WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 5, 584-600. Review Article ISSN 2277– 7105

CO-SOLVENCY AND ANTI-SOLVENT METHOD FOR THE SOLUBILITY ENHANCEMENT: AN OVERVIEW

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Article Received on
29 February. 2020,
Revised on 19 March 2020,
Accepted on 09 April 2020
DOI: 10.20959/wjpr20205-17317

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ABSTRACT

Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be the show. There is the various factor are responsible for poor solubility of a drug in systemic circulation. Hence various techniques are used for the improvement of the solubility of poorly water-soluble drug includes varies techniques in which antisolvent and cosolvency method are described below. Cosolvency and antisolvent crystallization technique are being used to prepare nanoparticles or micro particles for poorly water soluble drugs at research scale. This method has an ability to change the solid-state properties of pharmaceutical substances including the modification of crystal formation and particle size distributions. Due to this technique to achieve desirable systemic circulation.

KEYWORDS: Solubility, Co-solvency, Anti-solvent.

INTRODUCTION

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in a qualitative term, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular

dispersion. A saturated solution is one in which the solute is n equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under the specific condition of temperature, pH, and pressure. The drug solubility in saturated solution in a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate.[1]

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[2]

Process of solubilization

The process of solubilization contains three steps. The first step involves the separation of the molecules of the solvent to provide space in the solvent for the solute, the second step involves the breaking of intermolecular or inter-ionic bonds in the solute, third & final step involves the interaction between the solvent and the solute molecule or ion. [3]

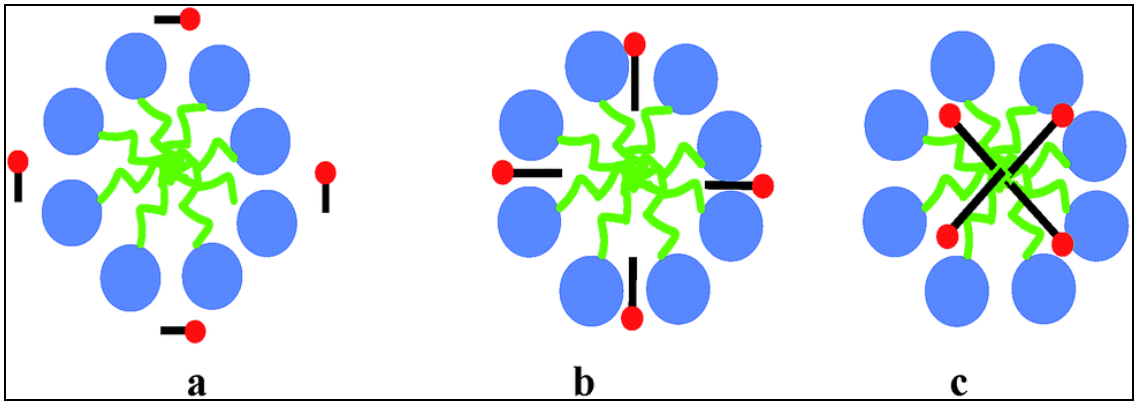


Fig. 1: Process of solubilisation.

Step a- Solid molecules and solvent

Step b- Between the solvent-solid molecules are slowly pass

Step c –Solid molecules are totally mixed in solvent

According to the BCS (Biopharmaceutical classification system), all drugs have been divided into four classes:

Table 1: USP & BP Solubility criteria.

Descriptive term	Part of solvent required per part of solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>10000

Need of Solubility[4]

Drug absorption from the GI tract can be limited by a variety of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water-soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increase the bioavailability for BCS class II & IV drugs.[4] BCS Classification System with examples of different drug is discussed in Table-2.

Table 2: Biopharmaceutical Classification System.[5]

BCS Class I	High Solubility High Permeability	B-blockers propranolol, Metoprolol
BCS Class II	Low Solubility High Permeability	NSAID's Ketoprofen, Antiepileptic Carbamazepine
BCS Class III	High Solubility Low Permeability	B blockers Atenolol, H2 antagonist Ranitidine
BCS Class IV	Low Solubility Low Permeability	Diuretics Hydrochlorothiazide, furosemide

Importance of solubility

1. Solubility also plays a major role for other dosage forms like parenteral formulations as well as solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response. [6, 7]
2. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.
3. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.[8]
4. More of the drug (>40%) belonging to BCS class II (Low solubility And High permeability).
5. As for BCS class II drug rate limiting step is drug release from the dosage form and solubility in the gastric fluid, so increasing the solubility in term increases the bioavailability for BCS class II drug. [9]

Factor Affecting the Solubility

1. Nature of solute and solvent

The nature of solute and solvent depends on the concentration of solute in the specific quantity of solvent at the specific temperature. Example: At room temperature in 100 gm of water, only 1gm of lead (II) chloride can be dissolved while 200 grams of zinc chloride can be dissolved. [10]

2. Particle size

Particle size affects on solubility. As article size decreases, the surface area to volume ratio increases. As the surface area of particle increases, it causes greater interaction with solvent.[11]

3. Molecular size

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

4. Temperature

Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature.[12]

5. Pressure

For solids and liquid solutes, solubility not affected by a change in pressure but for gaseous solutes, solubility increases as pressure increases and decrease as pressure decrease.

Techniques for Solubility Enhancement[13]

Various techniques have been used in the attempt to improve solubility and dissolution rates of poorly water soluble drugs such as pH Adjustment, Particle Size Reduction, Cosolvency, Antisolvent, Solid Dispersion, Supercritical Fluid (SCF) Process, Hydrotropy, Sonocrystallization, Complexation, Cryogenic techniques etc.

In these techniques, carrier plays an important role in improving solubility and dissolution rate. Polymers, super disintegrants, surfactants are extensively studied in recent years for dissolution enhancement in drugs. This part of this review discusses technological overview and effect of polymers, super disintegrants and surfactants on dissolution enhancement of drugs while describes the role and applications of cyclodextrins, carbohydrates, hydrotropes, dendrimers, acids and miscellaneous carriers in enhancing dissolution of drugs.[12]

CO-SOLVENCY

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as co-solvency and the solvent used in combination are known as co-solvent. Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by an addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensure water solubility.[14] Cosolvent system can increase the water solubility of a drug significantly. But the choices of biocompatible solvent are limited, such as to glycerine, propylene glycol, dimethylsulfoxide, ethanol and N,N dimethylformamide etc.

Advantages[15]

1. Simple and rapid to formulate and produce.
2. Removing the need for mixing solvent before administration.
3. No need for expensive pharmaceutical technology for a formulation of a dosage form.

Disadvantages

1. As with all excipients, the toxicity and tolerability related with the level of solvent administered have to be considered.
2. As with all solubilized forms, the chemical stability of the insoluble drug is worse than in crystalline state.
3. Toxic effects on renal, central, nervous, hepatic, and CVS system as well as cell lysis and local tissue irritation.

Methods of predicting solubility in Co-solvents

Apart from experimental determinations of solute solubility in water co-solvent mixtures, there are many mathematical models describing the solute solubility in mixed solvents.[16,17] By considering the chemical theory, some of them are theoretical and some others are semi-theoretical or empirical. Theoretical models provide some evidence for better understanding of solubility behavior for drugs in mixed solvents, while semi-theoretical or empirical approaches are very useful models for correlating experimental solubilities to the independent variables such as volume fraction of the co-solvent.

Theoretical methods

The progression of approaches for predicting solubility in co-solvents. One of the first advances beyond empirical trial-and-error was the use of the dielectric constant (∈) to optimize co-solvent systems. The dielectric constant is a dimensionless parameter because it is the ratio of the capacitance of a condenser filled with the material of interest versus a vacuum.[18] Co-solvents that are more polar have larger dielectric constants. Much work has been done around the use of the dielectric constant for optimizing pharmaceutical co-solvent systems.[19-22] Simply speaking, the optimal co-solvent system should have a dielectric constant analogous to the solute being dissolved. In general, it has been recognized that the ∈ of a mixture of two or more solvents is directly proportional to the fraction of the individual solvents.[23] In this method, to calculate ∈ of a solvent mixture, one needs to know the ∈ of

the pure solvents. The ∈ of acetate is mixture is calculated based on a simplified Onsager-Kirkwood equation shown below:

D.C. = ∑ *(fraction of solvent A* × *D.C. of solvent A)*
+(fraction of solvent B × *D.C. of solvent B)*

The co-solvents in binary and ternary systems. They determined that the solubility of poorly water-soluble drugs was approximately described by the log-linear solubility equation as applied to multiple solvent systems.[24-26]

$$\log \frac{S_m}{S_w} = \sum_{i=1}^{n} (\sigma_i f_i)$$

The drug solubility in co-solvent systems where the drug is semipolar and polar. Typically, semipolar drugs have parabolic log solubility curves. The peak in these plots is where the best mixture of co-solvent and water is for greatest solubilization of the Compound. Since the drug is semipolar, further addition of the more nonpolar co-solvent results in a decrease in the drug's solubility. a semiempirical quadratic equation for application to semipolar drugs.[25] For polar drugs, the addition of a less polar solvent tends to decrease the solubility of that compound. Therefore, their solubility curves show decreasing solubility with increasing co-solvent content. The solubility relationships of polar, semipolar, and nonpolar drugs in mixed co-solvent systems. As expected, the nonpolar compound showed a log-linear increase in solubility with increasing co-solvent content. The semipolar compound showed parabolic log solubility curves. The polar compound showed a log-linear decrease in solubility with an addition of co-solvent.[27]

Empirical Method

The theory behind solubilization, more empirical methods of characterizing the solubility of co-solvent systems can be utilized with the aid of statistical experimental design. Advantages to this approach are that one can add additional excipients, for example, surfactants, without having to consider assumptions used in the derivation of equations and their validity to the systems studied. Another advantage is that typically these studies provide very accurate predictions of solubilities within the design space studied. This allows determination of optimal mixtures of excipients for maximum solubility. Disadvantages to this approach are

that it gives no scientific insight as to the mechanism of solubilization. Therefore, the scientist must still interpret the meaning behind data from such studies.

Although factorial designs are very useful for studying multiple variables at various levels, typically they will not be applicable to co-solvent solubility studies because of the constraint that all of the components must add to 100%. For this reason, mixtures of experimental designs are typically used.[28-32]

Procedure for co-solvent method

In co-solvent evaporation technique 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, rotary evaporator was used for this process efficiently separates the solvents under controlled temperature and pressure.[33]

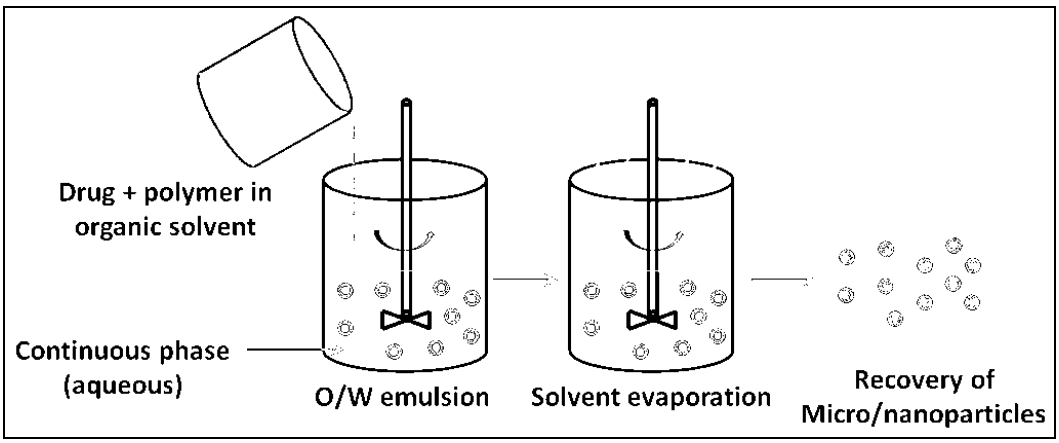


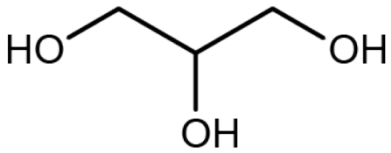
Fig. 2: Solvent evaporation process.

Commonly used Co-solvent

Co-solvents are employed to increase the solubility of the therapeutic agent within the formulation. The main co-solvents that are used in the formulation of oral solutions are detailed below.

1. Glycerol[34]

Glycerol (also termed glycerin) is an odorless, sweet liquid that is miscible with water and whose co-solvency properties are due to the presence of three hydroxyl groups (termed a triol). It has similar co-solvency properties to ethanol.



Example: Glycerol used to form the polymer gel.[49] Rapamycin.[50]

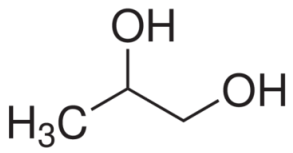
2. Alcohol USP (CH_3CH_2OH)[35]

Alcohol USP contains between 94.9 and 96.0% v/v ethyl alcohol (ethanol) and is commonly used as a co-solvent, both as a single co-solvent and with other co-solvents, e.g. glycerol. The known pharmacological and toxicological effects of this co-solvent have compromised the use of alcohol in pharmaceutical preparations. As a result, there are both labelling requirements for preparations that contain alcohol and upper limits the concentration of alcohol that may be used in formulations.

Example: Rapamycin[36]

3. Propylene Glycol USP[37]

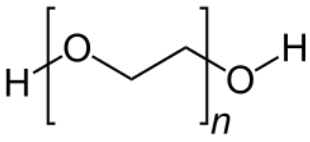
Propylene Glycol USP is an odorless, colorless, viscous liquid diol that contains two hydroxyl groups. It is used in pharmaceutical preparations as a co-solvent, generally as a replacement for glycerin.



Example: Aspirin and Caffeine.

4. Poly(ethylene glycol) (PEG)[38]

PEG is a polymer composed of repeating units of the monomer ethylene oxide (in parenthesis). The physical state of the polymer is dependent on the number of repeat units (*n*) and hence on the molecular weight. Lower-molecular weight grades (PEG 200, PEG 400) are preferred as co-solvents in pharmaceutical solutions.



Example: Cyanide Antidote.[39]

Application

1. Ultimate role in solubility enhancement of poorly water soluble drug
2. Improvement in absorption and bioavailability
3. Apart from increasing solubility, it has important in improvement solubility of volatile constituent used to impart a desirable flavor and odor to the product.
4. Solubility consideration at dosage form design.

Anti-solvent

Anti-solvent crystallization is the separation and purification method which is used as an effective way to prepare micro to nano-size drug particles.[23] This technique produces crystals from solutions and controls the crystalline properties such as particle size and their morphology.[40] The use of the anti-solvent in crystallization reduces the solubility of a solute in the solution and to induce rapid crystallization. The physical and chemical properties of the anti-solvent can alter the rate of mixing with the solutions and thereby affect the rate of nucleation and crystal growth of the crystallizing compounds. Generally, the anti-solvent contains hydrophilic stabilizer (i.e. Surfactants) which is absorbed on the crystal surface to inhibit crystal growth. Hydroxypropyl methylcellulose (HPMC) is a non-toxic in nature and has the good hydrophilic property which is widely used as the thickening, emulsifying and stabilizing agent in food and pharmaceutical formulations.[41] The technique involves dissolution, followed by precipitation and then drying. Thus, the mechanical energy input is minimized but the resulting nanoparticles might be crystalline or amorphous and also depending on the process conditions. Even if the particles are crystalline, the crystal growth rate must be controlled to limit the particle size.[15]

Anti-solvent Method

1) Crystallization

The basic strategy in crystallization is to reduce the solubility of the solute of interest and can be carried out by a variety of methods including cooling, evaporation, pH swing, chemical modification/reaction, and non-solvent addition (frequently referred to as anti-solvent crystallization).This experimental crystallization apparatus enables the study of key facts of anti-solvent crystallization: (a) effects of key parameters such as supersaturation and cooling/heating rates on solids content, morphology and crystal size distribution; (b) on-line control of crystallization processes The experiment and process described in this operating

manual are related to anti-solvent crystallization, generating sodium chloride crystals from an aqueous solution by addition of the anti-solvent ethanol which renders the solute less soluble in water, in a manner not dissimilar from experimental work of others in the field.[13,42]

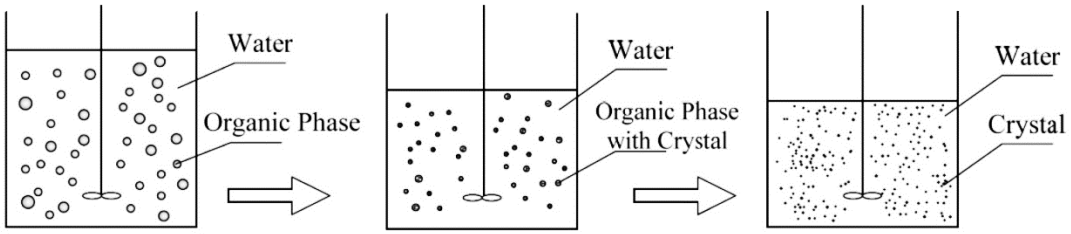
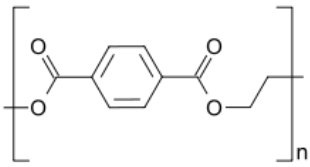


Fig. 3: Anti-solvent crystallization method.

Commonly used anti-solvent in crystallization method

1. Ethylene glycol

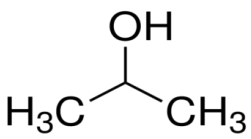
Ethylene glycol (IUPAC name: ethane-1,2-diol) is an organic compound with the formula (CH_2OH). Ethylene glycol is a clear, colorless, odorless liquid with a sweet taste. It is hygroscopic and completely miscible with many polar solvents, such as water, alcohols, glycol ethers, and acetone.



Example: Anhydrous Sodium Carbonate,[43] insulin production.[44]

2. Iso propyl alcohol[45]

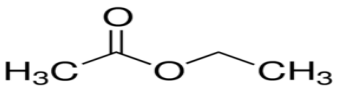
Isopropyl alcohol (IUPAC name propan-2-ol), also called isopropanol or dimethyl carbinol, is a compound with the chemical formula C_3H_8O or C_3H_7OH. It is a colorless, flammable chemical compound with a strong odor.



Example: Preparation of Ibuprofen Nanoparticle.[46]

3. Ethyl acetate

Ethyl acetate is the organic compound with the formula CH_3-COO-CH_2-CH_3, simplified to $C_4H_8O_2$. This colorless liquid has a characteristic sweet smell Ethyl acetate is the ester of ethanol and acetic acid; it is manufactured on a large scale for use as a solvent.



2) Supercritical whereas precipitation[47]

Supercritical anti-solvent micronization has been performed using different process arrangements and apparatuses. Different acronyms were also used by the various authors to indicate the micronization process. It has been referred to as GAS (gas anti-solvent), PCA (precipitation by com-pressed anti-solvent), ASES (aerosol solvent extraction system), SEDS (solution enhanced dispersion by supercritical fluids) and SAS (supercritical anti solvent) processes. In the author's opinion, the acronym SAS gives a better description of the process. Indeed, the other abbreviations do not point out the main characteristics of the anti-solvent used: the supercritical condition Since the results can be heavily influenced by the adopted process arrangement, a short description of the various techniques is presented below.

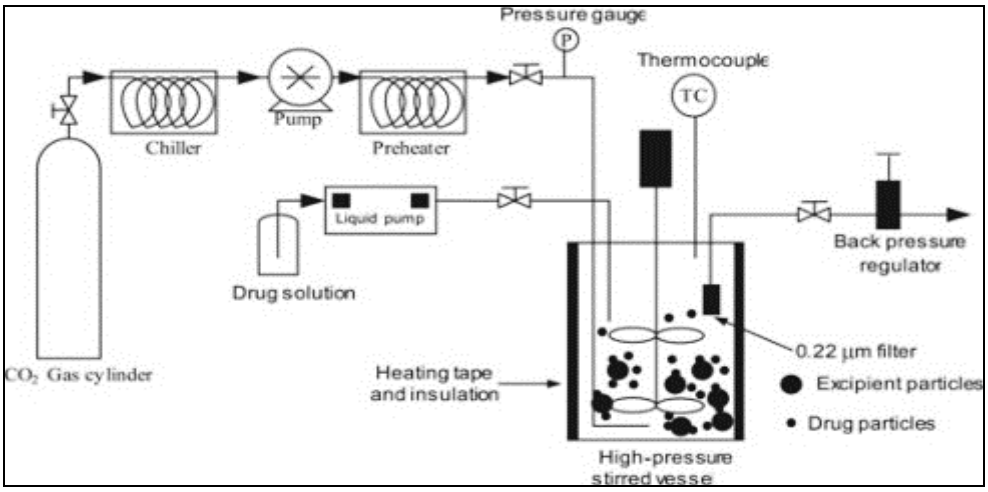


Fig. 4: Supercritical Anti-solvent precipitation.

a) Batch operation

The precipitation vessel is loaded with of the liquid solution and then the supercritical anti-solvent is added until the final pressure is reached. In this mode of operation, the rate of supercritical anti-solvent addition can be an important parameter in controlling the morphology and the size of the solid particles. The anti-solvent can be added from the bottom

or from the top of the chamber. This mode of operation can be referred to as the liquid batch operation.

It is also possible to charge the precipitation chamber with the anti-solvent and then to perform a discontinuous injection of the liquid solution. This mode of operation can be termed gas batch operation.

b) Continuous operation

The liquid solution and the supercritical anti-solvent are continuously delivered to the precipitation vessel in co-current or counter current mode. In this mode of operation, the flow rate and their ratio can be important for the evaluation of the precipitation process. The pressure at which the operation is performed can also be a revalent process parameter.

Application

1. The possibility of dissolving a large volume of a supercritical fluid by an organic solvent.
2. The reciprocal miscibility of the supercritical fluid CO2 and an organic solvent.
3. The low affinity of the supercritical fluid for the solute
4. Supercritical antisolvent method is used in various field including explosives, polymers, pharmaceutical compounds, coloring matter, catalysts and inorganic compounds.[47]

CONCLUSION

In this above study, the Co-solvency and Anti-solvent method describe because of the many drugs are categorized in low solubility. And the Dissolution of a drug is the rate determining step for oral absorption of the poorly water soluble drugs.so by using this method to enhance the solubility of the drugs.and to increase the oral bioavailability, and reduce a frequency of dosing.

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