal stress that may occur during comminution and spray drying is also taken into account. It is impossible to increase the solubility of poorly soluble drugs to a desirable level using only traditional methods of solubility enhancement.

**Micronization:**

It is a high-energy particle size reduction technique that can reduce coarse particles to less than 5 micrometres in diameter. Micronization produces a uniform and narrow particle size distribution, which is necessary for the development of a uniform dosage form. Micronization increases surface area and increases solubility as particle size decreases. The type of micronization technique used has an impact on the properties of the micronized drug substance, such as particle size, size distribution, shape, surface properties, agglomeration behaviour, and powder flow. The most commonly used techniques for producing micronized drug particles are mechanical communication, spray drying, and supercritical fluid (SCF) technology. The administration of a drug in micron size, according to the Noyes–Whitney hypotheses, is a popular method for improving bioavailability of poorly water soluble drug substances.

**Techniques for Micronization:**

a) Jet milling/fluid energy mill or micronizer.
b) Rotor stator colloids mills.
c) Microprecipitation & microcrystallization.
d) Controlled crystallization.
e) Supercritical fluid technology.
f) Spray freezing in to liquid.

**Advantages of micronization:**

- Gives uniform particle with increase in surface area and narrow particle size distribution.

**Disadvantages of micronization:**

- A high-energy process that disrupts the drug crystal lattice, potentially resulting in disordered or amorphous regions in the final product.
- Amorphous regions are thermodynamically unstable and prone to recrystallization when stored, especially in hot and humid environments.

**c) Nanosuspension:**

This technology is used on drugs that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system made up of nano-sized drug particles suspended in an aqueous vehicle stabilised by surfactants and intended for oral, topical, parenteral, or pulmonary administration. Solid particles in nanosuspensions typically have a particle size distribution of less than one micron, with an average particle size ranging between 200 and 600 nm. Bottom-up and top-down technologies are used to create nanosuspension. Top-down technology employs a variety of techniques, including nano engineering, nanojet technology, and milling technology (Nanocrystals).[40]

**Advantages of nanosuspension:**

- Drug particle size is reduced in nanosuspension, increasing surface area, which increases solubility, dissolution rate, and ultimately bioavailability.
- Nanosuspension results in an increase in permeability.
- Nanosuspension increases bioadhesion and the duration of residence action.
- High drug loading is a benefit of nanoformulation.
- Organic solvents should be avoided.

**Disadvantages of nanosuspension:**

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

**Other methods:**

- High pressure Homogenization.
- Solution Enhanced Dispersion by the Supercritical Fluids(SEDS).
- Rapid expansion from supercritical to Aqueous solution(RESAS).
- Spray freezing into liquid(SFL).
- Evaporative precipitation into aqueous solution(EPAS).
- Ultra-Rapid Freezing.

**2. MODIFICATION OF THE CRYSTAL HABIT:**

a) Polymorphs.

b) Pseudo polymorphs.

Polymorphism refers to an element's or compound's ability to crystallise in multiple crystalline forms. Polymorphs are different crystalline forms of a drug that may have different properties. Physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution rate, morphology, density, and biological activities, as well as bioavailability, may differ between polymorphs. Metastable crystalline polymorphs are associated with higher energy, increased surface area, and thus solubility, bioavailability, and efficacy among the stable, unstable, and metastable crystalline polymorphs. Order for the dissolution of various drug solid forms. Amorphous polymorph >Stable polymorph >Metastable polymorph.

**3.COMPLEXATION:**

Is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry.[41] Two type of complex:

**Stacking complexes:**

It is caused by the association of the non-polar area of the drug with the complexes agent, which prevents the non-polar area from coming into contact with water. The stacking can be uniform or uneven, but the end result is a clear solution.

**Inclusion complexes:**

It is made by putting a non polar molecule or a region of a molecule into the cavity of another molecule or a group of molecules. In complexation, cyclodextrine and its derivatives are commonly used.

**a) Physical mixture:**

In this the CDs or suitable polymer and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. It is simple trituration method.

**b) Kneading method:**

This method is based on soaking the CDs or suitable polymer with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time.

**c) Co-precipitate method:**

The required amount of drug is added in the solution of CDs or suitable polymer. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and non aqueous media.

**Advantages:**

The use of this method is very simple and requires a low cost equipment.

**Disadvantages:**

The drug needs to be soluble in at least one solvent and this solvent needs to be miscible with non solvent.

**INCLUSION COMPLEX FORMULATION BASED TECHNIQUES:**

The inclusion complex formation technique has been used more precisely among all the solubility enhancement techniques to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs.

Inclusion complexes are formed when a non polar molecule or a non polar region of a molecule (referred to as a guest) is inserted into the cavity of another molecule or group of molecules (known as host). The host's cavity must be large enough to accommodate the guest while also being small enough to keep water out. Cyclodextrins are the most common host molecules. Cyclodextrins are cyclic oligosaccharides that are non-reducing, crystalline, and water soluble. Cyclodextrins are made up of glucose monomers arranged in a ring. α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin are three naturally occurring CDs.[42]

**a) Kneading method:**

The CDs are impregnated with a small amount of water or hydro alcoholic solutions and then converted into a paste using this method. The drug is then mixed into the paste and kneaded for a set amount of time. After that, the kneaded mixture is dried and, if necessary, sieved. Kneading on a laboratory scale can be accomplished with a mortars and pestle. Kneading can be done on a large scale with the help of extruders and other machines. This is the most common and straight forward method for preparing inclusion complexes, and it has a very low production cost.[43]

**b) Lyophilization/ Freeze drying technique:**

The lyophilization/freeze drying technique is recommended for obtaining a porous, amorphous powder with a high degree of drug-CD interaction. Through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure, the solvent system from the solution is removed. Water's unique properties and role as a solvent, gas, diluents, plasticizer, and stabiliser are all important in lyophillization. Lyophilization/freeze drying is a technique that involves molecular mixing of drug and carrier in a common solvent as an alternative to solvent evaporation.[44]

**Advantages of lyophillization/freeze-drying technique:**

- The lyophillization/freeze drying technique is thought to be worthwhile for producing a porous, amorphous powder with a high degree of drug-polymer interaction.
- This method can successfully convert thermolabile substances into complex forms.

**Disadvantages of lyophillization/freeze-drying technique:**

- Specialized equipment is used.
- Time consuming process, and yield poor flowing powdered product.

**c) Microwave irradiation method:**

Using a microwave oven, this technique involves a microwave irradiation reaction between the drug and the complexing agent. In a round bottom flask, the drug and CD are dissolved in a definite molar ratio in a mixture of water and organic solvent in a specified proportion. In a microwave oven, the mixture is reacted for one to two minutes at 60 degrees Celsius. Following the completion of the reaction, a sufficient amount of solvent is added to the above reaction mixture to remove the un complexed free drug and CD. The precipitate is then separated using Whatman filter paper and dried for 48 hours in a vacuum oven at 40 °C.

Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.[45,46.]

**SOLUBILIZATION BY SURFACTANTS:**

Surfactants molecules that have polar and non polar regions. A hydrocarbon segment is usually connected to a polar group in most surfactants. An anionic, cationic, zwitterionic, or non ionic polar group can exist. Small polar molecules can accumulate in the micelles' hydrophobic core when they are added. This solubilization process is critical in both industrial and natural processes. Surfactants reduce surface tension between liquid-solid, liquid-liquid, or liquid-gas interfaces, increasing drug solubility by increasing lipophilic drug dissolution in aqueous medium. Surfactants are also used to keep drug suspensions stable. It also helps to improve wetting and penetration in solid drug dissolution when used as a fluid. Micelle formation occurs when the concentration of surfactants exceeds their critical micelle concentration (CMC), which for most surfactants is in the range of 0.05–0.10 percent. Micelle formation entraps the drugs within the micelles and is known as micellization and predominantly results in elevated solubility of poorly soluble drugs.[47]

**Advantages:** To improve the drug stability.

**Disadvantages:**

Micelle development happens which it entrap with the drugs within micelles and mostly results in the raised solubility of below par soluble drugs.

**a) Micro emulsions:**

A micro emulsion is an optically clear pre-concentrate, isotropic, thermodynamically stable transparent, translucent system containing a mixture of oil, hydrophilic surfactant, often in combination with a co-surfactant, with droplet sizes ranging from 20 to 200 nanometres and a hydrophilic solvent that dissolves a poorly water soluble drug. HLB and non-toxicity are the criteria for selecting a surfactant. When the formulations come into contact with water, they self-emulsify, forming a very clear emulsion of small, uniform oil droplets containing the solubilised poorly soluble drug. Many drugs that are practically insoluble in water have been increased in solubility using micro-emulsions, as well as the incorporation of proteins for oral and parenteral administration. The most suitable formulation is an oil-in-water (o/w) micro emulsion, which is expected to increase solubility by dissolving compounds with low water solubility in an oil phase. Even if the micro emulsions are diluted below the critical micelles concentration after oral administration, the resultant drug precipitates have a fine particle size allowing enhanced absorption. They can also enhance oral bioavailability by reducing the droplet size (< 100 nm), and hence increase the rate of absorption due to surfactant-induced permeability changes.[48]

**Advantages:**

- Ease of preparation, clarity, filterability, and ability to incorporate a wide range of drugs with varying solubilities and bioavailability.
- Thermodynamic stability is a technique that leads to increased drug loading and penetration.
- Pre-concentrates are relatively simple to produce.
- Drug release from well-developed micro emulsion pre-concentrates is normally independent of digestion. As a result, without the use of food, optimal bioavailability and reproducibility can be expected (i.e. the fasted state).

**Disadvantages:**

- The drug's affinity for precipitation on dilution, which causes it to advance due to polar head solvent dilution influences. Authorizing formulas with multiple components becomes more difficult.
- In cases where long-term chronic administration is intended, the tolerability of formulations containing high levels of synthetic surfactants may be poor.
- Formulations containing multiple components become more difficult to validate.

**b) Self-emulsifying drug delivery systems:**

The concept of emulsion formation in situ in the gastrointestinal tract is used. The self-emulsifying drug delivery system is a transparent isotropic solution made up of oil, surfactant, co-surfactant, one or more hydrophilic solvents, and co-solvent (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self micro emulsifying drug delivery systems (SMEDDS) are isotropic oil-surfactant solutions that form oil-in-water micro emulsions in the presence of water after mild agitation. On oral administration, these novel colloidal formulations behave like oil-in-water micro emulsions.

The rate of emulsification, the emulsion size distribution, and the charge of resulting droplets have all been proposed as parameters to characterise self-emulsifying performance. Emulsion droplet size, for example, is a critical factor in self-emulsification/dispersion performance because it determines the rate and extent of drug release and absorption61. Incorporating a small amount of cationic lipid (oleyl amine) into such a system could also result in positively charged emulsion droplets.[49]

**Advantages:**

One of the benefits of SEDDS in terms of scale-up and manufacturing is that they form spontaneously when their components are mixed with mild agitation and are thermodynamically stable**.**

**Disadvantages:**

This system's disadvantages include drug chemical instabilities and high surfactant concentrations. GIT is irritated by the large amount of surfactant in self-emulsifying formulations (30-60%).

Moreover, volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

**DRUG DISPERSION IN CARRIERS:**

**a) Solid Solutions**

**b) Solid dispersions.**

**Solid Dispersion:**

Sekiguchi and Obi first proposed the concept of solid dispersions in the early 1960s, when they investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water-soluble carrier. 8

Solid dispersions are a valuable pharmaceutical technique for improving drug dissolution, absorption, and therapeutic efficacy in dosage forms. A solid dispersion of one or more active ingredients in an inert carrier or matrix is defined as a dispersion of one or more active ingredients in a solid state. Polyvinyl pyrrolidone, polyethylene glycols, and Plasdone-S630 are the most commonly used hydrophilic carriers for solid dispersions. Surfactants are frequently used in the formation of solid dispersion. Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate were used as surfactants. Solid dispersion using suitable hydrophilic carriers can improve the solubility of celecoxib, halofantrine, and ritonavir.

**Applications of solid dispersions** It is possible that such a technique be used:

- To achieve a uniform distribution of a small amount of drug in a solid state.
- To keep the drug from becoming unstable.
- To dispense liquid or gaseous compounds in a solid dosage (up to 10%).
- To create a sustained-release version of a fast-acting primary dose.
- To reduce the inactivation of drugs like morphine and progesterone before they reach the bloodstream.
- Using poorly soluble or insoluble carriers to create a sustained release regimen for soluble drugs.
- To convert polymorphs in a system into solid isomorphs.[50.]

**Advantages of solid dispersion:**

- It has rapid dissolution rates.
- Increase absorption rate of drugs.
- Improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.
- Decrease the crystalline structure of drug into amorphous form.
- To make the better wettability and reduced the particle size.
- Prepare rapid disintegration oral tablets.
- Mask the taste of the drug substance.
- Avoid degradation or decomposition of drugs. Transformation of the liquid form of the drug into a solid form (Ex. Clofibrate and Benzyl benzoate can be incorporated into PEG-6000 to give a solid.)
- Avoidance of polymorphic changes and there by bioavailability problems.[51.]

**Disadvantages of solid dispersion:**

- Solid dispersion instability.
- Moisture and temperature cause solid dispersion to deteriorate.
- The solid dispersion conduct has a low degree of certainty due to the lack of an elementary consideration.
- It shows crystallinity and decrease in dissolution rate with aging.

**i) Hot melt method (fusion method/ process):**

Sekiguchi and Obi were the first to propose the melting or fusion method for preparing fast-release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated until it melted in this method. The melted mixture was then rapidly cooled and solidified in an ice bath while being vigorously stirred. The final solid mass was crushed, pulverised, and sieved, and tabletting agents were used to compress it into tablets. The melting point of a binary system is determined by its composition, which includes the carrier chosen and the drug's weight fraction in the system.

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermo stability of the drug and carrier.[52]

**ii) Solvent Method:**

In a suitable organic solvent, the carrier and active ingredient are dissolved. At a high temperature or under vacuum, this solvent evaporates. Super saturation occurs as the solvent is removed, followed by simultaneous precipitation of the constituents, resulting in a solid residue. The co precipitate is then vacuum dried to remove any solvent that has adhered to the particle. It is assumed that even trace amounts of the solvent are removed.[53]

**Advantages:**

Simple techniques and for the encapsulation of hydrophilic and hydrophobic drug.

**Disadvantages:**

It may cause the more preparation rate.

**iii) Fusion-Solvent Method:**

The drug(s) is/are incorporated in the form of a solution after the carrier(s) is/are melted. The need for solvent removal is eliminated if the carrier can hold a certain proportion of liquid while maintaining its solid properties, and if the liquid is harmless. The method works well with drugs that have high melting points or are thermo labile.

**iv) Spray Drying:**

The active ingredient and the carrier are dissolved and suspended in a suitable solvent. This solvent is evaporated by drying it and removing it with a stream of heated air. The solvent quickly evaporates due to the large surface area of the droplets, and a solid dispersion forms quickly.[54]

**Advantages:**

It is technologies system for the mass production method.

**Disadvantages:**

Spray drying is method experimental use to mechanical force commination it may degrade in certain pharmaceuticals development , and drying might cause the thermal pressure and dreadful conditions of some products use are used of the organic solvents.

**v) Lyophilization (Spray Freeze Drying Method) :**

Spray freeze drying is a method that has been successfully developed to prepare solid dispersions at room temperature and avoid heating during the preparation of thermo sensitive drugs (SFD). SFD technology involves atomizing a feed liquid containing insoluble or poorly water-soluble APIs and excipients directly into a cryogenic liquid at room temperature to produce a frozen micronized powder that is then dried. This process has a number of advantages over traditional solid dispersion technologies, including amorphous structure and a large surface area.[55,56,57.]

**vi) Hot melt extrusion:**

The first people to use this technology for pharmaceutical purposes were Speiser and Huttenrach. Hot melt extrusion is similar to fusion with the exception that the extruder causes intense mixing of the components. Miscibility of drug and matrix, just like in the traditional fusion process, can be a problem. For heat-sensitive materials, high shear forces resulting in a high local temperature in the extruder are a problem. In comparison to the traditional fusion method, however, this technique allows for continuous production, making it suitable for large-scale production. Furthermore, the product is easier to handle because the shape can be adapted to the next processing step without grinding at the extruder's outlet.[58]

**Advantages:**

It is continuous process and hot essential of any organic solvents or water.

**Disadvantages:**

Hot - melt extrusion is the tools have been imperfect because o temperature complex nature of the drug.

**vii) Dropping Method:**

Pipette a solid dispersion of melted drug-carrier mixture onto a plate, where it solidifies into round particles. Factors like the viscosity of the melt and the size of the pipette can affect the size and shape of the particles. Because viscosity is highly temperature dependent, it is critical to adjust the temperature so that the melt solidifies into a spherical shape when dropped on the plate.[59]

**III. pH ADJUSTMENT:**

Using a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may be dissolved in water. In theory, pH adjustments can be used for both oral and parenteral administration. Because blood is a strong buffer with a pH between 7.2 and 7.4, the poorly soluble drug may precipitate after intravenous administration. The buffer capacity and tolerability of the chosen pH are important factors to consider when evaluating the approach's suitability. Because the pH in the stomach is around 1-2, and the pH in the duodenum is between 5-7.5, the degree of solubility is likely to be influenced as the drug passes through the intestines after oral administration. The best candidates are ionisable compounds that are stable and soluble after pH adjustment. Acids, bases, and zwitterionic compounds are all possible. It can be used for both crystalline and lipophilic poorly soluble compounds. Solubilised excipients that raise the pH of the environment within a dosage form, such as a tablet or capsule, to a level higher than the pKa of weakly acidic drugs increase the drug's solubility; similarly, excipients that act as alkalizing agents may increase the solubility of weakly basic drugs. Because the solubility of the poorly soluble drug is increased when compared to water alone, the fraction of orally absorbed drug may be increased if compounds can permeate through the epithelium orally. To increase the solubility of a poorly soluble drug, pH adjustment is frequently combined with co-solvents.[60,61.]

**Advantages:**

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

**Disadvantages:**

- Dilution with aqueous media at a pH where the compound is less soluble increases the risk of precipitation. This may cause emboli intravenously, and it may cause variability orally.
- Tolerance and toxicity (local and systemic) associated with non-physiological pH and extreme pHs.
- A dissolved drug in an aqueous environment, like all solubilised and dissolved systems, is frequently less chemically stable than crystalline solid formulations. The chosen pH could hasten hydrolysis or catalyse other degradation processes.

**SUPERCRITICAL FLUID PROCESS:**

With the critical point of carbon dioxide, supercritical fluids (SCFs) can dissolve non volatile solvents. It is secure, eco-friendly, and cost-effective. Above its critical temperature and pressure, a SCF exists as a single phase. Because they are halfway between pure liquid and pure gas, SCFs have properties that are useful in product processing. Furthermore, around the critical points, small changes in operating temperature, pressure, or both affect density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity). SCFs have recently been adapted to pharmaceutical applications due to their unique processing capabilities, which have long been recognised and used in the food industry. Commonly used supercritical solvents are carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (CAP), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvent processes (SAS).[62]

**Advantages of supercritical fluid process :**

- The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.
- Once the drug particles are solubilised within SCF, they maybe recrystallized at greatly reduced particle sizes. Current SCF processes have demonstrated the ability to create nanosuspensions of particles 5-2000nm in diameter.
- The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

**Disadvantages:**

Precipitation by infusion or impregnation of the polymers with bioactive product, Anti-solvent, Compressed Fluid, Solution improved Dispersal by the Supercritical Fluid techniques.

**LIQUISOLID TECHNIQUE:**

**Liquisolid Compacts/Methods:**

Liquid Compacts are powdered liquid medications that can be compressed. Oily liquid drugs and solutions or suspensions of water insoluble drugs carried in suitable non volatile solvent systems are referred to as liquisolid medication. By blending a liquid medication with selected powder excipients such as the carrier and coating material, a liquid medication can be converted into a dry, non-adherent, free-flowing, and compressible powder. Tweens and other surfactants are used to improve the aqueous solubility of poorly soluble drugs.[63,64.]

**Advantages of Liquisolid Methods:**

- Provides acceptably flowing and compressible powdered forms of liquid medications.
- Method improves the solubility, bioavailability of orally administered water insoluble and is applicable in industry.
- Useful for the formulation of oily drugs/liquid drugs.
- Drug release can be modified by using different carrier and additives like PVP, PEG 60000, Hydroxyl Propyl Methyl Cellulose and Eudragit etc.
- A number of poorly soluble drugs can be formulated in to the system.
- This system is specifically for the powdered liquid medications.
- Production cost is low compared to that of preparation of soft gelatin capsules.

**Disadvantages of liquisolid method:**

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

**POLYMERIC ALTERATION:**

Polymorphs are different crystalline forms of a drug that may have different properties. Physical and chemical stability, melting point, vapour pressure, shelf-life, dissolution rate, morphology, density, biological activities intrinsic solubility, and bioavailability are some of the physicochemical properties that polymorphs can have. Metastable crystalline polymorphs are associated with higher energy, increased surface area, solubility, bioavailability, and efficacy among the stable, unstable, and metastable crystalline polymorphs. In terms of bioavailability, it is preferable to convert drugs from crystal to metastable or amorphous forms over the course of their shelf lives in a variety of real-world storage conditions.[65.]

**Advantages:**

Having high molecular weight polymers and fast polymerizations rate.

**Disadvantages**:

Bioavailability, required important to alteration drug and the crystal forms in meta-stable has done or shelf-life under a multiplicity of storage conditions.

## CONCLUSION

For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Solubility is the concept of any Physical and Chemical property including the pharmacokinetics therapy in consideration of medicine and Biopharmaceutical. Problem of solubility is a major challenge for formulation scientists**.** Various techniques, described in this review alone or in combination can be successfully used to enhance the solubility of hydrophobic drugs for improving their oral bioavailability, but successful improvement is mainly depends on selection of method. We tried to discuss all these methods available and we concluded that among all the solubility enhancement techniques Nanosuspension, co-crystallization, Super Critical Fluid, Solubilization by Surfactants, Solid dispersion, Hydrotrophy and Inclusion Complex formation are most attractive techniques to resolve the solubility problems of hydrophobic drugs. Recommend future Research.

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## ABBREVATIONS:

- BCS: Biopharmaceutical classification System.
- FDA: The US Food and Drug Administration.
- XRD: X-Ray Diffraction.
- DMSO: Dimethylsulfoxide.
- DMA: Dimethylacetoamide.
- API: Active Pharmaceutical Ingredient.
- SEDS: Solution enhanced dispersion by the supercritical fluids.
- RESAS: Rapid expansion from supercritical to aqueous solution.
- SFL: Spray freezing into liquid.
- EPAS: Evaporative precipitation into aqueous solution.
- CD: Cyclodextrin.
- CMC: Critical micelle concentration.
- HLB: Hydrophilic lipophillic balance.
- SEDDS: Self emulsifying drug delivery system.
- SMEDDS: Self micro Emulsifying drug delivery system.
- GIT: Gastro intestinal tract.
- SFD: Spray freeze drying method.
- SCF: Super critical fluids.
- CAP: Compressed Antisolvent Process.
- SEDS: Solution Enhanced dispersion by SCF.
- ASES: Aerosol supercritical extraction system.
- SAS: Supercritical antisolvent process.
- PVP: Polyvinyl pyrollidine.
- PEG: Polyethylene glycol.

## CONFLICT OF INTERESTS:

Declare none

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