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Review Article

Enhancement of Solubility; an Over View

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ABSTRACT

Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development, nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in vivo efficacy. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work .The present review deals in detail about the solubilisation by surfactants, cosolvents, complexation for the improvement of solubility of poorly water soluble drugs.

Keywords: Solubility, dissolution rate, physical and chemical methods, nanotechnology approaches.

INTRODUCTION

Bioavailability ultimately depends upon the solubility of drug molecules. Solubility is one of the important parameter to achieve. Therapeutic effectiveness of a drug depends upon the every desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability.[1] The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance. The substance to be dissolved is called as solute and the dissolving fluid in which the solute dissolve is called as solvent, which together form a solution. The process of dissolving solute into solvent is called as solution or hydration if the solvent is water. [2]The transfer of molecules or ions from a solid state into solution is known as dissolution. In essence, when a drug dissolves, solid particles separate and mix molecule by molecule with the liquid and appear to become part of that liquid. Therefore, drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase. The use of poorly soluble drugs has a number of drawbacks such as increasing the dosage, administration frequency and the resultant occurrence of side effects. Furthermore, the rate-limiting step in the absorption process for poorly water-soluble drugs is the dissolution rate of such drugs in the gastro intestinal fluids rather than the rapidity of their diffusion across the gut wall; it is however, important to improve the oral bioavailability of poorly water soluble drugs.

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Solubilisation

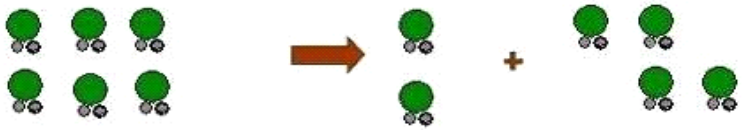
Solubilisation can be defined as the preparation of a thermodynamically stable solution of a substance, normally insoluble or very slightly soluble in a given solvent by the introduction of an additional component or components.

Process of solubilisation

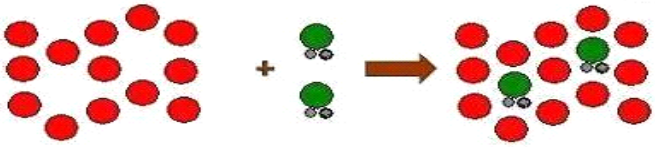
The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion [1].

Step 1: Holes opens in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3: The free solid molecule is integrated into the hole in the solvent



Need of solubilisation

*Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules

*Currently only 8% of new drugs have both high solubility and permeability

*More than one-third of the drugs listed in the U.S. P. fall into the poorly water-soluble or water-insoluble categories

*An average more than 40% of newly discovered drug candidates are poorly water-soluble.

Now the basic aim is to make that drug available at proper site of action within optimum dose so as Solubility & Permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like

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

1) PHYSICAL MODIFICATIONS

- Particle size reduction
- Modification of the crystal habit
- Drug dispersion in carriers
- Complexation
- Solubilization by surfactants

2) CHEMICAL MODIFICATIONS

- Use of prodrug

3) OTHER METHODS

- Cocrystalisation
- Cosolvency
- Hydrotrophy
- Solvent deposition
- Selective adsorption on insoluble carrier
- Functional polymer technology
- Porous microparticle technology

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●approaches Nanotechnology

SOLUBILISATION BY SURFACTANTS

Surfactants

Surfactants are agents that reduce the surface tension or interfacial tension. The reason for the reduction in the surface tension when surfactant molecules adsorb at the water surface is that the surfactant molecules replace some of the water molecules in the surface and the forces of attraction between surfactant and water molecules are less than those between two water molecules, hence the contraction force is reduced.

Surfactants are amphiphilic molecules composed of a hydrophilic or polar moiety known as *head* and a hydrophobic or nonpolar moiety known as *tail*. The surfactant head can be charged (anionic/cationic), dipolar (zwitterionic), or non-charged (non-ionic) and tail is usually a long chain hydrocarbon residue [2].

Surfactants classification

Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule.The four main groups of surfactants are defined as follows:

1**. Anionic surfactants,** where the hydrophilic group carries a negative charge, such as carboxyl, sulphonate or sulphate.

Examples of pharmaceutical importance include potassium laurate and sodium lauryl sulphate.

2**. Cationic surfactants**, where the hydrophilic group carries a positive charge (e.g., quaternaryammonium halides).

Examples of pharmaceutical importance include cetrimide, hexadecyltrimethyl ammonium bromides, as well as benzalkonium chloride.

3. **Ampholytic surfactants** (also called zwitterionic surfactants), where the molecule contains, both a negative and a positive charge, (e.g., the sulfobetaines).

Examples of pharmaceutical importance include N-Dodecyl-N,N-Dimethylbetaine.

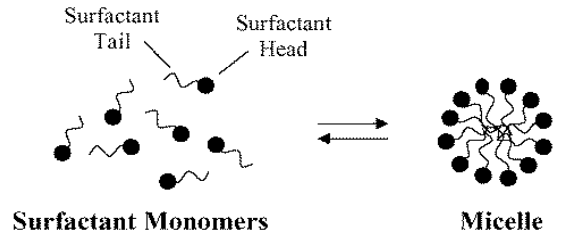
4. **Nonionic surfactants**, where the hydrophile carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene groups.

Examples of pharmaceutical importance include polyoxyethylatedglycolmonoethers (e.g., cetomacrogol), sorbitan esters (Spans) and polysorbates (Tweens) .

Micelles

One important property of surfactants is the formation of colloidal-sized clusters in solutions, known as micelles. When surfactants are added to a liquid at low concentrations, they tend to adsorbs at surface or interface. As additional surfactant is added, the interface becomes fully occupied, and the excess molecules are forced into the bulk of the liquid. At still higher concentrations, the molecules of surfactants in the bulk of liquid begin to form oriented colloidal size aggregates or micelles: this change in orientation occurs rather abruptly, and the concentration of surfactant at which it occurs is known as Critical Micellar Concentration (CMC).

In a micelle, the hydrophobic tails flock to the interior in order to minimize their contact with water, and the hydrophilic heads remain on the outer surface in order to maximize their contact with water [3]. Most micelles are spherical and contain between 60 and 100 surfactant molecules [2].



CMC of a surfactant can be determined by use of several physical properties, such as surface tension (γ), conductivity (κ), osmotic pressure (π), detergency, etc.

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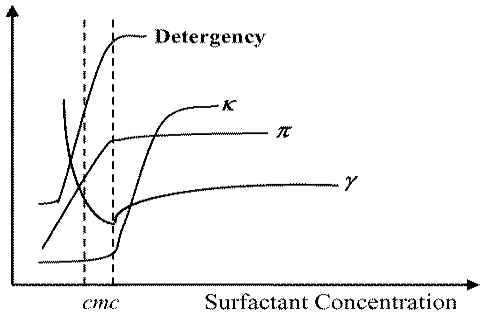
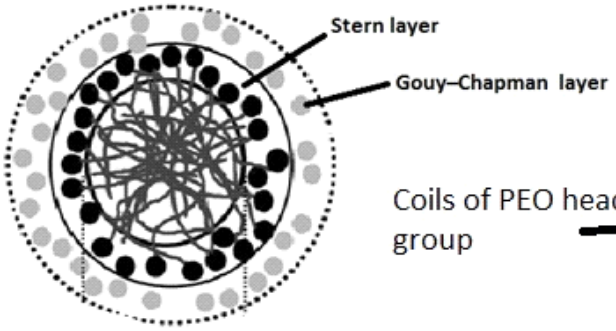
When these properties are plotted as a function of surfactant concentration, a sharp break can be observed at a particular point in the curves indicating the formation of micelles.



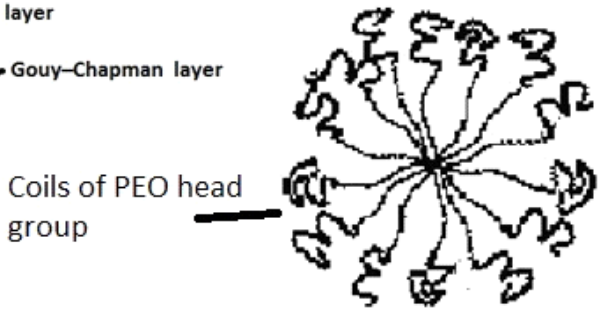
Structure of the micelles formed by *ionic* surfactants consists of:

Ahydrophobic *core* composed of the hydrocarbon chains of the surfactant molecule.
A Stern layer surrounding the core, which is a concentric shell of hydrophilic head groups with counterions.

A *Gouy–Chapman electrical double layer* surrounding the Stern layer, which is a diffuse layer containing the counterions required to neutralise the charge on the kinetic micelle.
The thickness of the double layer is dependent on the ionic strength of the solution and is greatly compressed in the presence of electrolyte.



Micelle of ionic surfactants



Micelle of non ionic surfactant

Structure of Micelles formed by *non-ionic* surfactants consists of:

- For the non-ionic surfactants having a polyethylene oxide (PEO) head group, the structure is essentially the same, except that the counter ions are not present in the outer region, but rather coils of hydrated polyethylene oxide chains
- Micelles formed in non-aqueous solution (reverse or inverted micelles) have a core composed of the hydrophilic groups surrounded by a shell of the hydrocarbon chains [2].

Micellar Solubilisation

Solubilisation can be defined as ‘‘the preparation of a thermodynamically stable isotropic solution of a substance normally insoluble or very slightly soluble in a given solvent by the introduction of an additional amphiphilic component or components.’’

If we plot the solubility of a poorly soluble compound as a function of the concentration of surfactant, usually what happens is that the solubility is very low until the surfactant concentration reaches the cmc. At surfactant concentrations above the cmc the solubility increases linearly with the concentration of surfactant, indicating that solubilisation is related to micellization.

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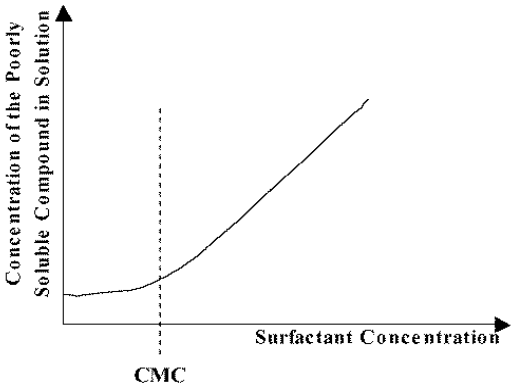

The location of a solubilised molecule in a micelle is determined primarily by the chemical structure of the solubilizate. Solubilisation can occur at a number of different sites in a micelle:

1. On the surface, at the micelle–solvent interface
2. Between the hydrophilic head groups
3. In the palisades layer, i.e., between the hydrophilic groups and the first few carbon atoms of the hydrophobic groups that comprises the outer regions of the micelle core
4. In the micelle inner core.

Selection of proper solubilisingagent :

Surfactants having HLB values higher than 15 are best solubilising agents. Final selection of the solubilising agent should be based on phase solubility studies (explained by Guttman et al).

●Guttman studies concerning the solubilisation of prednisolone, methy prednisolone, and fluorometholone with Triton WR-1339.

●They determined the equilibrium solubility of the steroids at 25 degree temperature as the function of surfactant concentration.

●The following plot show apparent solubility of steroids as the function of triton WR-1339.

●A similar plot could be constructed in which the solubility of a specific substance is determined as a function of surfactant concentration, and several surfactants of interest are included in the study.

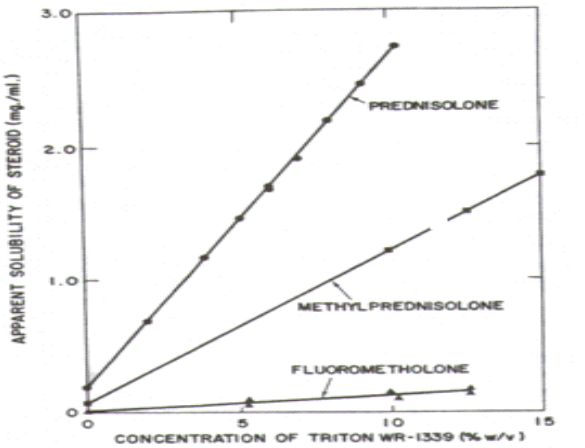

FIG. *The effect of varying concentrations of Triton WR-1339 in water on the solubility of some anti-inflammatory steroids. (From Guttman, D.E., Hamlin, W.E., Shell, J.W., and Wagner, J.G.: J. Pharm. Sci., 50:305, 1961.*

Factors effecting Micellar Solubilization

The capacity of surfactants in solubilizing drugs depends on

●chemical structure of the surfactant,
●chemical structure of the drug,
●temperature,
●pH,
●ionic strength, etc

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Non-ionic surfactants usually are better solubilising agents than ionic surfactants for hydrophobic drugs, because of their lower cmc values. Regarding the influence of structure of the drug, crystalline solids generally show less solubility in micelles than do liquids of similar structure. For polar drugs, the depth of penetration into the micelle varies with the structure of the drug.

In general, the amount of drug solubilised in a micellar system increases with the increase in temperature due to progressive dehydration of PEO chains. Temperature has a comparatively small effect on the micellar properties of ionic surfactants.

The ionic strength can influence significantly the solubilisation of a drug in micellar solutions, especially in case of ionic surfactants. The addition of small amounts of salts decreases the repulsion between the similarly charged ionic surfactant head groups, thereby decreasing the cmc and increasing the aggregation number and volume of the micelles. The increase in aggregation number favors the solubilisation of hydrophobic drugs in the inner core of the micelle. On the other hand, the decrease in mutual repulsion of the ionic head groups causes closer packing of the ionic surfactant molecules in the palisade layer decreasing the volume available for solubilisation of polar drugs.

The pH of micellar solutions can also show significant influence on the extent of solubilisation of drugs, since it may change the equilibrium between ionized and molecular forms of some drugs. In non ionic surfactant system, increasing pH leads to a decrease in the micellar uptake of organic acids because of increasing solute solubility in aqeous phase through increased ionisation. Regarding ionic surfactants, Enhanced solubility of a drug may be observed at pH values at which the drug is found mostly ionized, when surfactant and drug are oppositely charged. This behaviour is a consequence of the electrostatic interactions between the surfactant molecules and the charged drug that causes a decrease in the repulsive forces between the head groups of the surfactant molecules, contributing to the micellization process and thus decreasing the cmc value

Surfactants used in commercially available solubilizedoral formulations

●Polyoxyl 35 castor oil (Cremophor EL)

●Polyoxyl 40 hydrogenated castor oil (Cremophor RH40)

●Polyoxyl 60 hydrogenated castor oil (Cremophor RH60)

Surfactants used in commercially available solubilised Injectable formulations

●Polyoxyl 35 castor oil (Cremophor EL)

●Polyoxyl 60 hydrogenated castor oil (Cremophor RH60)

●Polysorbate 20 (Tween 20)

Surfactants used in commercially available solubilised Transdermal formulations

●Lecithin

●Sorbitanmonooleate (Span 20)

SOLUBILIZATION BY COSOLVENTS

Cosolvency and Cosolvents

A common and effective way by which to increase the solubility of a non-polar drug is through the use of cosolventsA common example of a class of formulation containing cosolvents is the elixir, which by definition is a sweetened, hydroalcoholic solution intended for oral use. Tinctures, which generally contain

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even higher amounts of alcohol, are another classic example of a liquid dosage form containing a cosolvent.

In many cases, cosolvency can increase the solubility of a non-polar drug up to several orders of magnitude above the aqueous solubility. This would be significant, for example, in a formulation problem where it might be necessary to increase the solubility of a drug 500-fold or more. The primary disadvantages of cosolvency include the potential for biological effects and the potential for drugs that have been solubilized using cosolvents to precipitate upon dilution with aqueous fluids [4].

When used as a method for increasing of solubulity a drug, the mechanism responsible for solubulity enhancement through cosolvency is by reducing the interfacial tension between the predominantly aqueous solution and hydrophobic solutes and reduces the contact angle between solid and liquid [5].Cosolvents have some degree of hydrogen bond donating and or hydrogen bond accepting ability as well as small hydrocarbon regions. The resulting solution will have physical properties that are intermediate to that of the pure organic solvent and water through the reduction of water–water interactions. This affords a system that is more favorable for nonpolar solutes.

Polarity Scales

An important concept for discussing solubilisation by cosolvents is polarity. The terms polar and non polar are frequently used to describe certain properties of solute and solvents. Unfortunately, there is no absolute measure of polarity but only several independent polarity scales. The most commonly used measures of polarity are dielectric constant, solubility parameter, and surface tension. One of the useful measures of polarity is organic solvent/water partition coefficient (PC). Conventionally octanol is used as the organic solvent. Based on the octanol/water partion coefficient, drugs that are less polar than either solvents component will be called nonpolar solutes. Those that are more polar than either solvent will be called polar solutes. Semipolar solutes are those that have polarities between the polarities of the solvent and cosolvent. Advantages of using octanol/ water partition coefficients is most drugs have very low solubilities in pure hydrocarbons and abundance of octanol / water partition coefficients in literature. The logarithm of octanol/ water partition coeffcient, will be used as reference polarity scale because of the great deal of reliable data available in literature. This operational definition emphasizes the fact that polarity is not an absolute property of molecule but rather a relative term which makes it easier to describe a system.

Mathematical Description for Cosolvency

A practical cosolvent model was developed by Yalkowsky and coworkers by assuming the mixed solvent system is a linear combination of the pure components. They found that this approach yields the log-linear relationship

$$\log S_{mix} = \log S_w + f_c \quad \text{----------Eq I}$$

Where the logarithm of the solubility of a non-polar solute S_{mix} will increase with the cosolvent fraction (fc), having a slope of , and an intercept of log Sw. On a linear scale, an exponential increase in solubility is observed with an increase in cosolvent composition. Following Fig. illustrates the linear and exponential solubilisation profiles.

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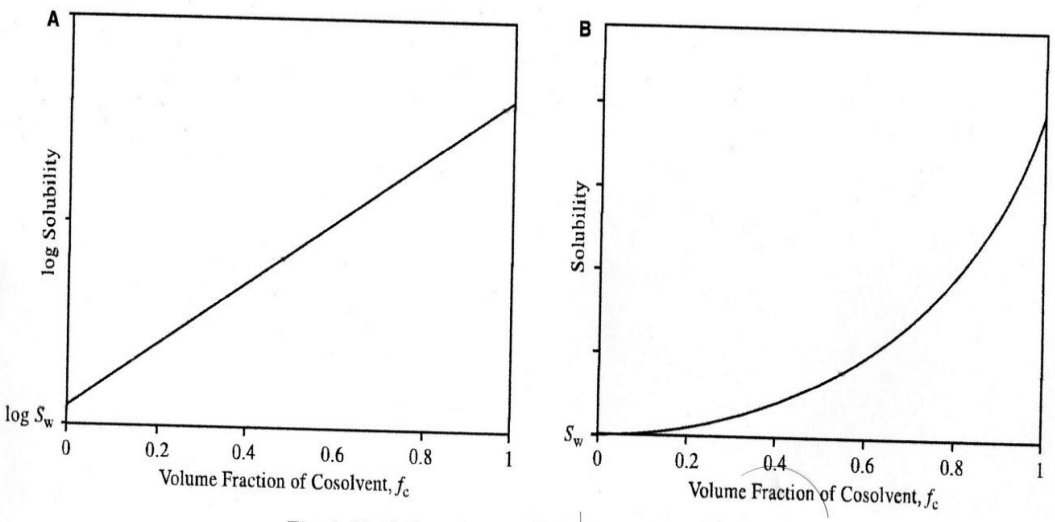

Fig. Typical cosolvent solubilization curves for a nonpolar drug. (A) Log-linear scale. (B) Linear scale.

The ability of a cosolvent to solubilize a given solute can be related to the properties of both the solute and cosolvent. The solubilization slope, for a given cosolvent system is dependent upon the polarity of the drug and the polarity of the cosolvent and can be related by,

S log Ko/w + t ----------**Eq II**

Where polarity of the drug is indicated by log Ko/w and the polarity and physical properties of the cosolvent are represented through the parameters S and t.

Dependence of Solubilization on Solute Properties

For non-polar solutes, or those solutes that are more non-polar than the cosolvent of choice, solubilisation generally follows the log-linear model of Eq I. The degree of solubilization is directly related to the polarity of the solute. From Eq.II it has been shown that the solubilization slope can be related directly to the logarithm of the octanol–water partition coefficient (logKo/w). Once again the trend maintains that as log Ko/w increases, solubilization is increased for a given cosolvent system (i.e., s and t are constant). For the most non-polar compounds (largest logKo/ws) solubilisation approaches several orders of magnitude.

For solutes that are semipolar and polar (polarities that are between water and a given cosolvent) little gain in solubility, if any, can be expected with the addition of an organic cosolvent. Semipolar solutes will have a maximal solubility at some mixed composition at a polarity that matches the solute. After a maximum solubility the slope becomes negative, and any additional cosolvent will decrease the solubility of the solute. The overall gain in solubility for semipolar solutes is generally less than a factor of five, which is significantly less than that of non-polar solutes.

The solubility of polar solutes decreases with the addition of an organic cosolvent to water. Although it is obvious that cosolvents would not be used for solubilizing polar solutes, it is important to understand that for formulations

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that have other components or excipients, the use of a cosolvent for a non-polar drug may cause solubility problems for polar excipients.

Dependence of Solubilization on Cosolvent Properties

The reduction of intermolecular hydrogen bonding interactions of water when an organic cosolvent is mixed with water creates a solvent system that favors the dissolution of a non-polar solute. The more nonpolar the cosolvent, the more non-polar the cosolvent/water system will become and the greater the solublizationof a nonpolar drug. In addition to polarity considerations, it is also useful to take into account hydrogen bond donating and accepting capabilities when evaluating cosolvent systems.

Multiple Cosolvents

The use of multiple cosolvents can be a valuable method for solubilizing a poorly water soluble drug when a dosage form necessitates limits on the amount and type of cosolvent that can be utilized. The effects of multiple cosolvents on solubility can be reasonably approximated by simply expanding Eq.I to include a liner addition of cosolvents, i.e.,

$$\log S_{mix} = \log S_w + {}_1fc_1 + {}_2fc_2 + {}_3fc_3 + \_ \_ \_$$

Where, the subscripts 1, 2, and 3 represent the slope and fraction of cosolvents 1, 2, 3, etc. The above Eq. adequately represented the solubility of a solute in mixed solvent systems. The above Eq. assumes that each cosolvent interacts independently. Of course this is not always the case. In addition, the use of one cosolvent can be used to increase the solubility of a partially miscible cosolvent in water.

Dilution of Formulations Containing Cosolvents as Solubilizers

The dilution of a cosolvent–solubilized preparation with an aqueous medium, such as blood or intravenous (IV) infusion fluids, can result in the opposite phenomenon, an exponential decrease in solubility. The effect is illustrated graphically in below Fig. The straight lines A and B represent the solubility of the drug as a function of cosolvent concentration in two different cosolvent–water systems. The curved lines represent the concentrations of drug at various degrees of dilution. Precipitation would be expected when one of the drug concentration curves crosses a solubility curve. For three concentrations of drug in system A, it can be expected that concentration III will precipitate when it is diluted to the point where approximately 30% cosolvent is present. Formulations I and II, which contain smaller initial concentrations of drug, do not cross the solubility curve Aand should be stable upon dilution. Alternatively, formulation of drug in a cosolvent or solvent mixture that produces a larger slope of the solubility curve (B) may also minimize or reduce precipitation upon dilution. In this case, even concentration III will not precipitate upon dilution. Thus, a careful selection of cosolvent and drug concentration can prevent such occurrences upon IV injection or dilution with aqueous fluids.

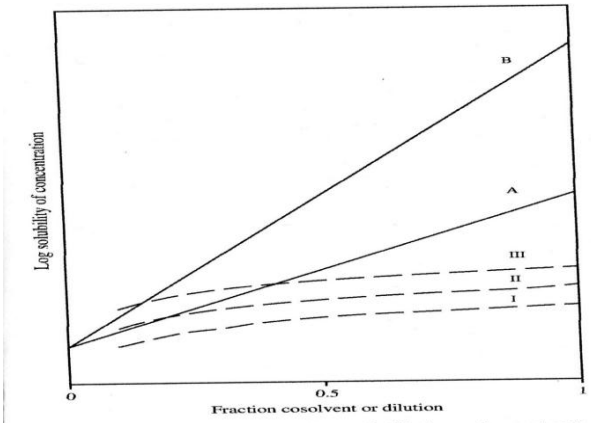

Fig. Illustration of the effect of dilution of cosolvent-solubilized formulations with an aqueous medium.

EXAMPLES OF THE USE OF COSOLVENTS FOR THE FORMULATION OF LIQUID DOSAGE FORMS

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Oral Dosage Forms

Ethanol has been used traditionally as a cosolvent for oral solutions. It has been incorporated with sucrose in elixir formulations, the alcoholic content of which may vary from 3–78%. Its use is often undesirable, however, in oral preparations intended for pediatric patients or other patients who cannot tolerate the effects of ethanol. Propylene glycol has been suggested as an appropriate substitute for ethanol in oral solutions. Liquid PEGs have been used as vehicles for soft gelatin capsules as well as pediatric elixir formulations.

Parenteral Dosage Forms

The use of cosolvents in small-volume parenteral preparations is often critical due to the limited volume of solution that can be administered by a single injection.The cosolvents most often used include ethanol, propylene glycol, glycerin, PEG 400, and, sometimes, dimethylacetamide. Irritation and hemolysis are primary considerations when choosing a cosolvent for parenteral preparations. Concentration and route of administration are important factors that determine the incidence and severity of local reactions.

Ophthalmic and Otic Dosage Forms

Ophthalmic formulations sometimes contain cosolvents, such as propylene glycol or PEG 300, as part of the vehicle. The greatest limitation to the use of cosolvents in ophthalmic preparations is their irritation potential. Osmotic effects of cosolvents are also important, and the strong osmotic effect of glycerin combined with its poor solubilising power limit its usefulness in ophthalmic preparations. Propylene glycol, PEG, glycerin, and isopropyl alcohol have been used in otic formulations.

Topical Dosage Forms

Liquid preparations intended for dermal application contain the largest variety of cosolvents. They most commonly include ethanol, isopropanol, propylene glycol, glycerin, and PEG 400. Irritation and sensitization are important considerations in choosing a cosolvent for dermal use. Preparations that are applied topically to the mouth and throat have contained glycerin, ethanol, propylene glycol

SOLUBILISATION BY COMPLEXATION

Complexation

Defination and Concepts

Complexation is the association between two or more molecules to form a nonbonded entity withwell-defined stoichiometry. It is reversible association of m molecules of a substrate **S** with n molecules of a ligand **L** to form a new species $\mathbf{S_mL_n}$. [mS + nL→Sm Ln]

The mathematical description for the equilibrium constant of a 1 : 1 complex, $K_{1:1}$, is defined by

$K_{1:1} = [SL]/[S][L]$

Where S is the concentration of the free solute, L is the concentration of the free ligand, and [SL] is the concentration of the solute/ligand complex. The equilibrium constant is also commonly referred to as the stability constant or the complexation constant.

If it takes two ligand molecules to complex with a solute molecule the complexation constant is defined by

$K_{1:2} = [SL]_2/[S][L]^2$

The total solubility of the solute, ST, for a solute that forms a 1 : 1 complex is

$S_T = Sw + [SL]$

Where, Sw is the intrinsic solubility of the solute in water.

Methods for studying complexation

There are numerous methods for studying complexation. Any methodology which can

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relate the changes in one or more properties of the system which are caused by intermolecular interaction may be utilized. Methods which have been used include calorimetry, refractive index, optical rotary dispersion, NMR, spectrophotometry, kinetics and solubility techniques.

Complex System Types and Phase diagram Interpretation

If the ligand interacts with the substrate to form a complex which is soluble in the solvent, the total concentration of substrate will vary as a function of quantity of ligand added. The data are normally presented as phase diagrams where the total substrate St in the solution phase is plotted as a function of the total added ligand Lt. Several different phase diagrams may be obtained from systems which form complexes. The systems are divided into two major classes: those producing either type A or type B diagrams. The type A phase diagram is obtained for systems in which the complex formed is soluble and does not form a precipitate regardless of the amount of ligand added. The type B diagram is obtained for those systems in which the complex actually precipitates from the solutions when the concentration of ligand exceeds some critical value.

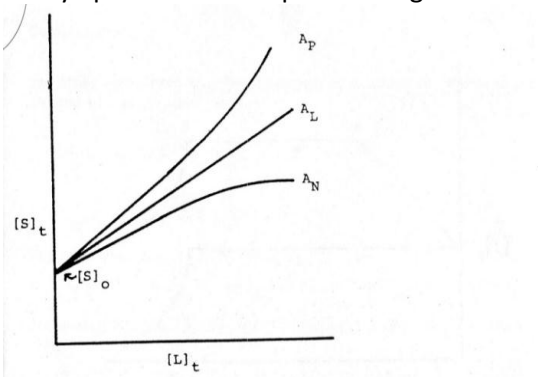

FIGURE Schematic representation of the A-type phase diagrams

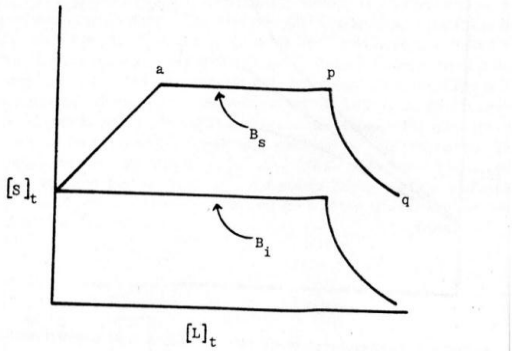

FIGURE Schematic representation of the B-type phase diagrams

Both type A and B systems can be further subdivided according to the detailed nature of the phase diagram obtained. The type A system may be one which exhibits a linear relationship between St and Lt. This is shown in below Fig. as A_L and is obtained when the complex has a first-order dependence on [L]t. The Ap diagram, which shows a positive deviation from linearity, is obtained when the complexes formed contain more than one molecule of ligand. As the ligand concentration increases the contribution of the higher order complexes increases. The remaining A-type diagram is that exhibiting a negative deviation which represents a decreasing dependence on ligand added at higher ligand concentrations.

The B-type diagram results when the system develops a third phase consisting of the complex. If the complex exhibits some solubility, the diagram shows an initial rise in [S]t and the diagram is said to be a Bs diagram. If the complex is insignificantly soluble relative to the inherent solubility of the substrate, then the system gives rise to the Bi diagram.

The two types of complexation that are most useful for increasing the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of another molecule (or group of molecules).

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Self-Association and Stacking Complexation

Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of the water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moities. This aggregation is favored by large planar nonpolar regions in the molecule. Just as micelles can be pure or mixed, stacked complexes can be homogenous or mixed. The former is known as self-association and the latter as complexation. Some examples of substances that interact in an aqueous media by stacking are purine, theobromine, caffeine, benzoic acid, salicylic acid, naphthalene, anthracene, pyrene, methylene blue etc.

Inclusion Complexes

An inclusion complex is produced by the inclusion of a nonpolar molecule or the nonpolar region of a molecule (guest) into the nonpolar cavity of another molecule or group of molecules (host). When the guest molecule enters the host molecule the contact between water and the nonpolar regions of both is reduced. Thus, inclusion phenomena are the result of the same driving force that produces micellization, self-association, and stacking; namely the squeezing out from water of nonpolar moities. The major structural requirement for inclusion complexation is a snug fit of the guest into the host cavity. The host cavity must be large enough to accommodate the guest and small enough to eliminate water so that the total contact between water and the nonpolar regions of the host and the guest is reduced.

The most commonly used host molecules are the cyclodextrins. These cyclic oligomers of glucose are relatively soluble in water and have cavities large enough to accept nonpolar portions of common drug molecules. The naturally occurring cyclodextrins contain 6, 7, and 8 glucopyranose units and are termed, and respectively. Modified cyclodextrins have one or more of the hydroxy groups of one or more of the glucopyranose units modified. Some of the more common modifications are with alkyl or hydroxyalky groups, or with anionic or cationic functionalities. Many of these modified cyclodextrins are more soluble than their naturally occurring precursors. The size of the cavity in the cyclodextrin is the major factor in determining which guest solutes will be most acceptable for complexation. In general, alkyl groups will fit well into the cavity of the -cyclodextrins. The -cyclodextrins are most well suited for accepting single aromatic rings, and the -cyclodextrins have large enough cavities to accommodate larger hydrocarbons such as pyrene. The degree to which a solute molecule will be solubilised by a cyclodextrinmolecule will depend on several properties. First the solute molecule must have a significant nonpolar portion in order to be squeezed out of the water and into the cyclodextrin cavity. Since the interior dimensions of a given cyclodextrin are fixed, a significant part of the molecule (or whole molecule) must then fit inside the cyclodextrin. Once presented to the interior cavity, it will be the fit, as well as the intermolecular interactions between the two molecules that will determine the strength of the complex.

Approaches for Making Inclusion Complexes:

Physical blending method: A solid physical mixture of drug and CDs are prepared simply by mechanical trituration. In laboratory scale CDs 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.

Kneading method: This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve if required.

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Co-precipitation technique: This method involves the co-precipitation of drug and CDs in a complex. In this method, required amount of drug is added to the solution of CDs. The system is kept under magnetic agitation with controlled process parameters and the content is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

Solution/solvent evaporation method: This method involves dissolving of the drug and CDs separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and finally evaporating the solvent under vacuum to obtain solid powdered inclusion compound. Generally, the aqueous solution of CDs is simply added to the alcoholic solution of drugs. The resulting mixture is stirred for 24 hours and evaporated under vacuum at 45 °C. The dried mass was pulverized and passed through a 60-mesh sieve. This method is quite simple and economic both on laboratory and large scale production and is considered alternative to the spray drying technique.

Neutralization precipitation method: This method is based on the precipitation of inclusion compounds by neutralization technique and consists of dissolving the drug in alkaline solutions like sodium/ammonium hydroxide and mixing with an aqueous solution of CDs. The resultant clear solution is then neutralized under agitation using HCl solution till reaching the equivalence point. A white precipitate is being formed at this moment, corresponding to the formation of the inclusion compound. This precipitate is filtered and dried.

Milling/Co-grinding technique: A solid binary inclusion compounds can be prepared by grinding and milling of the drug and CDs with the help of mechanical devices. Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Alternatively, the ball milling process can also be utilized for preparation of the drug-CD binary system. The ball mill containing balls of varied size is operated at a specified speed for a predetermined time, and then it is unloaded, sieved through a 60-mesh sieve. This technique is superior to other approaches from economic as well as environmental stand point in that unlike similar methods it does not require any toxic organic solvents. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impact effect on powder blend.

Atomization/Spray drying method: Spray-drying is a common technique used in pharmaceuticals to produce a dry powder from a liquid phase. Another application is its use as a preservation method, increasing the storage stability due to the water elimination.This method represents one of the most employed methods to produce the inclusion complex starting from a solution. The mixture pass to a fast elimination system propitiate solvent and shows a high efficiency in forming complex. Besides, the product obtained by this method yield the particles in the controlled manner which in turn improves the dissolution rate of drug in complex form.

Lyophilization/ Freeze drying technique: In order to get a porous, amorphous powder with high degree of interaction between drug & CD, lyophilization/ freeze drying technique is considered as a suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure. Thermolabile

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substances can be successfully made into complex form by this method. The limitations of this technique are long time process and yield poor flowing powdered product. Lyophilization/ freeze drying technique are considered as an alternative to solvent evaporation and involve molecular mixing of drug and carrier in a common solvent.

Microwave irradiation method: This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40°C for 48 hrs.

Supercritical antisolvent technique: In this technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. It is also non-toxic, nonflammable, inexpensive and is much easier to remove from the polymeric materials when the process is complete, even through small amount of carbon dioxide remains trapped inside the polymer, it poses no danger to the consumer. Supercritical particle generation processes are new and efficient route for improving bioavailability of pharmaceutically active compounds. In addition, supercritical fluid processes were recently proposed as a new alternative method for the preparation of drug cyclodextrin complexes. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improves transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of drug with CD in solid state. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising results, but it requires a quite high initial cost.

In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.

CONCLUSION

A lot of research has been carried out in this area and for better clinical efficiency, some improvements in solubility and dissolution rate has to be made generally. The basic approaches followed by all the currently available technologies engaged in the solubility and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy.

A study of solubility also yields information about the structure and inter-molecular forces of drugs. Use of solubility characteristics in bioavailability, pharmaceutical actions and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Dissolution enhancement of poorly water soluble drugs constitute an innovative approach, which overcome the problems of solubility and dissolution rate limiting step and provide a quick onset of action.

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