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# Solubility and Solubilization: For Formulation Scientists

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**ABSTRACT**

Number of new drug candidates produced in the past decade shows low soluble characteristics. This has promoted the interest in so-called drug-ability of the new drugs, i.e., formulations which shall make such drugs bio-available. Low soluble drugs (BCS class II) and their enhancement of solubility through various approaches is a well-known but still a big challenge to formulation scientists. In accordance to the Noyes-Whitney equation for low soluble drugs dissolution kinetics and solubility are particle size dependent, while the wetting properties of the used polymer may also play an important role. Here it is focused on the ways and means of enhancement of solubility hence dissolution rate. Here it is discussed on different solubilization techniques covering; BCS, chemical modification, physical modification, alteration of solvent system and carrier systems under solubilization. Various polymers being used as hydrophilic carriers for drug solubilization is outlined.



## INTRODUCTION

The solubility of one substance in another is a measure of the degree of molecular mixing between the two pure substances at thermodynamic equilibrium. A drug substance is said to be highly soluble, whose highest dose is soluble in 250 mL or less of aqueous media over a pH range from 1.0 to 6.8 at 37 ± 1°C. The approximate of 250 mL is derived from usual bioequivalence study protocols that suggest administration of an oral drug to a fasting human volunteer with an 8 fluid ounce glass of water.

The permeability term is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance through the intestinal membrane, it is a rate of mass transfer across the intestinal membrane. A drug substance is considered to be highly permeable when the systemic availability or the extent of absorption in humans is determined to be 85 percent or more of an administered dose.

The ability to accurately measure the aqueous solubility of a material is affected by the physico-chemical properties of the substance (e.g., particle size, surface area, polymorphic form), the properties of the solvent (e.g., polarity, pH, surface tension, added surfactants, co-solvents, salts etc.), and the control of the solubility measurement parameters (e.g., time, temperature, agitation method etc.). Control of these factors during solubility measurements is very important to obtain accurate, reliable values for the equilibrium solubility of a material.

There are several possible ways that can be considered to increase the solubility and dissolution, hence bioavailability of drug(s). The best formulation strategy for any given drug will depend on numerous factors, including shelf life of the drug, dose, scale up, and the physic chemical properties of the drug. Selecting the best formulation and manufacturing route for a new drug molecule is thus not a straightforward process [1]. According to a recent study more than 70% of new drug

substances in product development have solubility issues. Together, nearly half of the newly marketed drugs are low soluble hence aqueous solubility in such cases is a challenge to improve bioavailability and therapeutic efficacy [2]. It implies poor solubility continues to be a major issue and challenge for formulation development of new drug entities [3].The per oral administration is the most convenient, showing flexibility in formulating a dosage form and has good patient acceptance which makes it the most promising route [4]. Descriptive terms for solubility is given in table 1

**Table 1: Descriptive terms for solubility**

| Descriptive terms | Parts of solvent required for one part of solute |
|---|---|
| Very soluble | Less than 1 |
| Freely soluble | From 1to 10 |
| Soluble | From 10 to 30 |
| Sparingly soluble | From 30 to 100 |
| Slightly soluble | From 100 to 1000 |
| Very slightly soluble | From 1000 to 10000 |
| Practically insoluble, or insoluble | 10000 and over |

**Biopharmaceutics Classification System (BCS)**

Biopharmaceutical classification is based on factors; whether the drug is sufficiently soluble in the intestinal fluid (i.e., solubility) and permeation through the biological membrane (i.e., permeability). BCS is an essential tool used in drug formulation development [5]. The BCS classification of drugs and basic formulation strategies are given in table 2.

**Table 2: BCS classification of drugs and basic formulation strategies**

| | |
|---|---|
| **Class I**<br>**Wide flexibility to plan a formulation**<br>(Formulation independent) | **Class II**<br>**Use of Solubilization techniques**<br>(Formulation dependent) |
| **Class III**<br>**Incorporation of permeation enhancers**<br>(Dependent on barrier properties) | **Class IV**<br>**Incorporation of both the strategies for class II and IV drugs**<br>**(**Formulation and barrier properties dependent) |

The pi diagram showing nearly fraction of drugs lying under each BCS categories are shown in figure 1.

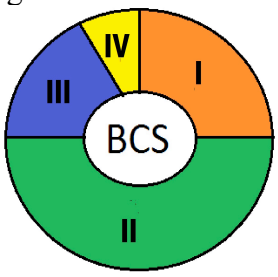


**Figure 1:** Diagram showing nearly fraction of drugs lying under each BCS categories

**Solubilization**

According to Mc Bain, solubilization has been defined as the spontaneous passage of poorly water soluble solute molecule into an aqueous solution of soap or a detergent in which a thermodynamically stable solution is formed. Mc Bain has stated "Any material can be solubilized in any solvent by proper choice of solubilizing agent." Final selection of solubilizing agent should be based on phase solubility studies [6, 7]. Various solubilization techniques that are used to improve the solubility of a poorly soluble drug are given under Figure 2

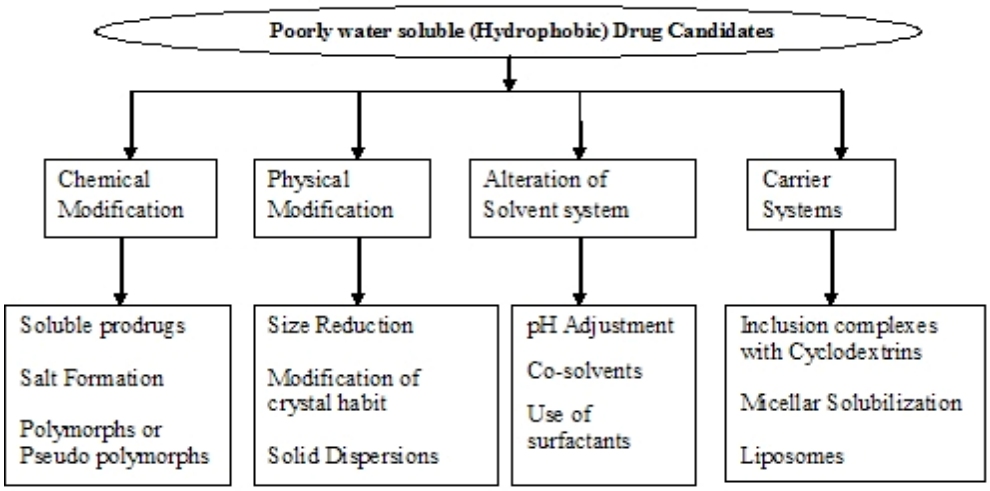


**Figure 2: Schematic representation of solubilization techniques**

**Hydrophilic carrier used commonly [8]**

Some commonly used hydrophilic carriers are: polyethylene glycols PEGs or Macrogols) of different grades PEG 1500-40000; polyvinyl pyrrolidones (PVPs) of different grades PVP K 30-90; poly (oxyethylene–co-oxypropylene) i.e., poloxamers of different grades 188, 407; fatty acid macrogol glycerides, Gelucires of different grades 44/14- 50/13 (The numerator indicates the melting point and denominator indicates the HLB value); poly(vinyl acetate-co-vinyl caprolactame-co-ethylene glycol) i.e., Soluplus® etc.

## SUMMARY AND FUTURE OUTLOOKS

The aqueous solubility of drugs is an important factor influencing their dissolution rate and bioavailability hence therapeutic efficacy following oral administration. The techniques described above only or in combination could be used to overcome the solubility challenges of BCS class II/ IV drugs. Correlation between *in vitro* and *in vivo* results must be considered for the formulations.

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