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Solubilization Enhancement Techniques: An Overview

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Abstract Solubility enhancement is a technique used for the hydrophobic drugs. Low aqueous solubility is the major problem, due to which drugs cannot reach the therapeutic level. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Among all newly discovered chemical entities about 40% drugs are lipophilic and fail to reach therapeutic range due to their poor water solubility. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. The Biopharmaceutics Classification System (BCS) reflects that Class II and IV drugs have low water solubility, poor dissolution, and low bioavailability. In this article various techniques are described to increase the solubility of drugs.

Keywords Dissolution rate, BCS Classification, Solubility

Introduction

Solubility in quantitative terms is defined as the concentration of the solute in a saturated solution at a certain temperature. The solubility of a solute in a solvent depends on the solvent used as well as on temperature and pressure. Solubility varies over an extended range from infinitely soluble such as ethanol in water to poorly soluble such as silver chloride in water. The poorly or very poorly soluble compounds are often termed as insoluble [1]. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable [2].

As the solubility increase bioavailability increases. Solubility defines as:

Table 1: Definition of Solubility [3]

Definition	Parts of solvent required for one part of solute
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Insoluble	> 10,000

BCS (Biopharmaceutics classification system) classify the drug in to four classes according to their solubility and permeability. Solubility challenges are faced in the Class II and Class IV of the BCS system (where dissolution becomes the rate limiting step for the absorption of drug) which comprises of newer generation of NSAIDs like Zaltoprofen, Aceclofenac, Flurbiprofen, their older congeners like Indomethacin, Ibuprofen, Ketoprofen and Diclofenac; anti-diabetics Gliclazide, Glipizide; newer calcium channel blockers (CCBs) like Nimodipine, Felodipine. The BCS was first devised in 1995 by Amidon *et al.* [4].

Table 2: BCS Classification of Drug [5]

Class	Permeability	Solubility	Example
I	High	High	Metoprolol, Caffein, Propranolol
II	High	Low	Neteglinide, Itraconazole, Nifedipine
III	Low	High	Cimetidin, Insulin, Neomycin
IV	Low	Low	Hydrochlorothiazide, Furosemide, Mebandazole

Factors Affecting Solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system [6].

- **Particle size**:

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be explained as per the following equation [7] where, S is the solubility of infinitely large particles, S is the solubility of fine particles, V is molar volume, G is the surface tension of the solid, R is the radius of the fine particle.

Figure 1: Holes opens in the solvent

- **Temperature:**

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature [8]. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases [9].

- **Pressure:**

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

- **Nature of the solute and solvent:**

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility of these two substances is the result of differences in their nature.

- **Molecular size:**

The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the

amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent [10].

- **Polarity:**

Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.

- **Polymorphs:**

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism.

Classification of solid dispersion

1. First generation solid dispersions

In first generation solid dispersion, formulation of eutectic mixtures or molecular dispersion improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Disadvantage related formulation of crystalline solid does not release drug quickly. Example: Crystalline carriers: Urea, Sugars and Organic acids[11].

2. Second generation solid dispersion

In second generation we use amorphous state of carrier which improves drug release; likes fully synthetic polymers include povidone (PVP),

Polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins [12].

3. Third generation solid dispersion

In third generation we use carrier which have surface activity and self emulsifying property. The surfactants decrease the re-crystallization of drug and thus improve the solubility of drug. Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14[13].

Advantages of solid dispersion

1. Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.
2. Improve wettability of particle: solid dispersion improves wettability of particle.
3. Improve porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate.
4. Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages of solid dispersion

1. Instability due moisture content.
2. Difficulty in incorporating into formulation of dosage forms.

Need of Solubility

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.

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

Poor aqueous solubility is caused by two main factors

1) Strong intermolecular interactions which make the solubilization of the solid energetically costly

2) High lipophilicity. Solubility plays an essential role in drug disposition, since the maximum rate of passive drug transport across a biological membrane, the main pathway for drug absorption, is the product of solubility and permeability. Compounds with insufficient solubility carry a higher risk of failure concentration of compound in the bulkmedium [14]. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug [15].

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:

Physical Method

Micronization: The solubility of drug is often intrinsically related to drug particle size[16]. Particle size reduction, leading to increased surface area, is a very promising approach to enhance dissolution rate and, thus, the bioavailability of poorly water soluble compounds [17-19]. According to the Noyes- Whitney equation, the rate of dissolution (dC/dt) depends on the effective surface area (A) of the drug particles. The rate of mass lost from the particle is given by

$$-dM/dt = DS/h\ (CS - CB)$$

Where, M is the mass of compound dissolved in time t, D is the diffusion coefficient of the compound in medium, S is surface area, h is thickness of the stagnant film layer, CS is the saturated solubility of the compound at the particle-media interface, and CB is the concentration of compound in the bulk medium[14].

Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

Nanonization: Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of numerous drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nanoscale level of approximately 100 nm or less.

Nanonization can result in improved drug solubility and pharmacokinetics, and it might also decrease systemic side-effects. There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification solvent evaporation technique, Pear milling, Spray drying etc[20].

Nanocrystals: The term drug nanocrystals imply a crystalline state of the discrete particles, but depending on the production method they can also be partially or completely amorphous. Drug nanocrystals can be produced by bottom up technologies (precipitation methods) or alternatively by top down technologies (size reduction methods).

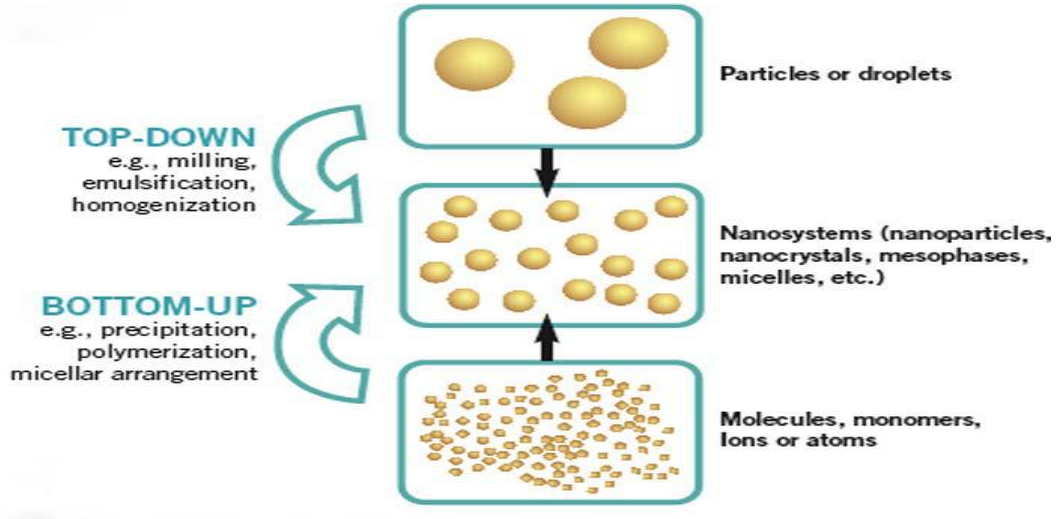

Figure 2: Formation steps of Nanocrystals

At the present most industrially feasible methods are the top down technologies, all products on the market are made by size reduction [21-22].

Nanosuspension: Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed. Techniques for the production of nanosuspensions are presented in Table 3.

Table 3: Nanosuspension Technology and drug used

S. No.	Preparation Technique Used	Drugs Used
1.	Precipitation	Carbamazepine, Simvavastin, Felodipine, Ezetimibe
2.	Microemulsion	Griseofulvin, Breviscapine, Amphotericin-B, Etoposide
3.	Homogenization	Ibuprofen, Diacerin, Cyadox, Albendazole
4.	Milling	Cefdinir, Gemfibrozil, Naproxen, Indomethacin

Nanoemulsion: Nanoemulsions are nonequilibrium, heterogeneous system consisting of two immiscible liquids in which one liquid is dispersed as droplets in another liquid. Emulsions with nanoscopic droplet sizes (typically in the range of 20-200 nm) are often referred to as submicronemulsions. Nanoemulsions are composed increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms.

Hydrates/solvates

The stoichiometric type of molecular adducts, in which solvent molecules are incorporated in the crystal lattice of solid is called as solvates. The solvates can exist in different crystalline forms and called as pseudo-polymorphs and this phenomenon is called as pseudo-polymorphism. When solvent in association with the drug is water, the solvate is known as hydrate and thus have less energy for crystal breakup when compared to anhydrous forms. For example, the antidiabetic drug glibenclamide has been isolated as pentane and toluene solvates which exhibited higher solubility and dissolution rate than the non-solvated polymorphs [23].

Particle size reduction

Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different equipment for reduction of the particle size.

Chemical modifications

Salt formation

It is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs, which are converted into respective salt forms, e.g., aspirin, theophylline, and barbiturates. Alkali metal salts of acidic drugs such as penicillins and strong acid salts of basic drugs such as atropine are water soluble than parent drugs.

Co-crystallization

It is a molecular complexation process to form co-crystals. A co-crystal may be defined as crystalline material that consists of two or more molecular species held together by non-covalent forces. Only three of the co-crystallizing agents are classified and generally recognized as safe. It includes saccharin, nicotinamide, and acetic acid limiting the pharmaceutical application. It is an alternative to salt formation, particularly for neutral compounds.

pH adjustment

By this method, the hydrophobic molecule can be protonated (base) or deprotonated (acid) and be dissolved in water by applying a pH change. Ionizable compounds that are stable and soluble after pH adjustment are best suited.

Co-solvency

Cosolvents are mixtures of water and/or more water miscible solvent used to create a solution with enhanced solubility for poorly soluble compounds, e.g., of solvents used in the co-solvent mixture are PEG 300, propylene glycol, or ethanol. Dimethyl sulfoxide and dimethylacetamide have been widely used as cosolvent because of their large solubilization capacity of poorly soluble drugs and their relatively low toxicity [24].

Hydrotrophy

Hydrotrophy was first coined by Neuberg [25] to describe the increase in the aqueous solubility of BCS Class 2 molecules by the addition of high concentrations of alkali metal salts of various organic acids**.** Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate have been observed to enhance the aqueous solubilities.

Miscellaneous methods

Super critical fluid technology

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used either as a solvent for drug and matrix or as an anti-solvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. However, the application of this technique is very limited because the solubility in CO_2 of most pharmaceutical compounds is very low (<0.01 wt. %) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical.

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystalline nature of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique.

Self-emulsifying drug delivery systems

Self-Emulsifying Drug Delivery Systems (SEDDS) are involved in lipid formulations. These formulations consist of isotropic mixtures of drugs, which are commonly lipids or surfactants with one or more hydrophilic co-solvents or co-emulsifiers. This system forms an emulsion instantly after slight agitation and dilution with water. These emulsions produced are a droplet size extending from a few nanometers to numerous microns. This system can be used with all BCS class drugs to help improve their solubility. SEDDS helps maintain solubility in the gastrointestinal tract by avoiding the dissolution step, which can limit the absorption rate of hydrophobic drugs. The two main factors that affect the release rate of the drug in SEDDS are the particle size and the polarity of the droplets. For the most effective formulation, it is best to keep the number of excipients to a minimum. Excipients are the backbone of SEDDS. The most frequently used excipients are lipids, surfactants and co-solvents. The best choices of excipient are those that increase drug solubility. Lipids are good for solubilizing lipophilic drugs and enhancing the transportation of lipophilic drugs.

Hydrotrophy

Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to

complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs [26, 27]. The hydrotropes are known to self-assemble in solution. The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants liked acids, SDS (sodium dodecyl sulphate), and dodecylatedoxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. Hydrotropes with cationic hydrophilic group are rare, for example salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of com- pounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, and so forth [28].

Solubility studies

Solubility is one of the most critical preformulation properties that have a significant impact on performance of a molecule. Solubility and permeability form the backbone of Biopharmaceutics Classification System (BCS) that provides scientific framework for designing of drug delivery systems and many regulatory decisions. Solubility assessment is one of the first most important and extensively studies, preformulation parameter. Various aspects like aqueous solubility, pH solubility profile, dissociation constant, partition coefficient and solubility in non-aqueous solvents are studied during preformulation.

Solubility and oral absorption

Orally administered drug has to first dissolve in gastrointestinal milieu before it can be absorbed. Dissolved drug then permeates through the intestinal membrane, before reaching systemic circulation. Newer tools of drug discovery like combinatorial chemistry and high throughput screening have led to increasing lipophilicity and decreasing aqueous solubility of discovery molecules. Estimates indicate that about 40% of drug molecules fail because of non-optimal biopharmaceutical properties like aqueous solubility. This puts a lot of strain on pharmaceutical development as technological interventions to overcome were solubility have to be employed. Discovery scientists assess the 'minimum acceptable solubility' for oral absorption, by considering the permeability and dose of the drug molecule. Various tools like Lipinski's rule of 5, Dabs (absorbable dose), MAD (maximum absorbable dose) and BCS are employed for solubility related decision-making during drug discovery.

Solubility and formulation development

Apart from important role during candidate drug selection, solubility plays a crucial role during formulation development. Parenteral formulations require sufficient aqueous solubility of the drug molecule. Similarly bioavailability from solid formulations like tablets and capsules is also dependent on solubility and dissolution rate. Numerous solubilization techniques are employed for drug molecules exhibiting non-optimal aqueous solubility.

Experimental determination of aqueous solubility

For a given solid solute and solvent, the solubility dependent on the intermolecular adhesive interactions between solute-solute, solute-solvent and solvent-solvent molecules. Hence, intrinsic solubility is governed by crystal packing, cavitation energy and solvation energy. Determination of solubility during preclinical (drug discovery) stage is carried out using DMSO based turbidimetry assays. This provides value of kinetic solubility which is an over-estimate of the equilibrium solubility. Automated robotic driven solubility screens have been developed, which provide a rapid means for rank ordering of lead molecules, based on their solubility. Later in the drug development, thermodynamic solubility is determined using traditional shake flask method. Additional studies in fasted state simulating intestinal fluid and the fed state simulated intestinal fluid, are also carried out, to understand role of pH on aqueous solubility.

Dissociation co-efficient (pKa)

Dissociation coefficient is defined as the pH value at which both the ionized and un-ionized species exist in equal amounts. This is an important parameter for ionizable drug molecules, as ionic species differ in solubility, permeability and absorption. Ionized species are more soluble in aqueous medium. In contrast, unionized species cross biological membranes more effectively, because of the fact that the gastro-intestinal membrane acts as a lipoidal sieve barrier. Gastrointestinal milieu exposes the drug molecule to a wide range of pH values. Information on pKa value allows understanding the behavior of ionizable drug molecule, under differential pH conditions.

Partition co-efficient

Partition coefficient it is an indicator of lipophilicity or hydrophobic bonding of drug molecule. It is expressed as logarithm of P called as log P and signifies distribution constant between and non-polar and polar solvent. Log P is the ratio of drug dissolved into immiscible solvents, most commonly it phosphate buffer of pH 7.4 and n-octanol that are in equilibrium. Log P is applicable to unionized compounds. The term D (distribution coefficient) is applicable to ratio of all species unionized and ionized, in two immiscible solvents. Log P and log D are extremely important parameters as they have direct forbearing on interaction with biological membrane and receptor site. Direct correlations have been demonstrated between log P and biological parameters like oral absorption, protein binding and binding to hepatic metabolizing enzymes.

Solubility studies in non-aqueous solvents

Solubility studies in non-aqueous solvents are important for development of analytical method, crystallization method and formulation development of soluble oral or parenteral formulations. Latter involves solubility assessment in solvents that are approved for use through a particular route of administration.

Importance of solubility

- Oral ingestion is the most convenient and commonly employed route of drug delivery (easy administration, high patient compliance, cost effectiveness, least sterility constrains and flexibility in the design of dosage form).
- However, the major challenge with the design of oral dosage forms lies within their poor bioavailability. The cause of low oral bioavailability is the poor solubility and low permeability.
- Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development
- Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. More than 40% of NCEs developed in the pharmaceutical industry are insoluble in water. For this reason, the problem of solubility is one of the major challenges for formulation chemists.

Conclusion

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug
is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability.
Therapeutically effective concentration of a drug at the target site of action depends on the bioavailability, which ultimately depends on the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response. Solubility is also the basic requirement for the formulation and development of different dosage form of drugs. We conclude that the various techniques described above can be used alone or in combination to enhance the solubility of the drug. Numerous technological advancements have been introduced for solubility and dissolution enhancement of poorly water-soluble drugs. Selection of suitable method is the key process for the improvement of solubility of hydrophobic

drugs. The selection of the techniques should be based on the nature of the drug, its compatibility, its interaction with other chemicals used, stability when the process is executed and yield of the final product.

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