
A Review of the Solubility Enhancement by Using a Co-Solvency Method

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Abstract

A series of equations are developed to study the effects of co-solvents on a solution's solubility in mixed solutions where a finite solubility is shown in the solution. The equations differ according to the scale used for the concentrations of the solute (and co-solvent). In the formulation of liquid pharmaceutical formulations, a poorly water-soluble drug's Solubilization has an important role. There are a variety of approaches used to affect solubility. A water-miscible cosolvent called co-solvency which is one of the most efficient and readily available methods. A simplified view of cosolvent selection includes the analysis of observable properties of various cosolvent systems and the application of empirical evidence. Solubility is a chemical property referring to a given substance's ability, the solute, to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution, and cosolvent is responsible for it. Cosolvents have some degree of hydrogen bond donating and or hydrogen bond accepting ability and 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 interaction.

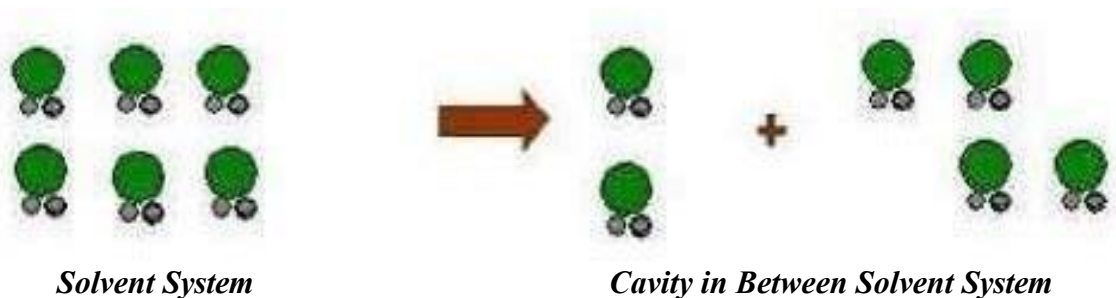
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INTRODUCTION

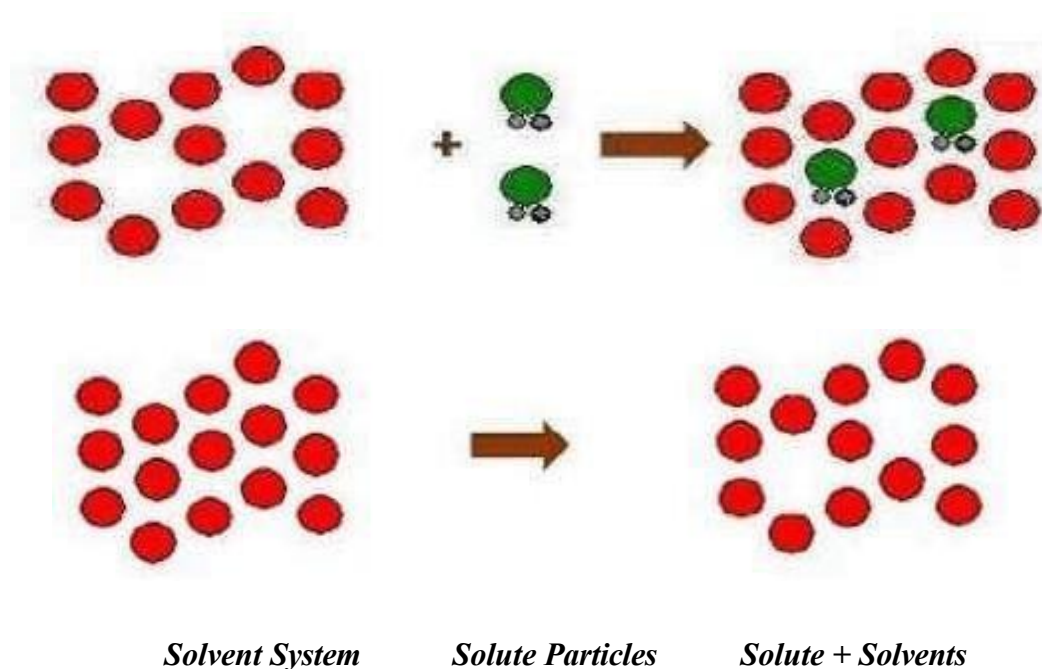
Solubility

The solubility of drugs is important for a poorly soluble drug. Solubility is defined as the 1gm of solute dissolved in several milliliters solvents at a constant temperature [1, 2]. Process of solubility are mentioning the following steps,

1. In the Solubilization process, break the solute-solute inter molecular bonds[3].
2. Like the same, the 1st step breaks the solvent-solvent intermolecular bonds.
3. After the breaking of solvent intermolecular bonds, they form a cavity in between to the solvents.



4. Then transfer the solute into the cavity of the solvent phase



5. After the good mixing solute and solvent phase, they form a great intermolecular bonding [3].

Cosolvents are secondary solvents that improve the solubility of the solution's main solvent. Most cosolvents themselves are organic solvents, but the solubility of the main solvent can be improved by a small amount. In the formulation of emulsifiable concentrates and oils, it is commonly used to increase the concentration of active ingredients in emulsifiable concentrate. And oils [4].

In particular, such cosolvents must be used in the processing of high concentrations of emulsifiable concentrates and ultra-low-volume oils. Cosolvents are substances applied in small quantities to the primary solvent to increase the solubility of poorly soluble material. Its use is most prevalent in pharmaceutical, food, chemical industries, and biological research.

A popular and efficient way of increasing the solubility of a non-polar drug is by using cosolvents. Elixir, which by nature is a sweetened, hydroalcoholic solution, intended for oral use, is a common example of a class of formulations containing cosolvents [4, 5].

Mechanism of Cosolvents

This process is known as co-solvency and the solvents used to increase solubility are

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.

Steps for solubility enhanced the drug by the using cosolvents are as given below:

Step 1st: Add a solvent in cosolvents for the enhancement of the drug which having the poor solubility in the solvent.

Step 2nd: After the addition of the cosolvent in the solvent, they interact with solvent and reducing the interfacial tension between the aqueous phase and hydrophobic phase.

Step 3rd: After the reduction of interfacial tension, they increase the solubility of poorly soluble drugs in solvents [6].

Surfactant/Cosolvent Contaminant

Analysis The ability to ensure that the surfactant/cosolvent does what it was intended to do is a key factor leading to the successful application of this technology. In some situations (e.g., Type III or ultralow interfacial stress floods), minor variations for concentrations or ratios of electrolytes could have profound effects on technology output because the chemical

system could be forced through unfavorable phase behavior.

The movement of the fluids injected should be tracked to ensure that they flow through the target areas.

Furthermore, cost and time savings could be achieved through tracking concentrations of contaminants of concern (COCs) in recovered fluids and assessing when on-site remediation targets were met as a consequence, controlling both the concentration of surfactants and pollutants in a surfactant/cosolvent flood is very much vital.

The duration and location of the monitoring depend on the conditions at the site and the specific conditions at the site [2, 7].

METHODS OF SOLUBILITY STUDIES

Experimental Method

Distilled water and cosolvents (PEG 400, PG, and glycerin) are mixed volumetrically to form mixtures containing 0,10,20,30,40,50,60,70,80,90, and 100% various cosolvents in screw cap amber color bottles. Excess product is added directly to the pure and mixed solvents and cosolvent.

To reach equilibrium, these bottles are shaken with a shaker at 50 rpm and room temperature (25 ± 1 ° C) for 24 h. Aliquots are collected, filtered (0.22 μ m pore size) and diluted correctly after 24 h of equilibrium.

Use of the UV-VIS spectrophotometer to analyze these samples and at standard wavelength, solubility is calculated [5].

Mathematical Method

Specific solution models for mathematical representation of solubility data in binary solvents have been published in the pharmaceutical and chemical literature [5].

The solubility of a non-electrolyte solute in any solvent was expressed by the general equation.

$$\text{LogX} = -\Delta H_f / 2.303RT \cdot T_m(T_m - T) - \text{Log}y$$

where, **LogX** = solutes mole fraction solubility ΔH_f = molar heat of fusion

R, T = constant

Y = activity coefficient

Table 1: Poorly Soluble Drugs Having Cosolvents Systems for Solubility Enhancement [6-26]

Dosage form	Drug	Cosolvent	Author of publication
Oral	risperidone	Transcutol+water	10
Oral	melocoxib	PEG400 +water	12
Oral	rofecoxib	PEG400+water	12
Oral	celecoxib	Ethanol+water	12
Oral	Etoricoxib	PEG400 +water	8
Oral	valdecoxib	PEG400 +water	13
Oral	valdecoxib	PEG600 +water	13
Oral	Progesteron	Propyleneglycol+ water	14
Oral	Progesteron	PEG400 +water	14
Parenteral	Tenoxicam	Dimethylsulfoxide (DMSO)/polyethoxylate d castor oil/ethanol	15
Oral	celecoxib	Ethanol+PEG400+water	16
Oral	Ibrutinib	2-(2-ethoxyethoxy)ethanol (Carbitol) + water	17
Oral+	N-methylpyrrolidone(NMP)	ethanol+propylene glycol	22
Oral	N-(4-chlorophenyl)-2-(pyridin-4-ylcarbonyl)-hydrazinecarbothioamide (isoniazid analogue)	diethyleneglycolmonoethyl ether (Transcutol) + water	23
Oral	carbamazepine	polyethyleneglycol(PEG- 300) + water	19
Parenteral	Meloxicam	PropyleneGlycol+Water	20
Oral	Sinapicacid	DMSO+water	26

oral+ parenteral	Satranidazole	Dioxane-Water	21
Oral	Amprenavir	PEG400,PG	21
Oral	Bexarotene	PEG400	21
Oral	Clofazimine	PG	21
Oral	Ciclosporin	Ethanol, glycerol, PG	21
Oral	Dronabiol	Ethanol	21
Oral	Lopinavirandritonavir	PG	21
Oral	Lopinavirandritonavir	Ethanol, glycerin, PG	21
Oral	Menatetrenone	Glycerin	21
Oral	Paricalcitol	Ethanol	21
Oral	Ritonavir	Ethanol,PG	21
oral+ parenteral	Satranidazole	Dioxane-Water	25

Criteria for Selection of Cosolvents

1. Biocompatibility
2. It must be non-toxic, non-irritating.
3. It should be able to solubilize the drug in the given solvent.
4. It should be able to cross the membrane.
5. It does not have potential systemic effects.

Advantages of the Cosolvent System

- In solubility enhancement of the drug, the cosolvent method is simple.
- They are very useful in the solubility enhancement.

Disadvantages of the Cosolvent System

1. If some time use in the solvent system cosolvent system they are produced some time toxicity after the

administration.

2. The solvent, cosolvent, and drug may produce precipitation.
3. Their iv products are form precipitation and the precipitation is insoluble and then they produce irritation at the injection site.

Examples of Cosolvents

The most commonly used cosolvents for solubility enhancement purposes are ethanol, propylene glycol, glycerine, glycofural, and polyethylene glycols.

CONCLUSION

A simplified view of cosolvent selection includes the analysis of observable properties of various cosolvent systems and the application of empirical evidence.

Solubility enhancement by the cosolvent system gives new approaches for designing and ordering new dosage forms of poor aq. soluble drugs. It also helps in improving the Bioavailability of drugs as well as the Stability of drugs.

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