An Overview of Technique for Solubility of Poorly Water Soluble Drugs

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ABSTRACT

Poor water solubility of newly discovered compounds has become the most common challenge in the drug development process. Indeed, poor solubility is considered as the root cause of failure of drug during drug development phases. Moreover, it has also been reported to be the main reason for bioavailability issues such as poor, inconsistent, incomplete and highly variable bioavailability of the marketed products. As per an estimate, approximately 90% of drug molecules suffer with poor water solubility at early stage and approximately 40% of the marketed drugs have bioavailability problems mainly due to poor water solubility. Solubility enhancement of the newly discovered compounds is primary research area for the pharmaceutical industries and research institutions. The conventional techniques to improve aqueous solubility of drugs employ salt formation, prodrug formation, co-crystallization, complexation, amorphous solid dispersion and use of co-solvent, surfactants or hydrotropic agents. Current advancement in the science and technology has enabled the use of relatively new techniques under the umbrella of nanotechnology. These include the development of Nano crystals, Nano suspensions, Nano emulsions, micro emulsions, liposomes and nanoparticles to enhance the solubility. This review focuses on the conventional and current approaches of multifold enhancement in the solubility of poorly soluble marketed drugs, including newly discovered compounds.

Keywords: Solubility, poorly soluble drug, bioavailability, advanced technique

DOI Number: 10.14704/nq.2022.20.6.NQ22798 **NeuroQuantology 2022; 20(6):8027-8038**

INTRODUCTION

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. [1]

The solubility can also be defined as the ability of one substance to form a solution with another substance. The substance which is to be dissolved is called the solute and the fluid or the dissolving fluid in which that solute dissolves is called the solvent. Solute and solvent together form a solution. If the solvent is water, this process is known as hydration.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in

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saturated solution is a static property where as the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. [2]

A "good compound" must be able to reach its target at effective concentrations. Therefore, the lowest acceptable solubility of a compound is related to its pharmacologic potency and its permeability. Low micromolar aqueous solubility can be acceptable only for extremely potent and/or permeable compounds. Potential complications arising from low aqueous solubility are Compounds precipitation during serial dilution in buffer, biochemical assays, functional assays and cell-base assays, Reduce target specificity and Low bioavailability in animal studies. [3]

Factors Affecting Solubility

The solubility of any drug or other components depends upon nature and composition of the solvent medium, Polarity of solute and solvent, physical form of the solid (particle Size, molecular weight**,** rate of solution and polymorph) and temperature and pressure of system

Importance of Solubility

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. For this reason, the problem of solubility is one of the major challenges for formulation chemists. [5]

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. 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. [3] There are numerous approaches available and reported in this article to enhance the solubility of poorly water-soluble drugs.

Techniques of Enhancement Solubility of Drugs

There are two methods used to enhance drug solubility:

1-Conventional Techniques to Improve Solubility of Drugs

There are several conventional techniques to improve solubility of the drugs

A- **Use of salt form**

Improvement of solubility of drug by preparing its salt is a classical technique and the dissolution rate of different salts is usually different from their parent compounds. The potassium and sodium salts of the weak acids dissolve rapidly than the pure salts. Example, salt form of various drugs like aspirin, barbiturates, theophylline etc. Thus it is the most effective and common method to increase the solubility as well as dissolution rate of any acidic or basic drugs. [6] Below table List of some poorly soluble drugs, their salt forms and degree of solubility enhancement [7, 8]

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Drug	Salt form	Solubility enhancement
Pyridoclax	Dihydrochloride	4 fold
Sildenafi	Glutarate salt	3.2 fold
Furosemide	Sodium salt	20 fold
Phenytoin	Sodium salt	60 fold
Bupivacaine	Chloride salt	200 fold
Indomethacin	Arginine & lysine	10000 & 2296 fold

B- co-solvent approach

It is generally known that addition of an organic co-solvent to water can greatly change the solubility of drugs. Nonpolar molecules and weak electrolytes are having poor water solubility and thus their solubility can be enhanced by altering the polarity of the solvent. This alteration in polarity of solvent can be achieved by the addition of another solvent. This process is known as co-solvency. The solvent which is used to increase the solubility is known as co-solvent. It is commonly referred to as solvent blending. Most of the co-solvents are having hydrogen bond donor and acceptor groups and small hydrocarbon regions. The hydrophilic hydrogen bonding groups of these co-solvents ensure the water miscibility; while the hydrophobic hydrocarbon regions interfere with the waters the commonly used co-solvents include ethanol, glycerol, propylene glycol and polyethylene glycols. [9]

C- Micellar solublization

The use of surfactants to improve the dissolution performance of poorly soluble drug products.

Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are also used to stabilize drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles as shown in figure (1, 2). This is known as micellization and generally results in enhanced solubility of poorly soluble drugs.

Surfactant also improves wetting of solids and increases the rate of disintegration of solid into finer particles. Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauryl macro glycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize micro emulsions and suspensions into which drugs are dissolved. [10]

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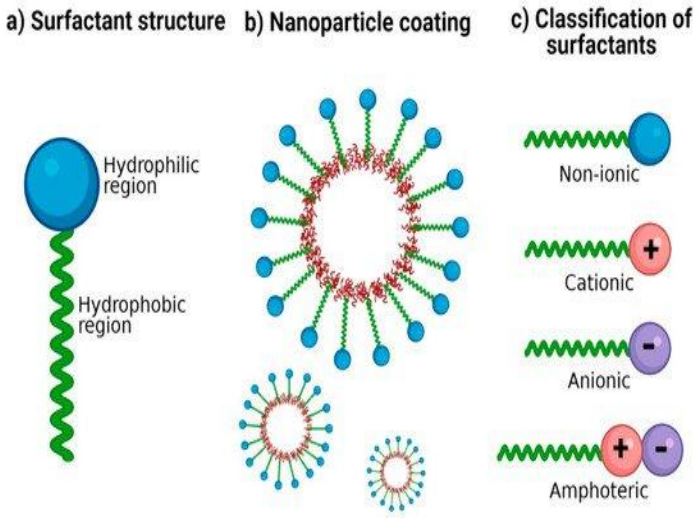

Figure (1): Structure of the surfactant [11]

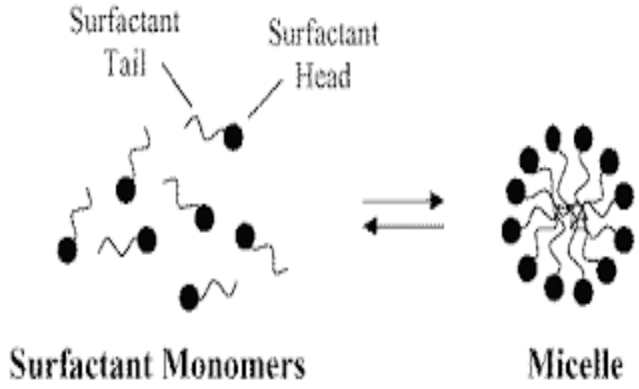

Figure (2): Solubilisation effect of the micelle [12]

D- complexation approach

The complexation approach of enhancing drug solubility is a classical and commonly used method and Complexation is a connection between the two or more molecules to create a non-bonded entity with a definite stoichiometry. Complexation depends on relatively weak forces such as hydrogen bonding, London forces and hydrophobic interactions.

Various examples of the complexing agents include; chelates- EDTA, EGTA, molecular complexes-polymers ,inclusion complexes cyclodextrin as shown in figure (3, 4). [13]

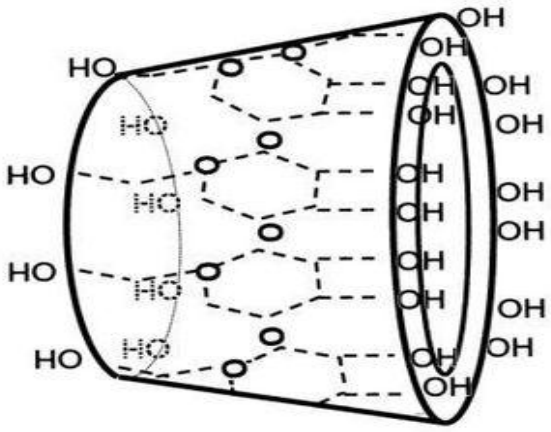

Figure (3): Structure of cyclodextrin [13]

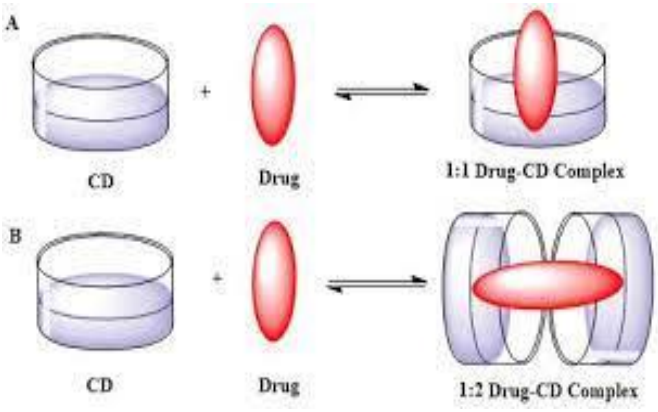

Figure (4): Cyclodextrin inclusion complex [13]

E- co-crystal approach

Co crystals are a crystalline mixture consisting of an active pharmaceutical agent bonded non-covalently with an inactive pharmaceutical agent called a 'conformer'. The advantage of co-crystal enhancement is that any kind of drug, whether acid, base or neutral, can be co-crystallized, unlike salt

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formations which require that the drug must possess certain characteristics. Co crystals are high energy forms and are known to increase solubility of the included drugs due to rapid dissociation in the medium, thus creating a supersaturated drug. [14]

F- solid dispersions

The solid dispersion technique is used to reduce the particle size and thus to increase the dissolution rate of drugs and also to enhance the absorption of drug . Also solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier in solid state and can be prepared by any method or technique of solid dispersion like melting method, solvent method or fusion solvent method. The matrix in a solid dispersion can be either crystalline or amorphous the hydrophilic carriers which are most commonly used for solid dispersions include, polyethylene glycols [polyvinyl pyrrolidone, plasdone S630 .Often ,surfactants may also be used in the formation of solid dispersion include sodium lauryl sulphate, tween-80, docusate sodium, pluronic-F68 and myrj-52. Moreover, the eutectic mixture combination of sulphathiazole/urea and chloramphenicol/urea are served as the examples for preparation of poorly soluble drug in a highly water soluble carrier. [15, 16]

✓ **The fusion (melt) method**

The amounts of carrier(s) are weighed accurately and are placed in an aluminum pan on a hot plate and are liquefied with the constant stirring at about 60°C temperature. Then the accurately weighed active drug is mixed into the molten carrier(s) with stirring to establish homogeneity. This mixture is then heated until a clear homogeneous melt is obtained. Then ,the pan is removed from the hot plate to cool the mixture to room temperature .The limitation of this method is that, at high temperature some drugs may get degraded .[17]

✓ **The solvent method**

In this method, a weighed amount of active drug and carrier(s) are dissolved in a minimum quantity of chloroform in a round bottom flask. Then this solvent is removed by using a rotary evaporator. The obtained solid dispersion is then transferred on to an aluminum pan and is allowed to dry at room temperature .An important requirement for the manufacture of solid dispersion by the use of this technique is that, both drug and carrier should be completely soluble in the solvent.

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents .However, some disadvantages are associated with this method such as: - [18]

- The higher cost of preparation .
- The difficulty in completely removing liquid solvent .
- The possible adverse effect of traces of the solvent on the chemical stability
- The selection of a common volatile solvent .

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- The difficulty of reproducing crystal form

✓ **Dropping method**

A solid dispersion of a molten drug carrier mixture is pipetted and is dropped on to a plate. It then solidifies into round particles. The size and shape of these particles can be affected by factors like the viscosity of the molten mixture and the size of the pipette. As, viscosity is dependent on the temperature, thus it is necessary to adjust the temperature so that when the molten mixture is dropped onto the plate then it solidifies to a spherical shape**.** [19]

✓ **Supercritical fluid process (SCF)**

A supercritical fluid is a dense non condensable fluid which is having greater temperature and pressure than its critical temperature i.e. Tc and critical pressure i.e. Tp. A supercritical fluid (SCF) process allows the micronization of the drug particles within narrow range of the particle size, often to submicron levels. The current SCF processes have revealed the capability to create nanoparticle suspensions of particles having diameter in the range of 5 -200nm .Once the drug particles get solubilized within the SCFs then they may be recrystallized at a greatly are widely particle size. The various methods of SCF processing which are widely employed for micronizing the particles are Rapid Expansion of Supercritical Solutions (RESS) and Gas Anti Solvents Recrystallization (GAS). Both of these methods are used in the pharmaceutical industries. Carbondioxide (CO2) is used as the SCF because of its favorable processing characteristics such as its low critical temperature (i.e .Tc= 31.1.c) and pressure (Pc= 73.8 bar). In RESS there is solubilisation of a drug or drug -polymer mixture in the SCF and then spraying this SCF solution in a lower pressure environment through a conventional nozzle or capillary tube. The rapid expansion undergone by this solution reduces the density of CO2, as a result reducing its solvent power and also supersaturating the lower pressure solution. This super saturation will result in recrystallization and precipitation of the pure drug or the drug-polymer particles of high purity, narrow size distribution and of greatly reduced size. Advantages over other methods are [20]

- Preparation of solid-cyclodextrin complexes in single step process ,
- Achievement of high complexation efficiency (avoidance of excess cyclodextrin in powder.
- Possibility to minimize the contact of drug with cyclodextrin during the process
- Achievement of enhanced dissolution rate of the drug which is comparable to the dissolution behavior of micronized drug cyclodextrin complex).

✓ **Kneading Method**

This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to convert into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then

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dried and passed through a sieve if required. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production. [21]

G- Micronisation

The solubility of drug is related to the drug particle size. When particle size is reduced then it will increase the surface area which leads to the improved dissolution properties of the drug . The various conventional methods which are used for particle size reduction like commination and spray drying depends upon the mechanical stress to break the active compound. The micronization technique is used to enhance the dissolution by increasing surface area but it does not increase equilibrium solubility. Micronization of drugs is achieved by various melting techniques by using jet mill, colloid mill, rotor stator etc .Micronisation is not suitable for those drugs which have a high dose number because micronization does not change saturation solubility of the drugs .[22]

H- Use of buffer

Buffers are used to maintain the pH of solution over the time and also used to reduce or to eliminate the potential for the precipitation which may occur upon dilution. When dilution of a solution is done then pH alteration occurs which results in the decreased solubility. When the pH is changed by 1 fold, it increases the solubility by 10 fold and if it changes by the 1 pH unit, then this will decrease the ionization of drug and the solubility decreases by 10 fold .[17]

2- Advanced technique to improve drug solubility

Nanotechnology Approach to Improve Solubility of Drugs

Nanotechnology is a recently emerged multidisciplinary scientific technology dealing with objects or materials at nanoscale. The nanofabrication techniques of solubility enhancement, whether based on lipoid carriers such as fabrication of liposomes, micro emulsions, Nano-emulsions, or based on polymeric carriers such as fabrication of nanoparticles, Nano-suspensions and Nano-crystals, generally result in enormous increase in surface area of the fabricated Nano-medicines, thereby improving saturated solubility and rate of dissolution. [23]

A- Nano emulsion

Nano emulsions 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 submicron emulsions.

Nano emulsions are composed of oil droplets dispersed in an aqueous medium and stabilized by surfactant molecules. The methods used for the production of Nano emulsions include HPH, micro fluidization, ultra-sonication and spontaneous emulsification. Commercial products that are Nano emulsions include Estrasorb and Flexogan. [24]

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B- Nano suspension

A pharmaceutical Nano suspension is a biphasic system which consists Nano sized drug particles stabilized by the surfactants. These are used either for oral and tropical use or for parenteral and pulmonary administration. Nano suspension technology has been developed as an able candidate for the efficient delivery of hydrophobic drugs. This technique is generally applied to those poorly soluble drugs which are insoluble in both water and oils. The average particle size of solid particles in Nano suspensions ranges between 200 and 600nm. The advantage of this technique is the increase the dissolution rate because of layer surface area exposed as shown in figure (5). [25, 26]

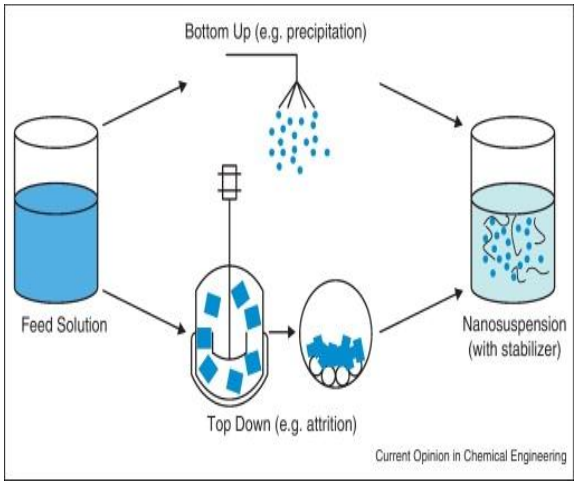

Figure (5): Nano suspension process

C- Liposome

A liposome is a bubble (vesicle) like structure, made out of the same material as a cell membrane. Liposomes filled with drugs, and used to deliver drugs. These are bilayer lipid structure. The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Structurally, liposomes are concentric vesicles in which aqueous volume is entirely enclosed by a membranous lipid bilayer. Membranes are usually made of phospholipids, which are molecules that have a hydrophilic head group and a hydrophobic tail group. The head is attracted to water, and the tail, which is made of a long hydrocarbon chain, is repelled by water as shown in figure (6).

Liposomes are drug delivery for both hydrophilic and hydrophobic drugs. Surface of the liposomal microcapsule can be modified to alter their bio distribution and pharmacokinetic and drug distribution according to their size. Hydrophilic polymers can be grafted with liposomes to certain advantages like reduction of uptake by macrophages. [23]

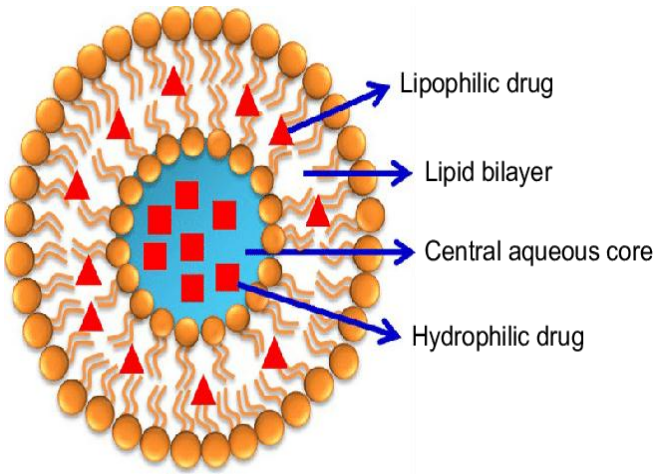

Figure (6): structure of liposome

D- Micro emulsion

A micro emulsion can be defined as a four component system composed of internal phase , external phase, surfactants and co-surfactants. On the addition of surfactant, which is mostly

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soluble in internal phase unlike the co-surfactant will result in formation of an optically clear thermodynamically stable, isotropic emulsion. It is having <0.1-micron droplet diameter, thus termed as micro emulsion .The formation of micro emulsion does not involve he input of any external energy like in coarse emulsions and is very spontaneous. The surfactants and co - surfactant alternate each other and make a mixed film at the interface, which plays a part in the stability of the micro emulsion.

To ensure the immediate formation of oil-in-water droplets during the production. Some non-ionic surfactants with high hydrophilic-lipophilic balance are often used, such as tweens (polysorbates) and labrafil (polyoxyethylated oleic glycerides). Advantages of the micro emulsion over coarse emulsion are: - [27, 28]

- ❖ It is easy to prepare due to spontaneous formation
- ❖ Transparent and elegant appearance
- ❖ Thermodynamic stability
- ❖ Enhanced penetration through biological membranes
- ❖ Increased bioavailability
- ❖ Less intra and inter individual variability in drug pharmacokinetics .

E- Self-micro emulsifying drug delivery system (SMEDDS)

SMEDDS or SEDDS is an important method to enhance the solubility and bioavailability of the poorly water soluble drugs. SMEDDS can be defined as the isotropic mixture of solid or liquid surfactant, natural or synthetic oils, or alternative, one or more hydrophilic solvent and surfactant/co-solvent. SMEDDS form a transparent micro emulsion which have a droplet size of less than 50 nm while SEDDS typically produce an emulsion with a droplet size between (300-100 nm) [29,30]

On a little stirring followed by the dilution in aqueous media like GI fluids ,these systems may form fine oil-in-water emulsions or micro emulsion. Self-emulsifying formulations spread easily in the GI tract and the intestine; and the digestive motility of the stomach provide the agitation necessary for the self-emulsification. SEDDS are physically stable and easy to manufacture. The composition of SEDDS is combination of drugs, oils ,surfactants and co-surfactants or the co-solvent. The self-emulsifying process depends on: - [31]

1- The concentration of surfactant
2- The nature of oil and surfactant
3- The temperature at which self-emulsification occurs .

Conclusion

The solubility of the drug in the GIT is the rate limiting step in the absorption of poorly soluble drugs and hence its bioavailability at its site of action. For this reason, various technologies could be implemented to achieve this goal. The selection of the proper method to increase the solubility of a specific product depends on the properties of the given product, the dosage form requirement and the special

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requirements for both drug and excipients, in addition to the cost and the yield of the given process.

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