Drug Solubility: Importance and Enhancement Techniques

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ABSTRACT:
One of the key factors in achieving the optimum drug concentration in the systemic circulation for the desired (expected) pharmacological response is solubility, the phenomenon of solute dissolving in solvent to produce a homogeneous system. The main issue in developing formulations for new chemical entities as well as for generic development is low water solubility. Over 40\% of NCES (new chemical entities) created in the pharmaceutical business are essentially water Insoluble. A significant difficulty for formulation scientists is solubility. Any medicine that is to be absorbed must be present in solution at the absorption site. Poorly soluble medications can be made more soluble using a variety of strategies, including physical and chemical drug changes and other approaches like Changed Words – Structural Changes Longest Unchanged Words particle reduction, crystal engineering, salt creation, solid dispersion, surfactant use, complexation, and other processes. The choice of a solubility-improving technique depends on the drug’s properties, the site of absorption, and the requirements for the dosage form. [1]

Keywords: solubility, homogeneous, particle size, chemical modification, salt formulation.

INTRODUCTION: [2]
Solubility is the characters of the solid liquid and gases the solubility are mainly two parts are important like solvent and solute. The solubility solvent and solute are play in important role in the solubility. Therapeutic efficiency of the drug are not only depends on the bioavailability but also depends on the solubility of the drug compound and particles. The drug solubility is depends on the concentration of solute and solvent .The same drug are not soluble in the water organic inorganic solvent. Drug solubility is many depends upon the greater spaces concentration of the drug dissolved in the solvent under specific condition of temperature pH and pressure. Temperature are many effect on the solubility. When temperature are increase solubility are increase.

EXAMPLE:- Water + sugar + heat \xrightarrow{} Increases the solubility
Effect on solubility the pH are enhance solubility are producing and pH are reducing solubility are enhance
FORMULA:- pH = -log (H+)

➢ PRESSURE :-[2]
The pressure are change in solid and liquid they are not change in solubility but also having gases are increases the pressure and solubility are increase.

General terms of solubility

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<table>
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<tr>
<td>1</td>
<td>Very soluble</td>
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<tr>
<td>2</td>
<td>Freely soluble</td>
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<tr>
<td>3</td>
<td>Soluble</td>
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<tr>
<td>4</td>
<td>Sparingly soluble</td>
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<tr>
<td>5</td>
<td>Slightly soluble</td>
</tr>
<tr>
<td>6</td>
<td>Very insoluble</td>
</tr>
<tr>
<td>7</td>
<td>Insoluble</td>
</tr>
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</table>

Types of solubility [3]

1) Unsaturated solution
   Unsaturated solution are define the solvent dissolve the higher concentration in solvent as called is unsaturated solution
2) Saturated solution
   Saturated solution it is defined as the solute are dissolve in the very low concentrated is called as the saturated solution
3) Super saturated solution
   Super saturated solution it is define as the solute dissolve in the solvent with all of crystal is called is super saturated solutions
Importance of solubility[4,5]
The orally administrated drug more important in solubility and they are more suitable in the administrated generally employed route of drug delivery because of it there are easy to old age patient low price and minimum sterility limitation and flexibility in development of the dosage form as a result many of generic drug companies are inclined extra product bioavailability oral drug products. Solubility are ply major for dosage from like parental formulations. Pharmacological response having the solubility is good parameters achieve the concentration of drug

Techniques to enhancement of solubility
1) Physical modification
   Particle size reduction
   A) Micoranization
   B) Sonocrystallization
   C) Nano-suspension
   D) Super critical fluids

2) Modification of crystal habit
   A) Polymorphism
   B) Pseudo Polymorphism

3) Drug dispersed in carriers
   A) Eutectic mixture
   B) Solid dispersion

4) Solubilization by surfactant
   A) Micro emulsion

5) Chemical modification
   A) Change in pH
B) use of buffer  
C) Derivatization  

6) Other method  
A) Co-crystallization  
B) Co – solvent  
C) Hydrotrophy  

1) Physical modification  
   • Particle size reduction[6,7,8]  
Particle size are play in a important role in the solubility. When the small particle size are easily soluble and form the solution with respect to the large particle size .Particle size are increase the bioavailability of the product. Particle size reduction mainly four types :-  
A) Micronization  
Micro -small & nization - process. 
They are loss the dissolution rate of drug by increase the surface area. They are practical size are reduction with the help of milling. It is used in the different milling equipment like jet mill, rotor mill, colloidal mill,boll mill, hammer mill. They are not used in the higher dosage number. Sex steroid drug solubility the Micronization. Dose number is defined as volume of bio relevant media per kilogram of animal or human being that would be needed to completely dissolve the dose. The dose number is more than one the drug are less soluble and the dose number is less than one the higherly or more soluble. 

HAMMER MILL
B) Sono-crystallization

A process in which the particle size reduction take place through crystallization by Sonication is called as a Sono-crystallization. It is a control the size reduction and size distribution. Ultrasound are used in the sono-crystallization to nucleation to form the crystallization. They are used in the mostly supersaturated solution.

C) Nano suspension

Nano suspension is the sub micron collider dispersion with soluble in surfactant nano-suspension particle size is the less than 1 micrometer and more than 200 to 600 nm. The nano-suspension are research in the many compounds like paclitaxel, tarazepide. Nano suspension preparation of different method like media milling high pressure homogenization in water, high pressure homogenization, in non aqueous media and combination of precipitation and high pressure homogenization.

D) Super critical fluids (SCF)

It is more dense and non condensable fluids in temperature and pressure higher than the critical pressure and temperature. They are applying only liquid and gases. The gas having important characteristics are identified like high diffusibility, low surface tension and low viscosity to control solubility of drug with super critical fluid. They are often from sub micron Particle size range. The compound like florouacil, a chemotrupin and amoxiciliin may be enhanced by scf method.

2) Modification of crystal habit

a) polymorphism [9]

Polymorphism is Greek word poly- many and morph -relating. The solid chemical compounds are show in one or more crystalline from is called as polymorphism. The more crystalline phase are different melting point x-ray diffraction pattern solubility, stability and biological activities.

EX – Calcite and Aragon

a) Monotropic
b) Enantiotropic

A) Monotropic

The different Temperature are for the only one Form crystalline

Ex :- metalazone

B) Enantiotropic

The are different temperature range are different form of crystalline

Ex :- carbamazepine, acetazolamide
Crystalline substance are more hydration energy in the amorphous substance. When more hydration energy they are easily soluble in the solvent and form the solution. Metastable state is middle state of two other state like amorphous and crystalline state
Amorphous > Metastable > crystalline

Method for the characterization of polymorphism
The polymorphism characterization are used in analytical method like thermal method of analysis microscopic crystallography x-ray diffraction, thermogravimetry differential thermal analysis, differential scanning calorimetry and nuclear magnetic resonance spectrometry (NMR)
1) Microscopy crystallography
They are used for study of morphology as well as different polymeric from .The are not s used study in polarizing microscope to detect the melting point of polymorphism.
2) Thermal analysis
It is used form the characterization in polymorphism system. DTA are used in controlled the temperature in two and more specimens .DSC method are identified the controlled temperature range different specimens .
3) X-ray depression methods
They are used in the life to the expose the plans monochromatic x-ray they are different polymorphism have light is passing through the sample light are scattering in the different angle and they are determine the rotation sample .
4) IR spectroscopy
They are used in the different compound like cis – trans rotating .The two crystal structure are non equivalent magnetic environments. The nuclear magnetic resonance spectrometer (NMR) are separated with polymorphism nuclear exist .NMR used to the understand in polymorphism variation

b. Pesudo polymorphism [10]
Pesudo - false
Pesudo polymorphism it is defined as the crystalline compound are obtained from the different nature of solvent molecules.
Ex :- ampiciline trinitydrate

Water interacted polymorphism are less energy to break up the crystal and see the less solubility
Ex :- sultonyurea

The one or more active ingredients are hydrophilic inert carrier metric at molecule level. This are occurring and carrying out the three phase
1) Hot melt method
2) Solvent evaporated method
3) Hot melt extrusion method
1) **Hot plate method**
In this method organic solvent are used in the drug dissolved with the help of heating because of organic solvent are rapidly cooling and they are finally from the solid dispersion when the drug is thermostable

2) **Solvent evaporating operating method**
This method are mainly to use in the inert vehicle solvent and organic solvent firstly the drug are mixed with the inert vehicle and dis mixture are added or [mixed]with organic solved they are show the solubility and solution follow by evaporating in organic solvent the are organic solvent evaporating with the help of freeze drying and they are from the precipitation is known as solid dispersion

3) **Hot plate extrusion method**
Hot melt extrusion method are used in the mainly drug, polymer and excipients and they are properly mixed with each other and form the solution they are not used in organic solvents and insert vehicle.

1) **Eutectic mixtures[12]**
Eutectic mixtures are used in the two component. The are solid and liquid miscible in each other in liquid state and immiscible in the solid state. Because of the solid state is pure compound this mixture the is known is eutectic mixture and eutectic temperature are existing in the liquid phase. The higher temperature are show the liquid phase and low temperature show the solid phase.

Ex :- salol thymol, camphor menthol

Eutectic mixture are exposed in gastrointestinal fluids. Hydrophilic agent increases the solubility of eutectic mixture

![Diagram](image)

• **Complexation [13]**
Complexation are used in covalent and non covalent interaction between two or more compound to existing the independent. The ligand are intract with substrate and from the complex molecules. Drug are from the complex with other small or micro molecules. The complex are from the solubility, stability partitioning, energy absorption and emission. Complex molecules are enhance the solubility and stability of drug. They are mostly used in optimization.

Classification of the complexation

1) **metal ion or co-ordination complexes**
A) Inorganic type
B ) Chelates  
C ) olefin type  

2 ) Organic molecular complex  
A ) Quinhydrone type  
B ) picric acid type  
C ) Caffeine and other drug complexes  
D ) Polymer type  

3 ) Inclusion or occlusion complexes  
A ) Chanel lattice type  
B ) layer type  
C ) Clathrates  
D ) Monomolecular type  
E ) Macro molecular  

2) SOLID DISPERSION [14,15]  
Sekiguchi and obi are firstly proposed by the solid dispersion. They are study in the eutectic melts of sulfonamide drug and water soluble carrier in the early in 1965. It is useful from pharmaceutical technique like dissolution , absorption , and therapeutic effect of drugs in dosage form . Solid dispersion are only follow the solid drug product. They are mostly used in hydrophilic nature and hydrophobic drug. They are mostly used in the hydrophilic nature in solid dispersion. The celecoxib , halofantrine and ritonavir care increase the solid dispersion using the hydrophilic nature like cerecoxib  

4) Solubilization of Surfactant[16,17]  
It is made up of the polar and non polar region. They are hydrophilic and lipophilic in nature. Surfactant are play in important in solubility. Surfactant are enhance the surface area of the drug and solvent as well as reduce the surface tension of drug and solvent. The surfactant are also know as amphiphilic. The low level of surfactant are Separated to each other & High level of Surfactant are form the combination. They are thermodynamically stable solution in to slightly soluble and insoluble substance.  
With used to surfactant. The surfactant Inhance the solubility of small intestine.  
\[(SR) = 0.64 \times \log (p) + 2.09\]
Micro emulsion

The word “emulsion” comes from the Latin word for “to milk”. An emulsion is a mixture of two or more liquids that are normally immiscible. A system of water oil and Amphiphilic substance a single optically isotropic and thermodynamically stable liquid solution is known as a micro emulsion. Micro emulsion are sometimes through of miniature versions of emulsion i.e. droplet type dispersions of water in oil (w/o) or oil in water (o/w) with size range of microemulsion is 5 to 50 nm in drop radius.

Three different forms of micro emulsions can be created depending on the composition:

1) Continuous aqueous phase
2) micro emulsion of oil in water
3) Bi-continuous micro emulsion

1) Continuous aqueous phase
Micro emulsion of oil in water in which oil droplet are distributed
2) micro emulsion of oil in water
Micro emulsion of water and oil in which the oil phase is continuously mixed with small droplets of water
3) Bi-continuous micro emulsion
Bi-continuous micro emulsion which contain interspersed microdomains oil and water

5) Chemical modification [18-20]

1) Change in pH
2) use of buffer
3) Derivatization

1) Change in pH

The solubility decreases as the pH rises while the solubility rises of the pH decreases. Solubility is influenced by factor other than PH such as temperature, Weak bases and acids can be dissolved in water depending on the pH of the dissolving medium and their & ionization. Constants The solubility of a substance in its free acid or basic form is know of the Intrisic solubility This is approximated for weak acid by their solubility at PH values more than one unit below their pka.

<table>
<thead>
<tr>
<th>Location</th>
<th>Average pH-fasted state</th>
<th>Average pH-fed state</th>
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<tbody>
<tr>
<td>Stomach</td>
<td>1.3</td>
<td>4.9</td>
</tr>
<tr>
<td>Duodenum</td>
<td>6.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Jejunum</td>
<td>6.6</td>
<td>5.2–6.0</td>
</tr>
<tr>
<td>Ileum</td>
<td>7.4</td>
<td>7.5</td>
</tr>
</tbody>
</table>
2) Uses of buffer

Buffer are useful in maintain the pH. A buffer keeps a solution’s pH stable throughout time and lessen reduce or completely eliminates the possibility of Precipitation after dilution. pH changes during dilution that reduce Solubility. If the pH change by one pH unit the drug’s ionization is reduced and the solubility drops by factor. Of 10 increasing solubility by one fold Buffer solution age form the combination of HCl acid and NaOH basic.

3) Derivatization

This approach involves changing the parent form of a poorly soluble medicine into a derivative of that drug. Derivatization can be accomplished in one of two ways: either by creating a prodrug or by creating a Salt formulations.

a) Prodrug

It is a result the of the covalent attachment of the drug moiety. Because of the medicine is less stable. Outside the body and may be degraded there as a result. It is bound an inert matrix or carrier. Drug solubility will be reduced as a result. When prodrug injected the covalent Connection between the drug and the inert matrix is broken making the drug available inside the body in its parent form or in the short term the body produces 4 – hydroxy cyclophosphamide as active metabolite.

b) Salt formulations

Drug solubility may differ greatly improved by creating or altering the Salt form of the medication. For example: Clindamycin hydrochloride dissolve is 3 mg/ml however solubility of clindamycin phosphate is significantly changed i.e 150 mg/ml.

6) Other method[20-23]

1) Co crystallization
2) Co-solvency
3) Hydrotrophy

1) Co-crystallization

A crystalline substance that comprises two or more molecular species help together by no-covalent forces is referred to as a co-crystal. Because the co-crystallizing agents are solids at room temperature Co-crystals are more stable. Co Crystals can be created by combining the components in a grinder or by [crush mil] evaporating a heteromeric solution-sublimation growth form the melt and slurry. Preparation are further co-crystal preparation method only three co-crystallizing substance-. Acetic acid, nicotinamide, and saccharin are categorized as generally recognized as safe (GRAS) which limits use in pharmaceuticals.

2) Co-solvency

A water miscible solvent that the medicine is readily soluble in can be added to water to increase the solubility of drugs that are poorly soluble in water. The combination of the two solvents is known as a co-solvent and the process is referred to co solvency. By lowering (decreasing) the interfacial tension between the aqueous solution and hydrophobic solute, co-solvent. System function it is additionally sometimes called solvent bleeding. By adding on organic Co-solvent to the water the Solubility of medicines is dramatically altered (changes significant).
3) Hydrotrophy
-A solubilization process know as hydrotropy. Occurs when a second solute is added in significant quantity increasing the first solute’s water solubility current substance. (Active ingredient) many poorly water soluble medications have been see to have the aqueous solubilities increased by concentrated aqueous hydrotropic sodium benzoate, sodium salicylate, urea, nicotinamide sodium. Citrate and sodium acetate.

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