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## REVIEW ON: SOLUBILITY ENHANCEMENT AND FORMULATION OF SUSTAINED RELEASE DRUG DELIVERY SYSTEM OF BCS CLASS II DRUG

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### ABSTRACT :-

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous System. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological activity. Water is the solvent of choice for liquid pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Hence various techniques are used for the improvement of the solubility of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotrophy etc. The purpose of this review article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

**Keywords:**

Solubility, solubility Enhancement, pH, Emulsions.

**INTRODUCTION:**

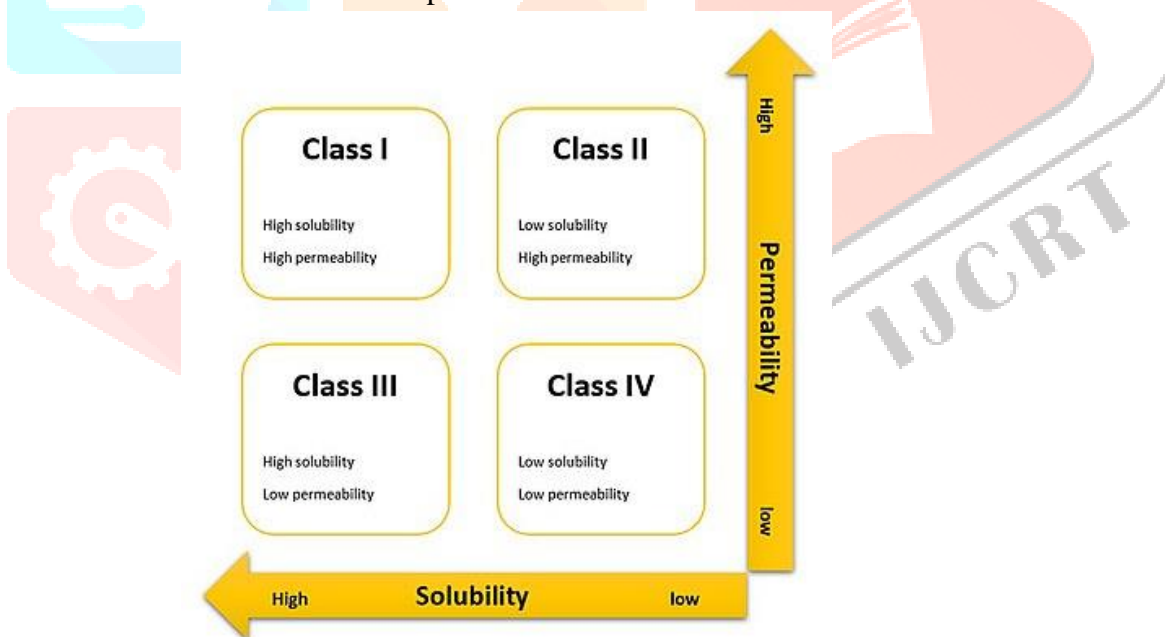
A wide variety of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc. Solubilization of poorly soluble drugs is a regularly encountered project in screening studies of new chemical entities as well as in formulation design and development. 1,2

The aim in designing sustained or sustained transport systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by way of localization at the website online of action. 3

The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. 4

❖ According to BCS Classification all drugs have been divided into four classes:

1. class I—high soluble and high permeable
2. class II—low soluble and high permeable
3. class III—low soluble and high permeable and.
4. class IV—low soluble and low permeable.



**Dig: BCS Classification**

The property of a solid, liquid, or gaseous active ingredient called a solution to dissolve in a solid, liquid, or gaseous solvent to create a homogeneous solution of the solute in the solvent is known to as solubility. A substance's soluble is largely regulated by the solvent used, as well as temperature. The concentration percentage is a measure of a substance's solubility in a specific solvent. where adding additional solute does not result in a higher concentration of the solute in the solution [5]

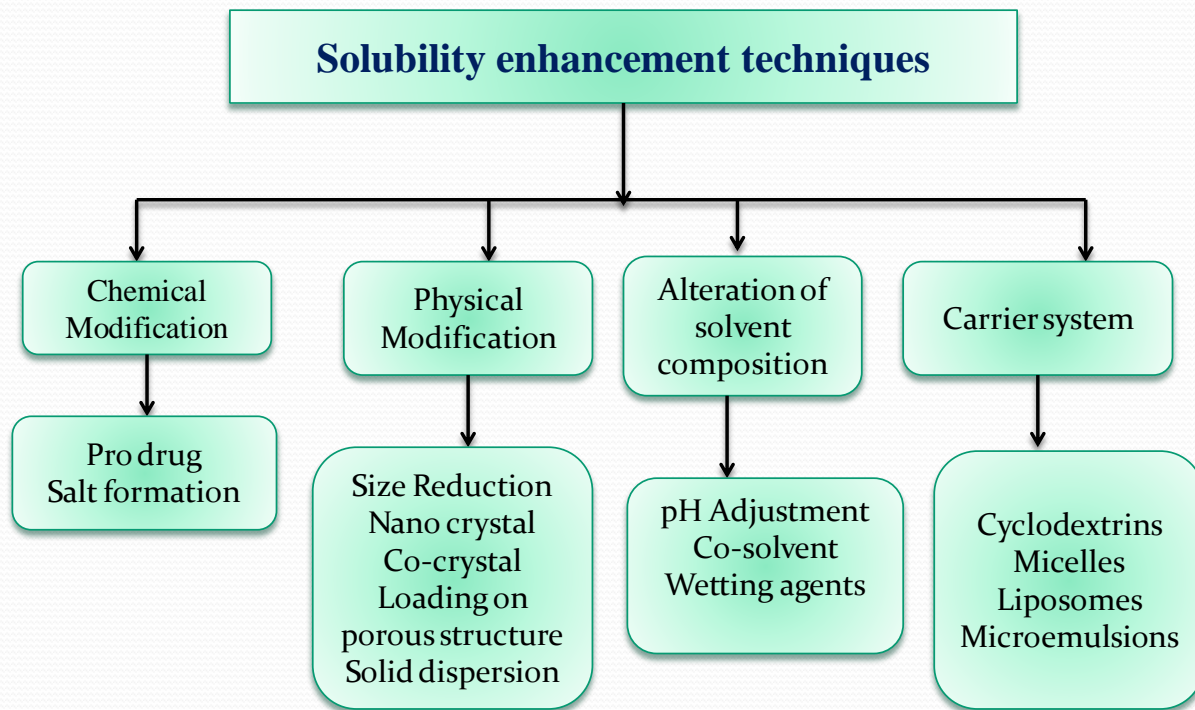
**Table: USP and BP solubility criteria.**

Type of Solubility	Part of Solvent Required Per Part of Solute
Very soluble	<1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000

➤ **Techniques for Solubility Enhancement:**

Physical modifications, biochemical modifications of the drug substance, and other techniques are all types of solubility methods. Physiological changes Drug distribution in carriers, particle size reduction including such micronization and nanosuspension, crystal habit modification including such polymorphs, amorphous form, and covalent binding, and drug diffusion in carriers like eutectic mixtures, solid dispersions, solid solutions cryogenic techniques. Chemical Modifications. Change of pH, use of buffer, derivatization, complexation, and salt formation. Miscellaneous Methods. Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydro-trophy, and novel excipients. (6)

# Solubility Enhancement Techniques



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## 1. PH ADJUSTMENT

That used a pH change, poorly water soluble drugs with parts of the molecule that can be hydrated (base) or uncharged (acid) may be diluted with water. In principle, pH changes can be used for both oral or parenteral administration. Because blood is a strong buffer with a pH range of 7.2–7.4, the poorly soluble drug may precipitate following intravenous injection.

The buffer capacity and tolerability of the chosen pH are crucial factors to consider when evaluating the approach's suitability. So because pH in the stomach is around 1 to 2, and the pH in the duodenum is between 5-7.5, the degree of solubility is likely to be influenced as the drug passes through the intestines after oral delivery. The best candidates are ionizable compounds that are stable and soluble following pH adjustment. Acids, bases, and zwitterionic molecules all are possible. It could be used for either crystalline or lipophilic poorly soluble compounds..(7-10), Solubilized excipients that raise the pH of the microenvironment within a dosage form, such as a tablet or capsule, to a level higher than the pKa of weakly acidic drugs increase the drug's solubility; similar, excipients that act as neutralising agents may improve the solubility of weakly basic drugs. So because solubility of the poorly soluble drug is increased as compared to water alone, the percentage of orally absorbed drug may be raised if compounds can permeate through the barrier orally. To increase the solubility of a poorly soluble pharmaceutical, pH modification is frequently combined with co-solvents.(11-12)

Advantages:

- Simple to formulate and analyse.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages:

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

## 2. CO-SOLVENCY

Cosolvents, which are water miscible solvents in which the medicine has good solubility, can be used to augment the solubility of a poorly water soluble drug.(13), Cosolvents are solutions made up of water and one or more water miscible solvents that improve the solubility of poorly soluble substances. Because it is simple to make and evaluate, this has been one of the most extensively employed strategies in the past. PEG 300, propylene glycol, and ethanol are examples of solvents used in co-solvent combinations. Poorly soluble medicines can be given orally or parenterally in co-solvent formulations. To lower the solvent content before administration, parenteral formulations may require the addition of water or a dilution step using an aqueous media.

Pharmaceuticals are always in liquid form. A co-solvent technique may be appropriate for poorly soluble chemicals that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. When compared to the water solubility of the medicine alone, co-solvents can boost the solubility of weakly soluble substances by thousands of times. When compared to other solubilization methods, very high drug concentrations of weakly soluble substances can be dissolved. However, because the poorly soluble medication will often uncontrollably crash out upon dilution into a crystalline or amorphous precipitate, the bioavailability may not be greatly boosted.

For oral absorption, breakdown of this precipitate is essential in this circumstance. To boost the solubility of weakly soluble substances, co-solvents can be used with various solubilization procedures and pH adjustments. The use of co-solvents to improve the solubility of poorly soluble medicines is a highly effective strategy.(14–16) The most commonly used for low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol.(17-20),Dimethylsulfoxide (DMSO) and dimethylacetamide (DMA) have been widely used as cosolvents because of their large solubility capacity for weakly soluble drugs and their relatively low toxicity.(21-23)

Advantages:

- Simple and rapid to formulate and produce.

Disadvantages:

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media. The precipitates may be amorphous or crystalline and can vary in size. Many of the insoluble compounds Phares works with are unsuited to co-solvents alone, particularly for intravenous administration. This is because the drugs are extremely insoluble in water and do not readily redissolve after precipitation

from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.

- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

### 3. PARTICLE SIZE REDUCTION

The bioavailability of a medicine is inextricably linked to its particle size. Increased surface area increases dissolving capabilities by reducing particle size. Milling techniques such as jet mills, rotor stator colloid mills, and others are used to reduce particle size. Because it does not modify the drug's saturation solubility, it is not suited for medications with a high dosage number. (24,25) Nowadays Particle size reduction can be achieved by micronisation and nanosuspension.

Advantages:

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Typically, low excipient to drug ratios is required.
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation.
- Generally, crystal forms are chemically and physically more stable than amorphous particles.
- A method to consider for stubborn compounds that defeat previous attempts to increase solubility.

Disadvantages:

- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
- Developing a solid dosage form with a high payload without encouraging agglomeration may be technically challenging.
- Technically, development of sterile intravenous formulations is even more challenging.

### 4. MICROEMULSIONS

Microemulsions have been used to enhance the solubility of several medications that are nearly insoluble in water, as well as to include proteins for oral, parenteral, and transdermal applications. (26-27). A microemulsion is an optically transparent pre-concentrate that dissolves a poorly water soluble medication by combining oil, hydrophilic surfactant, and hydrophilic solvent. When the formulations come into contact with water, they spontaneously disperse (or self emulsify) into a highly transparent emulsion of extremely minute and uniform oil droplets carrying the solubilized weakly soluble medication. Microemulsions are transparent (or translucent) isotropic, thermodynamically stable systems of oil, water, and surfactant, sometimes in combination with a co-surfactant, with droplet sizes ranging from 20 to 200 nm. These homogeneous systems, which can be made using a variety of surfactant concentrations and oil-to-water ratios, are all low-viscosity fluids

. An anhydrous system of microemulsions is a self microemulsifying drug delivery system (SMEDDS). Some researchers have referred to it as microemulsion pre-concentrate. It is made up of oil, surfactant, and co-surfactant, and when dispersed in aqueous phase with mild agitation, it can create an o/w microemulsion. Stomach and intestine movement provide the necessary agitation for self-emulsification. (28-30)



Advantages:

- The pre-concentrates are relatively easy to manufacture.
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state).

Disadvantages:

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
- Formulations containing several components become more challenging to validate.

## **SUSTAINED RELEASE DRUG DELIVERY SYSTEM:-**

Sustained release dosage forms are intended to provide such a long-lasting therapeutic effect by consistently releasing medication after a single dose has just been given. The main goal of creating sustained release formulations was to modify and improve pharmacological performance by limiting the range of drug action, decreasing dosing frequency, minimizing the required dose, and ensuring uniform drug distribution. There has been a strong increase in interest in sustained release drug delivery systems over the last 2-3 decades.

This is due to the number of aspects, such as the prohibitive cost of developing new drug entities, the expiration of existing international patent applications, the discovery of new synthetic polymers suitable for prolonging release of the drug, and the improvement in therapeutic efficiency and safety that these delivery systems had already achieved. Sustained release dosage forms are made by coating tablets that control the rate of solubility or separately containing micro particles of various sizes to manage the rate of dissolution. [31, 32].

Drug from the combination is administered for 8-12 hours in the GI tract. SRDDS reduced toxicity by slowing drug absorption, increased stability by protecting the drug from hydrolysis or other metabolizing changes in the gastrointestinal tract, and improved mouth feel and availability of formulation in liquid and solid SRDDS.

### **Advantages [33]**

- Improved patient compliance due to less frequent drug administration.
- Reduced fluctuation in steady-state drug levels.
- Maximum utilization of the drug
- Increased safety margin of potent drug
- Reduced healthcare costs through improved therapy
- Shorter treatment period
- Less frequency of dosing.

**Disadvantages [34]**

- Delivery of a part of a tablet or capsule in order to obtain fine dose modulation is more difficult with some sustained release drugs compared with others..
- Even though a drug with such a short half-life should be administered frequently, there is a danger of forgetting a dose..
- Necessitate for additional patient education and counsel. E.g., “do not crush or chew the dosage unit” and “tablet residue may appear in stools”
- Cost of the formulation is high.
- Poor IVIVC (In vitro – in vivo correlation).

1. **Sustained release system:** Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.
2. **Site-specific targeting:** Site-specific and receptor targeting refer to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is adjacent to or in the diseased organ or tissue.
3. **Receptor targeting:** For receptor release, the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered to be controlled drug-delivery systems.

**Criterion for Drug Selection of SRDDS [35, 36]**

Parameter	Criteria for drug selection
1. Physiochemical parameters for drug selection	
Molecular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from all GI segments	Release Should not be affect by pH and enzymes



## 2. Pharmacokinetic parameters for drug selection

Elimination half-life ( $t_{1/2}$ )	Between 2 to 8 hours
Absolute bioavailability	Should be 75% or more
Absorption rate constant ( $K_a$ )	Must be higher than release rate
Apparent volume of distribution ( $V_d$ )	Larger $V_d$ and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration ( $C_{ss}$ )	The lower $C_{ss}$ and smaller $V_d$ , the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form



Drug/s	Polymer used	Ref
sustained release tablet formulations		
Indomethacin	HPMC K100LV, HPMC K4M, HPMC K15 M	[37]
Metformin HCl	HPMC K100M, Xanthan gum	[38]
Metformin HCl & Gliclazide	HPMC K4M, HPMC K15M, PVP K90 D	[39]
Ambroxol HCl	HPMC K15M, Eudragit RSPO	[40]
Metformin HCl	HPMC K100M, HPMC K4M, HPMC K15 M, PVP K30	[41]
Repaglinide	HPMC K15M, HPMC K100M, Guargum	[42]
Carbamazepine	HPMC K100M Eudragit RLPO, Eudragit RSPO,	[43]
Glimepiride & Metformin HCl	Eudragit L100, Eudragit RSPO, PVP K30	[44]
Amisulpride	HPMC K4M, PVP K30, Polyox, Carbopol 71G, Cross Povidone, Kollidone SR, Xanthenes Gum	[45]
Tramadol HCl	HPMC K15M, HPMC K100M, PEO N80	[46]
Metformin HCl & Glimepiride	HPMC K15M, HPMC K100M, Guargum, Sodium alginate, Carbopol 934, Carbopol 940	[47]
Galantamine HCl	HPMC K15M, HPMC K100M, Starch	[48]
Isosorbide mononitrate	HPMC K4M, Polyox WSR 303, PVP K30	[49]
Flupirtine Maleate	HPMC K4M, HPMC K100M	[50]
Diclofenac Sodium	HPMC K4M, Sodium CMC, Sodium alginate	[51]
Diclofenac Sodium	HPMC, Cashew nut tree gum, Carbopol	[52]
Diclofenac Sodium & Tramadol HCl	HPMC K4M, HPMC K15M, HPMC K100M	[53]
Diclofenac Sodium	HPMC K100M, EC	[54]
Diclofenac Sodium	HPMC, Sodium alginate, Sodium CMC	[55]
Diclofenac Sodium	HPMC, Cashew gum, Xanthan gum	[56]

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