Solubility Enhancement Methods

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INTRODUCTION

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since thisprocess may occur not only because of dissolution but also because of a chemical reaction.Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach therapeutic range due to their poor water solubility. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. This present review details about the different approaches used for the enhancement of the solubility of poorly water-soluble drugs include particle size reduction, nanonization, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropy etc. The purpose of this article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent.The solubility of a drug may be expressed as parts, percentage, molarity, molality, volumefraction, and mole fraction. Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. The solubility of a drug is described in various descriptive terms which is based on the amountof drug dissolved in solvent and discussed in.

Definitions:

Solution: Is A Mixture of Two Or More Components That Form A HomogenousnMixture. The Components Are Referred To The Solute And/or Solutes & The Solvent And/or Solvents Solute: Is The Dissolved

Agent. (Less Abundant Part of the Solution)

Solvent: Is The Component In Which The Solute Is Dissolved (More Abundantn

Part of the Solution

A Saturated Solution: Is One in Which An Equilibrium Is Established Betweenn Dissolved And Undissolved Solute At A Definite Temperature. Or A Solution That Contains The Maximum Amount Of Solute At A Definite Temperature

An Unsaturated Solution: sub saturated solution is one containing then dissolved solute in a concentration below that necessary for complete saturation at a definitetemperature.

A supersaturated solution: Contains more of the dissolved solute than it would normally contain in a saturated state at a definite temperature.

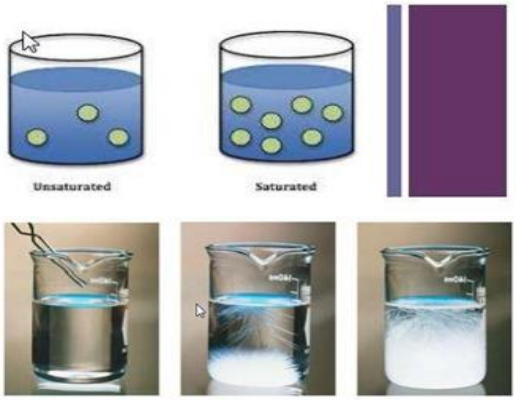
In a quantitative way: it is the concentration of solute in a saturatedn solution ata certain temperature

In a qualitative way: it is the spontaneous interaction of two or moren substances(solute & solvent) to form a homogeneous molecular dispersion

2) Degree of saturation

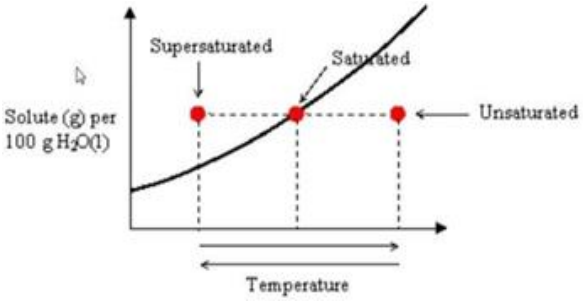
Unsaturated, Saturated or Supersaturated?

How much solute can be dissolved in a solution?



Solubility Curve

Any solution can be made saturated, unsaturated, or supersaturatedn by changing the temperature.



Thermodynamic solubility of drugs

The thermodynamic solubility of a drug in a solvent is the maximumn amount of the most stable crystalline form that remains in solution in a given volume of the solvent at a given temperature and pressure under equilibrium conditions. The equilibrium involves a balance of the energy of three interactions against each other:

Solvent With Solvent

Solute With Solute

Solvent And Solute

Steps of solid going into solution.

Step: Hole open in the solvent

Step: One molecule of the solid breaks away from the bulk

Step: The solid molecule is enter into the hole in the solvent.

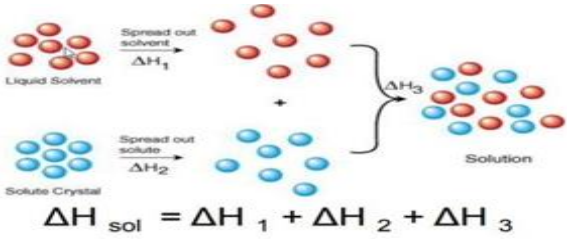
Solubility process

A mechanistic perspective of solubilization process for organic solute in waterinvolves the following steps:

- Break up of solute-solute intermolecular bonds
- Break up of solvent-solvent intermolecular bond
- Formation of cavity in solvent phase large enough to accommodate solute molecule
- Transfer of solute into the cavity of solvent phase 5. Formation of solute-solventintermolecular bonds

Tree types of interaction in the solution process:

1. Solvent – Solvent Interaction
2. Solute – Solute Interaction
3. Solvent Solute Interaction



Classification of solvents & their mechanism of action

1. Polar solvents
2. Non polar solvents
3. Semi polar solvents

Polar solvents:

The solubility of a drug is due in large measure to the polarity of the solvent, n thatis, to its dipole moment.

Polar solvents dissolve ionic solutes and other polar substances.

The ability of the solute to form hydrogen bonds is a far more significant factor than is the polarity as reflected in a high dipole moment.

Water dissolves phenols, alcohols and other oxygen & nitrogen containingcompounds that can form hydrogen bonds with water.

The solubility of a substance also depends on structural features suchn as the ratioof the polar to the nonpolar groups of the molecule.

Non polar solvents:

- Non-polar solvents are unable to reduce the attraction between then ions of strong and weak electrolytes because of the solvents' low dielectric constants.
- They are unable to form hydrogen bonds with non electrolytes.

Non polar solvents can dissolve non polar solutes through weak van dern Waalsforces

Example: solutions of oils & fats in carbon tetrachloride or benzene.

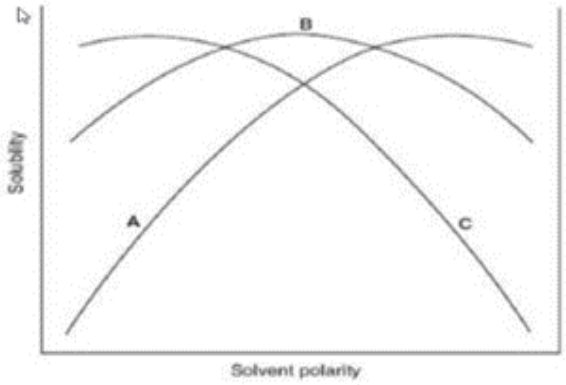
- Polyethylene glycol 400
- Castor oil

Semi polar solvents:

- Semi polar solvents, such as ketones can induce a certain degree ofn polarity in non polar solvent molecules.
- For example, benzene, which is readily polarizable, becomes soluble in alcohol They can act as intermediate solvents to bring about miscibility ofn polar & non polar liquids.
- Example: acetone increases solubility of ether in water.
- Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and of water and benzyl benzoate

Factors affecting soubilisation

- Partical size
- tempeature
- pressure
- molecular size
- nature of solute and solvent
- polarity
- polymorphs



Influence of solvent polarity on the solubility of drugs: (A) Polar drug (B) semipolar drug; and (C) nonpolar drug.

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

- ✓ S is the solubility of infinitely large particles
- ✓ S0 is the solubility of fine particles
- ✓ V is molar volume
- ✓ γ is the surface tension of the solid
- ✓ r is the radius of the fine particle
- ✓ T absolute temperature in degree Kelvin.
- ✓ R universal gas constant.

Temperature:

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.

Molecular size:

The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.

Nature of solute and solvent:

The nature of solute and solvent depends on concentration of solute in specific quantity of solvent at specific temperature. Example: at room temperature in 100gm of water only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved.

Pressure:

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have no effect on solubility.

Polarity:

Polarity of both solute and solvent molecules affects the solubility. Generallypolar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.

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.

Soluble	Insoluble
Group I (expect lithiumphosphate) and NH_4^+ compounds	Carbonates (Except Group I, NH^+ and uranyl compounds) 4
Nitrates	Sulfites (Except Group I and NH_4^+ compounds)
Acetates (ethanoates) (Except Ag^+ compounds)	Phosphates (Except Group I (except for Li^+) and NH_4^+ compounds)
Chlorides (chlorates and perchlorates), bromides and iodides (Except Ag^+, Pb^{2+}, Cu^+ and Hg_2^{2+})	Hydroxides and oxides (Except Group I, NH_4^+, Ba^{2+}, Sr^{2+} and Tl^+)
Sulfates (Except Ag^+, Pb^{2+}, Ba^{2+}, Sr^{2+} and Ca^{2+})	Sulfides (Except Group I, Group II and NH_4^+ compounds)

Objectives:

After completion of this chapter, the student should be able to:

Understand the various types of pharmaceutical solutions.

Define solubility, saturated & unsaturated solutions and polar & non polar solvents.

Understand the factors controlling the solubility of strong & weak electrolytes.

Define partition coefficient & its importance in pharmaceutical systems.

Need of Solubility

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in gastric fluid and not theabsorption, so increasing the solubility in turn increase the bioavailabilityfor BCS class II & IV drugs . BCS Classification System with examples of different drug is discussed in Table-2.

Solubility of ionic compounds in water:

Some ionic compounds (salts) dissolve in water, which arises because of the attraction between positive and negative charges (see: solvation). For example, the salt's positive ions (e.g. Ag^+) attract the partially negative oxygens in H_2O. Likewise, the salt's negative ions (e.g. Cl^-) attract the partially positive hydrogens in H_2O. Note: oxygen is partially negative because it is more electronegative than hydrogen, and vice versa (see: chemical polarity).

Techniques for Solubility Enhancement

When the solubility of substances in aqueous media is limited, formulation strategies are required early on in the drug discovery and they remain of critical importance for lead substance selection and commercial drug product development.

Various techniques have been used in attempt to improve solubility and dissolutionrates of poorly water soluble drugs which include as following:

A. Particle Size Reduction
B. Nanonization
C. Cosolvency
D. Hydrotropy
E. PH Adjustment
F. Sonocrystallization
G. Supercritical Fluid (SCF) Process
H. Solid Dispersion
I. Inclusion Complexation
J. Self-Emulsifying or Self-Micro Emulsifying Systems
K. Liquisolid Methods

Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allowsgreater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to

comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation.

Nanonization

Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects.

Cosolvency

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as cosolvency and the solvent used in combination are known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.

Hydrotropy

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a secondsolute results in an increase in the aqueous solubility of existing solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs.

Advantages of Hydrotrophy

Hydrotropy 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.

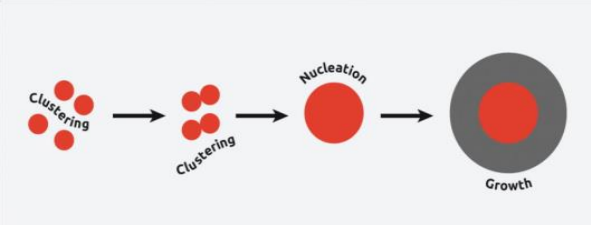
Solvent character is independent of pH, hydrotrophy has high selectivity and doesnot require emulsification. It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

PH Adjustment

Poor water-soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs

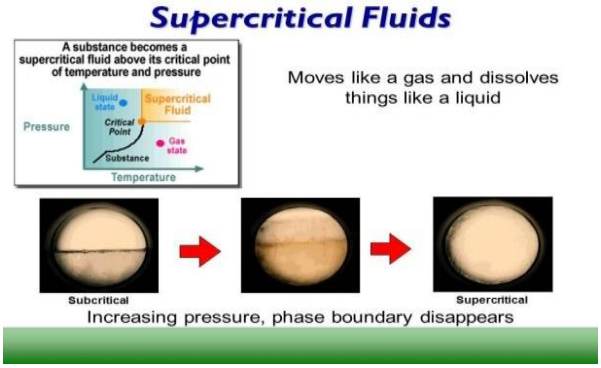
Sonocrystallisation

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size.



Supercritical Fluid (Scf) Process

The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) candissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. It is safe, environmentally friendly, and economical.



Solid Dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the

generation and dissolution performance of eutectic melts of a sulfonamidedrug and a water-soluble carrier in the early 1960s Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution

Fusion Process

In the fusion method of preparation, the carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix.

Solvent Method

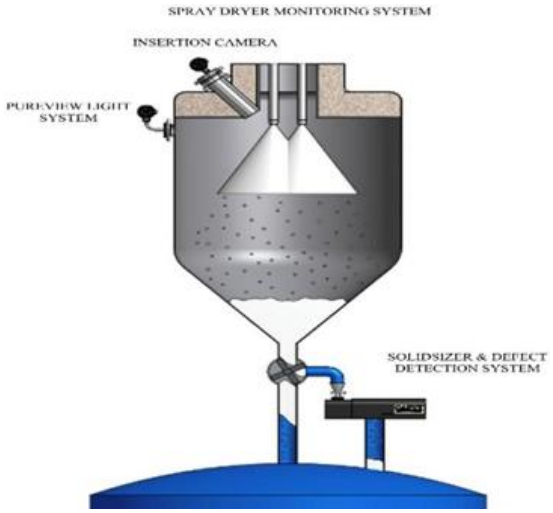
In the solvent method of preparation, the carrier and the active ingredient are dissolved in a suitable organic solvent

Fusion-Solvent Method

In the fusion methods a carrier(s) is/are melted and the drug(s) is / are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Otherwise, this method faces the same criticism of solvent retention described before. This method is particularly useful for drugs that have high melting pointsor that are thermolabile. The feasibility of the method has been demonstrated for spironolactone and griseofulvin dispersions in polyethylene glycol 6000

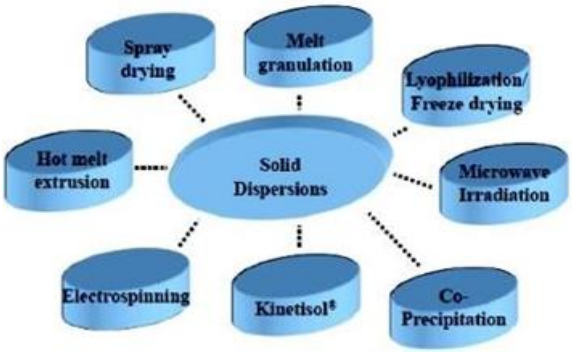
Spray Drying

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



Lyophilization (Spray freeze Drying Method)

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



Hot-melt Extrusion

It is a very common method used in the polymer industry. But Speiser and Huttenrach werethe first persons who use this technology for pharmaceutical purpose. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and

an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated.

CONCLUSION

By this article we conclude that, Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs, therapeutic efficacy of the drug and for quantitative analysis. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. The different techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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