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SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY SOLUBLE DRUGS : A REVIEW

Mahesh I. Limbachiya[*1],
Milan Agrawal[1], Amit Sapariya[1], Shailesh Soni[2]

[1]Department of Pharmaceutics, Saraswati Institute of Pharmaceutical Sciences, Gandhinagar, Gujarat, India.
[2]Department of Pharmaceutics, B. S. Patel Pharmacy College, Linch, Mehsana, Gujarat, India.

ABSTRACT

Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Key words: *Solubility, Solubility Enhancement, Cyclodextrin, Nanosuspension, Supercritical Fluid, Hydrophobic drugs.*

Correspondence to Author

Mahesh Limbachiya

Department of Pharmaceutics, Saraswati Institute of Pharmaceutical Sciences, Gandhinagar,Gujarat, India.

Email:
Limbachiyamahesh25@gmail.com

INTRODUCTION

DEFINITION:

Solubility:

Solubility is defined as the number of milliliters of solvent in which 1 gm of solute will dissolve.[1]

Solubility definitions:

Descriptive term	Approximate volume of solvent in milliliters per gram of solute
very soluble	less than 1
freely soluble	from 1 to 10
Soluble	from 10 to 30

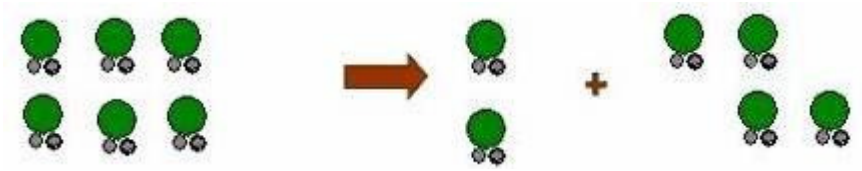
sparingly soluble	from 30 to 100
slightly soluble	from 100 to 1000
very slightly soluble	from 1000 to 10,000
Insoluble or practically insoluble	more than 10,000

PROCESS OF SOLUBILISATION

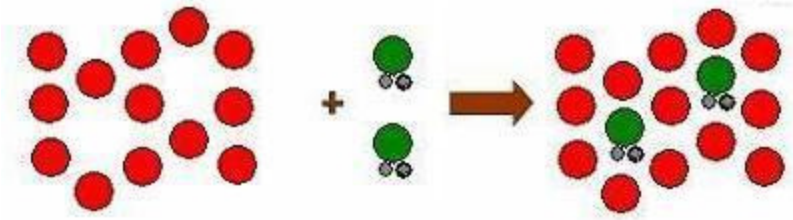
The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Step 1: Holes opens in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3:The freed solid molecule is intergrated into the hole in the solvent



TECHNIQUES OF SOLUBILITY ENHANCEMENT:

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are:

I. PHYSICAL MODIFICATIONS

A. Particle size reduction

a. Micronization
b. Nanosuspension

B. Modification of the crystal habit

a. Polymorphs
b. Pseudopolymorphs

C. Drug dispersion in carriers

a. Eutectic mixtures
b. Solid dispersions
c. Solid solutions

D. Complexation

a. Use of complexing agents

E. Solubilization by surfactants

F. Solubilization by salt formation

G. Nanotechnology approaches

II. CHEMICAL MODIFICATIONS

I. PHYSICAL MODIFICATIONS:

A. PARTICLE SIZE REDUCTION:

Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

a. Micronization

Micronisation increases the dissolution rate of drugs through increased surface area, it does not

increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[2

Nanosuspension[3]

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.

Techniques for the production of nanosuspensions

Homogenization:

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles.Three types of homogenizers are commonly used for particle size reduction in the pharmaceutical and biotechnology industries: conventional homogenizers, sonicators, and high shear fluid processors.

Wet milling:

Active drug in the presence of surfactant is defragmented by milling.Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.

The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquone. All the formulations are in the research stage. One major concern related to particle size reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one. Drying of nanosuspensions can be done by lyophilisation or spray drying.

Other Techniques For Reduction Of the Particle size:

Sonocrystallisation

The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation.Sonocrystallisation utilizes ultrasound power characterised by a frequency range of 20–100 kHz for inducing crystallisation. It's not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients (API). Most applications use ultrasound in the range 20 kHz-5 MHz.

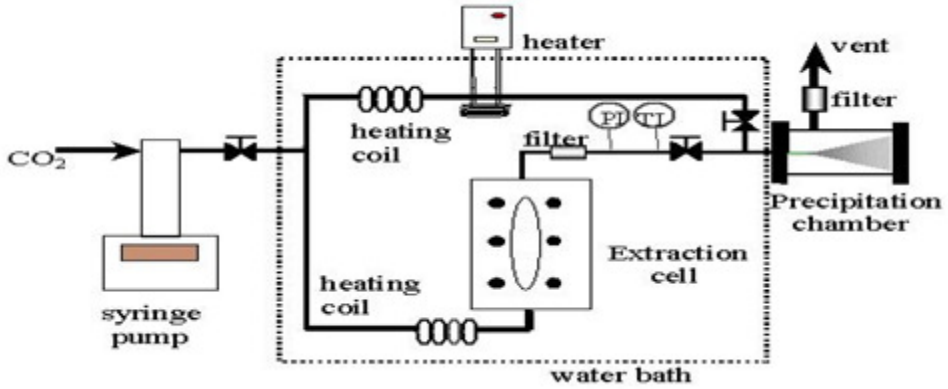
Supercritical fluid process[4]

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense noncondensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). Through manipulation of the pressure of SCFs, the favorable characteristics of gases- high diffusivity, low viscosity and low surface tension may be imparted upon liquids to precisely control the solubilisation of a drug with a supercritical fluid. SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determine its solvents power. Once the drug particles are solubilised within SCFs, they may be recrystalised at greatly reduced particle sizes. A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter.

The most widely employed methods of SCF processing for micronized particles are **rapid expansion of supercritical solutions (RESS)** and **gas antisolvents recrystallisation (GAS)**, both of which are employed by the pharmaceutical industry using carbon dioxide (CO_2) as the SCFdue to its favourable processing characteristics like its low critical temperature (Tc = 31.1-C) and pressure (Pc = 73.8 bar).]

RESS involves solubilising a drug or a drug-polymer mixture in SCF and subsequently spraying the SCF

solution into a lower pressure environment via a conventional nozzle or capillary tube. The rapid expansion undergone by the solution reduces the density of the CO_2, correspondingly reducing its solvent power and supersaturating the lower pressure solution. This supersaturation results in the recrystallisation and precipitation of pure drug or drug-polymer particles of greatly reduced size, narrow size distribution and high purity. The solubility of nifedipine has been improved by RESS.

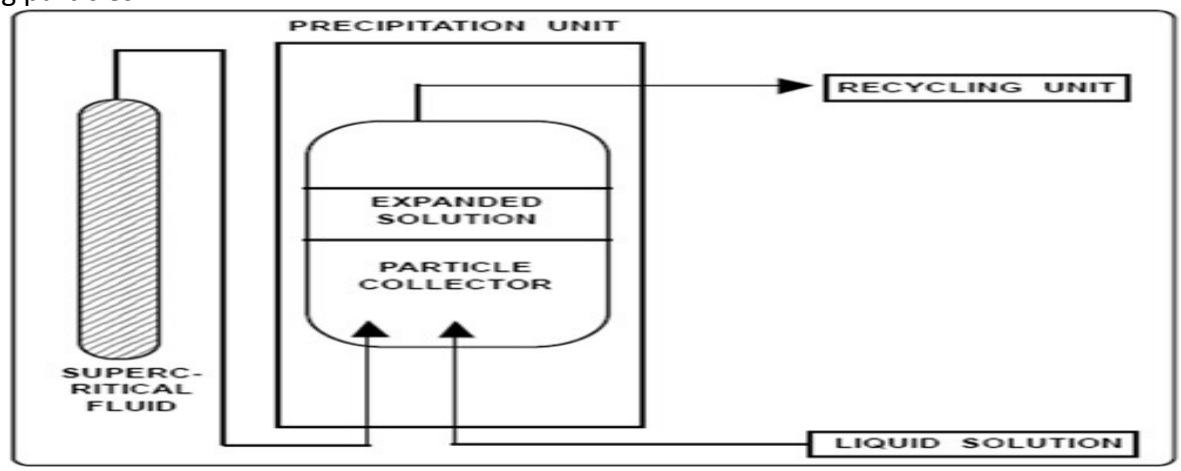


Rapid expansion of supercritical solution apparatus

PI - Pressure Indicator and TI - Temperature Indicator

GAS processing requires the drug or drug-polymer mixture be solubilised via conventional means into a solvent that is then sprayed into an SCF; the drug should be insoluble in the SCF, while the SCF should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles.

The low solubility of poorly water-soluble drugs and surfactants in supercritical CO_2 and the high pressure required for these processes restrict the utility of this technology in the pharmaceutical industry.



MODIFICATION OF THE CRYSTAL HABIT:

Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Once the drug has been characterized under one of this category, further study involves

the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous >Metastable polymorph >Stable polymorph

DRUG DISPERSION IN CARRIERS:

EUTECTIC MIXTURE[2]

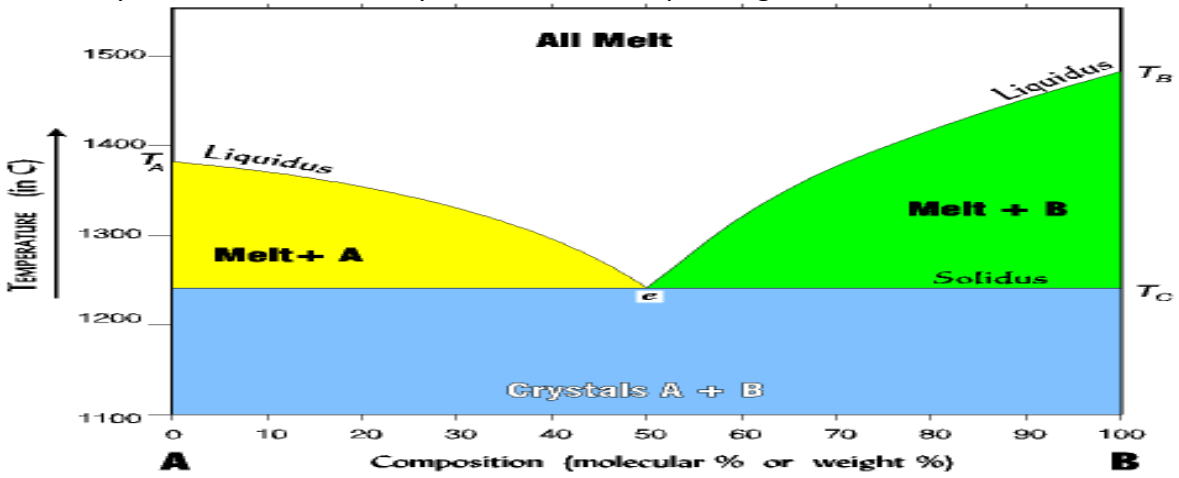
- The word "eutectic" comes from Greek and means "**easily melted**"
- **Eutectic mixture** is a mixture at such proportions that the melting point is as low as possible, and that furthermore all the constituents crystallize simultaneously at this temperature (eutectic temp.) from molten liquid solution.
- These are prepared by rapid solidification of fused melts of two components that shows complete liquid miscibility but negligible solid-solid solubility.
- Thermodynamically, such a system is intimately blended physical mixture of two crystalline components. Thus x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components.

Phase diagram of Eutectic mixture:

1. The liquidus line separates the all melt phase from the melt+crystal phase.
2. The solidus line separates the melt+crystal phase from the all crystal phase.

NOTE that the solidus and liquidus lines are experimental, they have been determined by melting and cooling many melts at different percent compositions.

3. The eutectic is the point at which all three phases can exist simultaneously, A, B, and melt. The eutectic here is 50% B, but can be any percent depending on the minerals involved.



Organization of the Binary Eutectic Phase Diagram

SOLID DISPERSION[5]

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961.The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as **melt extrusion**. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630. Many times surfactants may also used in the formation of solid

dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used.

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib celecoxib, halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

METHODS OF PREPARATION OF SOLID DISPERSION

Hot Melt method

Sekiguchi and Obi used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. 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. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

Solvent Evaporation Method

Tachibana and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier polyvinylpyrrolidone. An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 C.The solid dispersion of the 5-lipoxygenase/cyclooxygenase inhibitor ER-34122 shown improved in vitro dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation. These techniques have problems such as negative effects of the solvents on the environment and high cost of production due to extra facility for removal of solvents. Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

Hot-melt Extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. The process has been useful in the preparation of solid dispersions in a single step.

Melting –solvent method

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

SOLID SOLUTION[2]

"A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the 2 components crystallize together in a homogenous one phase system, solid solutions are also called as **molecular dispersions or mixed crystals OR MELTS**

SOLID SOLUTION CAN BE CLASSIFIED BY TWO WAYS

According to the extent of miscibility of two components.

Continuous solid solution (isomorphous,unlimited,complete)

Discontinuous solid solution(limited,restricted,partial,incomplete) solid solution

According to molecular size of two molecules of

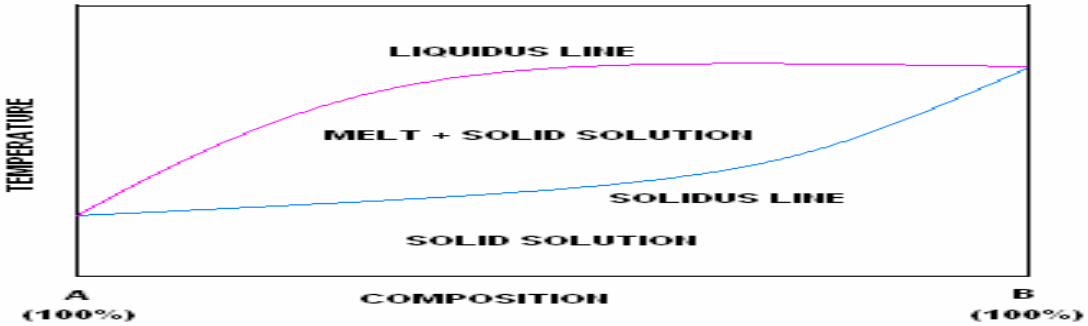
solid solution

Substitutional solid solution

Interstitial solid solution

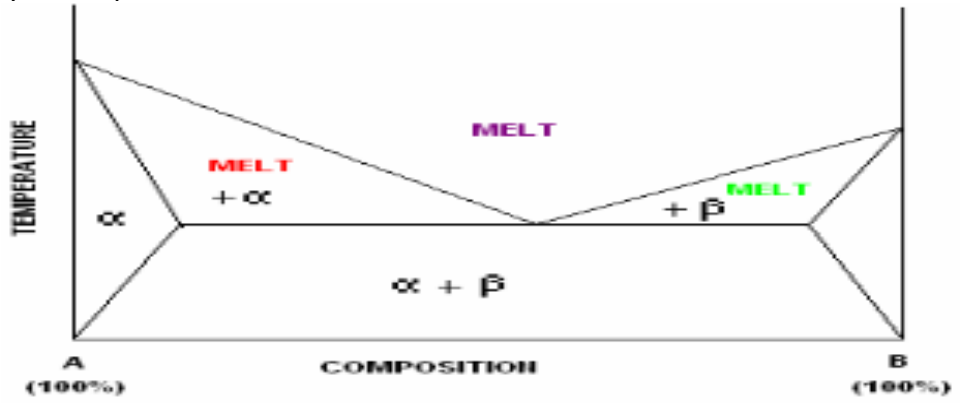
CONTINUOUS SOLID SOLUTION

- In this type of solid solution the two components are miscible in the solid state in all proportion.
- The total lattice energy of continuous solid solution at various compositions theoretically should be greater than that of bond between the different components at solid state.



DISCONTINUOUS SOLID SOLUTION

- In contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solution
- As given in the fig. the regions of solid solution is represented by α and β
- Each component shown is capable of dissolving the other components to a certain degree above the eutectic temperature
- As the temperature is lowered, the solid solution regions become narrower



SUBSTITUTIONAL SOLID SOLUTION

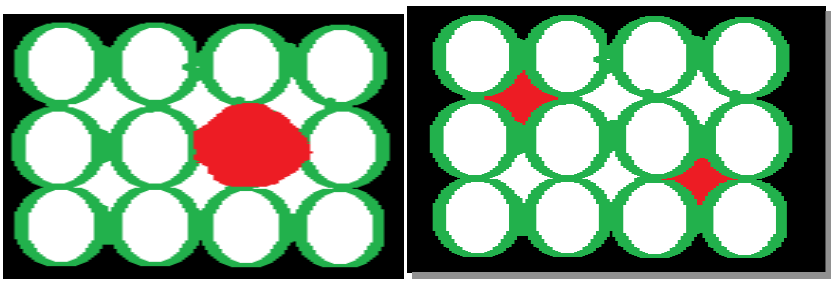
- In this type of solid solution the solid molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. it can form a continuous or discontinuous solid solution
- The size and steric factor of the solute molecule were shown to play a decisive role in the formulation of solid solution, the size of the solute and the solvent molecule should be as close as possible
- EXAMPLES:

(1) Anthracene – acenaphthalene

(2) Ammonia – potasium thiocyanate

INTERSTITIAL SOILD SOLUTION

- In this type of solid solution, the solute (guest) molecule occupies the interstitial space of the solvent (host) lattice usually forms only discontinuous (limited) solid solution
- The size of solute is critical in order to fit into the interstices.
- EXAMPLE -Solid solution of digitoxin, methyl testosterone, prednisolone acetate & Hydrocortisone acetate in matrix of PEG – 6000.



SUBSTITUTION **INTERSTITIAL**

COMPLEXATION:

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in below table.

List of Complexing Agents

Sr.No.	Types	Examples
1	Inorganic	I_B^-
2	Coordination	Hexamine cobalt(III) chloride
3	Chelates	EDTA, EGTA
4	Metal-Olefin	Ferrocene
5	Inclusion	Cyclodextrins, Choleic acid
6	Molecular Complexes	Polymers

STACHING COMPLEXATION

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation. Some compounds that are known to form staching complexes are as follows:

- Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene etc.
- Higuchi and Kristiansen proposed a model according to which the compounds capable of undergoing stacking can be classified into two classes (classes A and B) based on their structure. The compounds in class A have higher affinity for compounds in class B than for those in class A and vice versa.

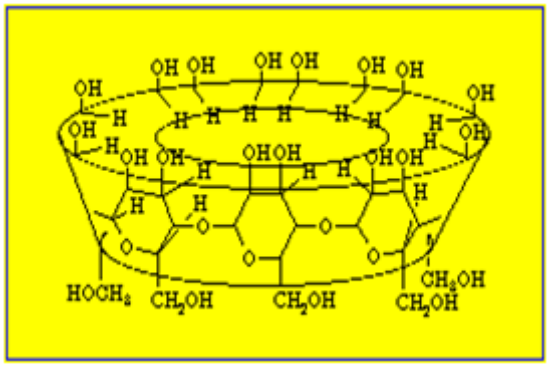
❖ **INCLUSION COMPLEXATION**

- Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The major structural requirement for inclusion complexation is a snug fit of the guest into the cavity of host molecule. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, so that the total contact between the water and the nonpolar regions of the host and the guest is reduced.
- The most commonly used host molecules are **cyclodextrins**. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins. Cyclodextrins are non-reducing, crystalline, water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ- Cyclodextrin. The complexation with cyclodextrins is used for enhancement of solubility. Cyclodextrin

inclusion is a molecular phenomenon in which usually only one guest molecule interacts with the cavity of a cyclodextrin molecule to become entrapped and form a stable association. The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule.

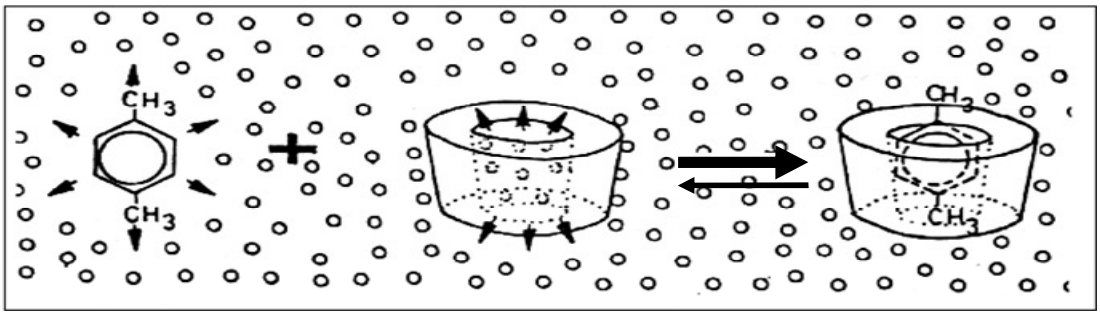
- Molecules or functional groups of molecules those are less hydrophilic than water, can be included in the cyclodextrin cavity in the presence of water. In order to become complex, the "guest molecules" should fit into the cyclodextrin cavity. The cavity sizes as well as possible chemical modifications determine the affinity of cyclodextrins to the various molecules.
- The kinetics of cyclodextrin inclusion complexation has been usually analyzed in terms of a one-step reaction or a consecutive two-step reaction involving intracomplex structural transformation as a second step. Cyclodextrins is to enhance aqueous solubility of drugs through inclusion complexation. It was found that cyclodextrins increased the paclitaxel solubility by 950 fold. Complex formation of rofecoxib, celecoxib, clofibrate, melarsoprol, taxol, cyclosporin A etc. with cyclodextrins improves the solubility of particular drugs.

STRUCTURE OF CYCLODEXTRIN



	α-CD	β-CD	γ-CD	δ-CD
Molecular formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$	-
Optical rotation[α]d	+150.5	+160.0	177.4	-
GP units	6	7	8	9
Molecular weight	972	1135	1297	1459
Cavity diameter(A)	4.7-5.3	6-6.5	7.5-8.3	10.3-11.2
Solubility(g/100ml)25` c	14.5	18.5	23.2	-

CYCLODEXTRIN INCLUSION COMPLEX:



The formation of inclusion complex with CD occur in following step:

- Approach of the guest or substrate molecule to CD molecule

- Loss of the water structure within the cavity with removal of some water molecules
- Break down of water structure around the portion at the substrate that will be included and
- transport of some water molecules in solution.
- Interaction of the substituent groups of substrate with groups on the rim or inside the cyclodextrin ring
- Possible formation of bonds between the CD and the substrate.
- Re-establishment of water structure around the external parts of substrate after the inclusion has occurred.
- In aqueous solution the slightly a polar cyclodextrin cavity is occupied by water molecule which are energetically unfavoured and so can be readily substituted by guest molecule which are less polar than water.
- The dissolved cyclodextrin is the 'host' molecule and the driving force of the complex formation is the substitution of the high enthalpy water molecule by appropriate 'guest' molecule.
- Cyclodextrin complexes are relatively stable their water solubility compared to pure cyclodextrin is strongly reduced so they rapidly separated from the solution in crystalline form.

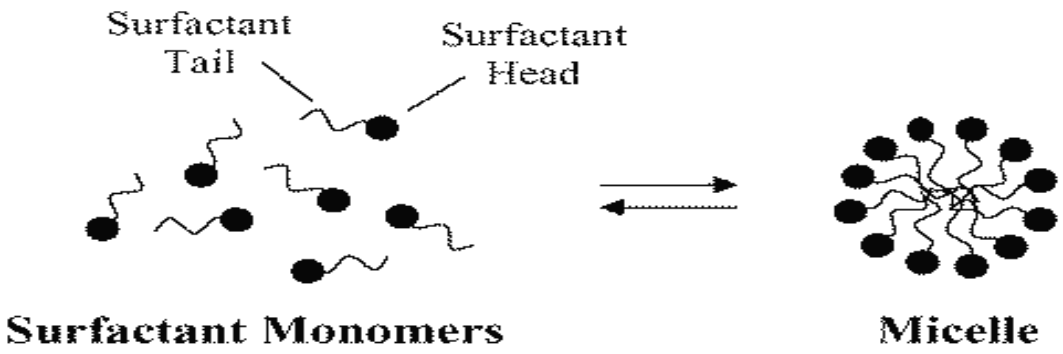
E. SOLUBILIZATION BY SURFACTANTS:

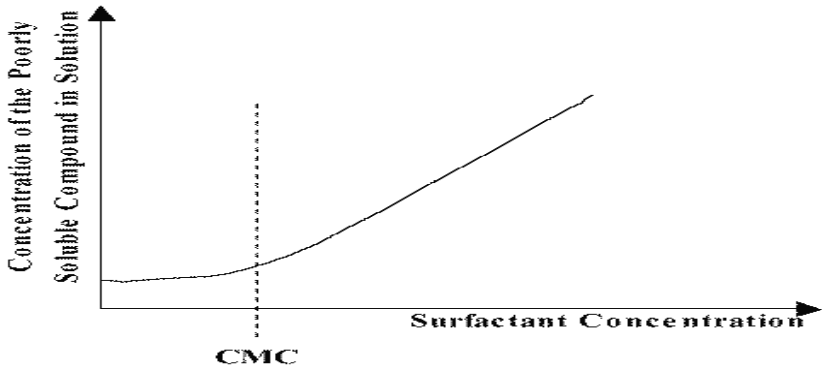
Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment (usually in the form of along aliphatic chain segment) connected to a polar group. The polar group can be anionic (such as a carboxylate, sulfate, or sulfonate), cationic (such as ammonium, trialkylammonium or pyridinium), zwitterionic (such as glycine or carnitine) or nonionic such as polyethylene glycol, glycerol or sugar.Non-classical surfactants like cholic acid, polysorbate, and poloxamer do not contain a single aliphatic chain and a simple polar head group but they contain distinct polar and nonpolar regions.

Ideal Properties of Surfactants[2][7]

- In the water, as the concentration of surfactant increases above a critical value, its molecules self associate into soluble structures called micelles.
- The concentration at which they begin to form is called the critical micelle concentration (or the CMC).
- These micelles are normally spherical with the nonpolar regions of the surfactant molecules gathered in the center (core) and surrounded by a mantle of the Polar Regions which are in contact with the water as shown in the figure. Thus, solubilization can be defined as the spontaneous dissolving of a substance by reversible interaction with the micelles of a surfactant in water to form a thermodynamically stable isotropic solution with reduced thermodynamic activity of the solubilized material.
- Micelles are labile entities formed by the noncovalent aggregation of individual surfactant monomers. Therefore, they can be spherical, cylindrical, or planar (discs or bilayers). Micelle shape and size can be controlled by changing the surfactant chemical structure as well as by varying solution conditions such as temperature, overall surfactant concentration, surfactant composition (in the case of mixed surfactant systems), ionic strength and pH.Solubilizing capacity for surfactant with the hydrocarbon chain length increases in the order:

  Anionic < Cationic < Non-ionic
- The general solubilization curve for surfactants is given in the following figure . If the monomers of surfactant in solution do not affect the solubility of the solute, then the solute concentration will remain constant (at the intrinsic solubility, Sw) until the CMC. After the CMC the solute concentration will increase linearly with increasing surfactant (micelle) concentration.





Schematic plot of the concentration of a poorly soluble compound as a function of the surfactant concentration in aqueous solution.

SOLUBILIZATION BY SALTS

Salt have improved solubility and dissolution characteristics in comparision to the original drug. It is generally accepted that a minimum difference of 3 units between the pka value of the group and that of its counterion is required to form stable salts. Alkali metal salts of acidic drugs like penicilins and strong acid salts of basic drugs like atropine are more water-soluble than the parent drug. Factors that influence salt selection are physical and chemical properties of the salt,safety of counteron,therapeutic indications and route of administration.[2]

Salt formation does have limitation:

- It is not feasible to form salts of neutral compounds.
- It may be difficult to form salts of very weak bases or acids.
- The salt may be hygroscopic,exhibit polymorphism or has poor processing characteristics.
- Conversion of salt to free acid or base form of the drug on surface of solid dosage form that prevents or retards drug release.
- Precipitation of unionized drug in the GI milieu that has poor solubility.

G. NANOTECHNOLOGY APPROACHES[8]

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation.

NANOCRYSTAL:

A nanocrystal is a crystalline material with dimensions measured in nanometers; a nanoparticle with a structure that is mostly crystalline. The nanocrystallization is

defined as a way of diminishing drug particles to the size range of 1-1000 nanometers.Nanocrystallization is thought to be a universal method that can be applied to any drug.Here are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

a) Milling:

Nanoscale particles can be produced by wet-milling process. In ball mills, particle size reduction is achieved by using both impact and attrition forces. The most common models are a tumbling ball mill and a stirred media mill. One problem of this method is the degradation of mill surfaces and subsequent suspension contamination.

b) High pressure homogenization:

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenisation can be performed in water (DissoCubes) or alternatively in non-aqueous media or water-reduced media (Nanopure). The particles are disintegrated by cavitation and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

c) Precipitation:

In the precipitation method a dilute solution is first produced by dissolving the substance in a solvent where its dissolution is good.The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air.

d) Cryo-vacuum method:

In the cryo-vacuum method the active ingredient to be nanonized is first dissolved in water to attain a quasi-saturated solution. The method is based on sudden cooling of a solvent by immersing the solution in liquid nitrogen (-196 ºC). Rapid cooling causes a very fast rise in the degree of saturation based on the decrease of solubility and development of ice crystals when the temperature drops below 0 ºC. This leads to a fast nucleation of the dissolved substance at the edges of the ice crystals. The solvent must be completely frozen before the vessel is removed from the liquid nitrogen. Next the solvent is removed by sublimation in a lyophilization chamber where the temperature is kept at constant -22 ºC and the pressure is lowered to 10^{-2} mbar. Cryo-assisted sublimation makes it possible to remove the solvent without changing the size and habit of the particles produced, so they will remain crystalline. The method yields very pure nanocrystals since there is no need to use surfactants or harmful reagents.

NANOMORPH:

The NanoMorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Water redispersable dry powders can be obtained from the nanosized dispersion by conventional methods, e.g. spray-drying.

II. CHEMICAL MODIFICATIONS:

For organic solutes that are ionizable, changing the pH of the system may be simplest and most effective means of increasing aqueous solubility. Under the proper conditions, the solubility of an ionizable drug can increase exponentially by adjusting the pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Similar to the lack of effect of heat on the solubility of non-polar substances, there is little effect of pH on nonionizable substances. Nonionizable, hydrophobic substances can have improved solubility by changing the dielectric constant (a ratio of the capacitance of one material to a reference standard) of the solvent by the use of co-solvents rather than the pH of the solvent.

The use of salt forms is a well known technique to enhanced dissolution profiles. Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs.An alkaloid base is, generally, slightly soluble in water, but if the pH of medium is reduced by addition of acid, and the solubility of the base is increased as the pH continues to be reduced. The reason for this increase in solubility is that the base is converted to a salt, which is relatively soluble in water (e.g. Tribasic calcium phosphate).The solubility of slightly soluble acid increased as the pH is increased by addition of alkali, the reason being that a salt is formed (e.g. Aspirin, Theophylline, Barbiturates).

OTHER TECHNIQUES[2][9]

Co-crystallisation:

The new approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystal, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clathrate (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces.

Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystallisation between two active pharmaceutical ingredients has also been reported. This may require the use of subtherapeutic amounts of drug substances such as aspirin or acetaminophen. At least 20 have been reported to date, including caffeine and glutaric acid polymorphic co-crystals. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation. The formation of molecular complexes and co-crystals is becoming increasingly important as an alternative to salt formation, particularly for neutral compounds or those having weakly ionizable groups.

Cosolvency:

The solubilisation of drugs in co-solvents is an another technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs.

Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility known as cosolvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending.

Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall

intermolecular attraction of water. By disrupting waters self-association, cosolvents reduce waters ability to squeeze out non-polar, hydrophobic compounds, thus increasing solubility. A different perspective is that by simply making the polar water environment more non-polar like the solute, cosolvents facilitate solubilization. Solubility enhancement as high as 500-fold is achieved using 20% 2-pyrrolidone.

Hydrotrophy:

Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents (sodium benzoate, sodium acetate, sodium alginate, and urea) and the solute.

Example: Solubilisation of Theophylline with sodium acetate and sodium alginate

Solubilizing agents:

The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine. The aqueous solubility of the antimalarial agent halofantrine is increased by the addition of caffeine and nicotinamide.

Microemulsion:

A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant. The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant, results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal or dispersed phase is < 0.1 μ droplet diameter. The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsions. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production**.**

Preparation Of Microemulsion

The drug is be dissolved in the lipophilic part of the microemulsion i.e. Oil and the water phases can be combined with surfactant and a cosurfactant is then added at slow rate with gradual stirring until the system is transparent. The amount of surfactant and cosurfactant to be added and the percent of oil phase that can be incorporated shall be determined with the help of pseudo-ternary phase diagram. Ultrasonicator can finally be used so to achieve the desired size range for dispersed globules. It is then be allowed to equilibrate.Gel may be prepared by adding a gelling agent to the above microemulsion. Carbomers (crosslinked polyacrylic acid polymers) are the most widely used gelling agent.[10]

EXAMPLE:

- Etoposide emulsion
- Methotrexate emulsion

Clathrates

Defination: A special type of inclusion compound in which the host molecules form a crystal lattice containg spaces into which guest molecules can fit.The macrocyclic molecule is called the HOST. The small included molecule is the GUEST.The inclusion process gives rise to HOST-GUEST CHEMISTRY.[2]

- Speciality of the clathrates:-chemical bonds are not involved & only the molecular size of the encaged component is of importance.
- Ideal requirement: Host molecule-must be hydrophilic yet able to bind the lipophilic guest molecule by means of hydrophobic interactions.
- Stability of a clathrate is due to the strength of the structure.

Buffers:

The practical use of a buffer is to simply maintain the pH of the system over time. For pH solubilized drugs, another practical use of a buffer is to reduce or eliminate the potential for precipitation of the drug upon dilution. It has been shown that drug

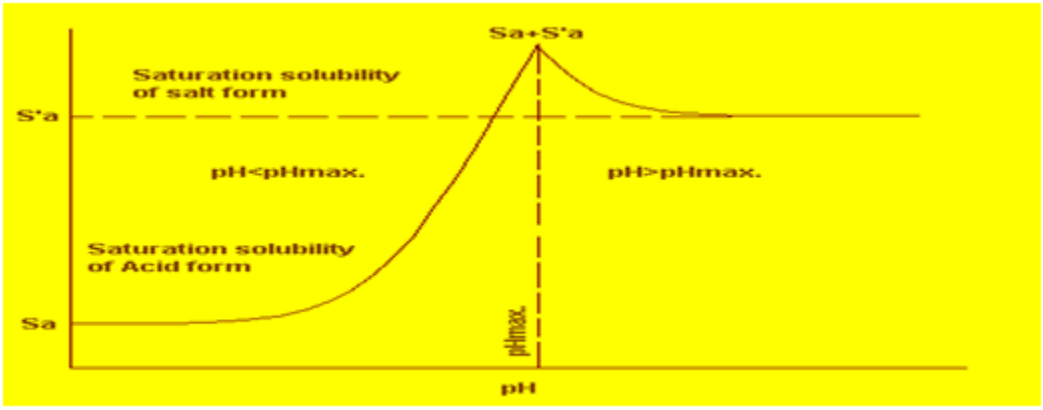
precipitation upon i.v. injection has been due linked to phlebitis.

If a pH solubilized formulation is diluted with a medium by one half, then the drug concentration will decrease by one half. At the same time the pH of the new mixture may change. If it changes by one pH unit in a direction that decreases ionization of the drug then the solubility of that drug will decrease 10 –fold. The drug can precipitate if the concentration in the solution exceeds the new solubility.The degree and extent of precipitation will depend on the ability of a formulation to resist pH change when diluted. The pH change on dilution of one solution by another will depend on the initial pH and buffer capacities of both solutions.It was observed that pH changes as a function of dilution with Sorenson phosphate buffer for phosphate buffers with different initial pH values and concentrations.The unbufferd formulation precipitated upon dilution and resulted in phlebitis in vivo, whereas the buffered formulations did not precipitate and did not elicit any phlebitis in vivo.[2]

Selection of buffer

- The buffer must have adequate capacity in desired pH range.
- Biologically safe for intended use.
- No Deleterious effect on stability of the final product.
- Should permit the use of other excipients like flavoring or coloring agents.

A very small change in pH may result in 30% more drug going into the solution. So, by observing pH solubility profile; it helps in selection buffer for optimum pH range.



BUFFERS USED IN PHARMACEUTICAL

Formulation	Buffers
Tablets & capsules	Mg carbonate; sodium bicarbonate
Ointments & creams	Citrate, acetate, phosphate
Ophthalmic	Boric acid, isotonic phosphate, citrate
Parenterals	Citrate, Acetate, Tartrate, glutamate

APPLICATIONS:

- Solubility is of fundamental importance in a large number of scientific disciplines and practical applications, to the use of medicines, and the transport of pollutants.
- Solubility is represents a fundamental concept in fields of research such as chemistry, physics, food science, pharmaceutical, and biological sciences.
- The solubility of a substance becomes specially important in the pharmaceutical field because it often represents a major factor that **controls the bioavailability of a drug substance.**
- solubility is commonly used to describe the substance, to indicate a substance's polarity,to help to distinguish it from other

substances, and as a guide to applications of the substance.

- Solubility of a substance is useful when separating mixtures.
- Moreover, solubility and solubility-related properties can also provide important information regarding the **structure of drug substances**, and in their **range of possible intermolecular interactions.**

For these reasons, a comprehensive knowledge of solubility is essential.

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