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IMPORTANCE OF SOLUBILITY AND SOLUBILITY ENHANCE TECHNIQUE: A REVIEW

Harshada Y. Mahakalkar*, Ashwini L. Patil, Harshal L. Tare

TSPM's, Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India.

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For Correspondence:

Harshada Y. Mahakalkar
TSPM's, Trimurti Institute of Pharmacy, Jalgaon, Maharashtra, India.

ABSTRACT

For a drug to elicit its pharmacological action it should be absorbed from the site of administration. Rate determining step for oral absorption of drug is solubility and dissolution of drug in GI fluid. More than 40% NCE's (New Chemical Entities) developed in pharmaceutical industry are practically insoluble in water and therefore, enhancement of solubility of poorly water soluble drug remain one of the most challenging aspects of drug development. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation and solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

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INTRODUCTION:

The term 'Solubility' is defined as a maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively solubility can be defined as the concentration of the solute in a saturated solution at a certain temperature. Whereas, qualitatively it may be defined as spontaneous interaction of two or more substances toform a homogeneous molecular dispersion. The maximum extent of the solute whichcan be dissolved in a fixed amount of solvent at definite temperature is called as saturated solution and beyond this amount no more solute is taken up by the solution.

The concentration of solute is saturated solution is called as saturation concentration ofthe solution and beyond that it begins to precipitate the excess amount of solute .Thebio-availability of an orally administered drug depends primarily on its solubility in theGIT and its permeability across cell membrane. To transport across biological membrane, drug molecules are required to be present in dissolved form With present day drug discovery techniques, about 40% drugs coming in to the market are Lipophilic and fail to reach therapeutic range due to their poor aqueous solubility Poor aqueous solubility of drug not only limits biological application of drug but also challenge its pharmaceutical development. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas.

Table 1: Solubility criteria as per I.P., 1985, B.P. 2010

Descriptive Term	Parts of Solvent required for 1 part of solute
Very soluble	Less Than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 30 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	Above 10,000

FACTORS AFFECTING THE SOLUBILITY

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. It is the case for most of the solvents. The situation is though different for gases. With increase of the temperature they became less soluble in each other and in water, but more soluble in organic solvents.

Particle size

The changes in the interfacial free energy that accompany the dissolution of particles ofvarying sizes cause the solubility of a substance to increase with decreasing particle size. The size of the solid particle influences the solubility because as a particle becomessmaller, the surface area to volume ratio increases. The larger surface area allows agreater interaction with the solvent. For solids and liquid solutes, solubility not affectedby change in pressure but for gaseous solutes, solubility increases as pressure increasesand decrease as pressure decrease. The solubility dependent bioavailability problem has become a major hurdle in drug development processes. Drug nanocrystals have been widely accepted by the pharmaceutical industry to improve the bioavailability of poorly water-soluble compounds. Top-down and bottom-up technologies are the two primary technical approaches of drug nanocrystal production. Though the top-down approach has been hugely successful on the commercial front, it has some inherent drawbacks that necessitate the emergence of alternate approaches.

pH

If the pH of a solution of either a weakly acidic drug or a salt of such a drug is reduced then the proportion of unionized acid molecules in the solution increases. Precipitationmay occur therefore, because the solubility of the unionized species is less than that ofthe ionized form. Conversely, in the case of solutions of weakly basic drugs or their saltsprecipitation is favoured by an increase in pH. The relationship between pH and thesolubility and pKa value of acidic and basic drugs is given by Eqn,]1[Acidic drugs: pH= pKa + log s-s0/ s0 Basic drugs: pH = pKa + log s 0/ S- s0 Where pKa = dissociation constant of drug, s0 = solubility of unionised form, moles/litre, S=overall solubility ofdrug, moles/litre.

3.4. Dielectric Constant

The solubility is a function of dielectric constant of polar and nonpolar medium. Mostoften, with hydrophobic drugs, the solubility decreases with increasing dielectric
constant .

Molecular size

The larger the molecules of the solute are, the larger is their molecular weight and their size. It is more difficult it is for solvent molecules to surround bigger molecules. If all of the above mentioned factors ale excluded, a general rule can be found that larger particles are generally less soluble.

Polarity

In most cases solutes dissolve in solvents that have a similar polarity. Chemists use a popular aphorism to describe this feature of solutes and solvents: "Like dissolves like". Non-polar solutes do not dissolve in polar solvents and the other way round.

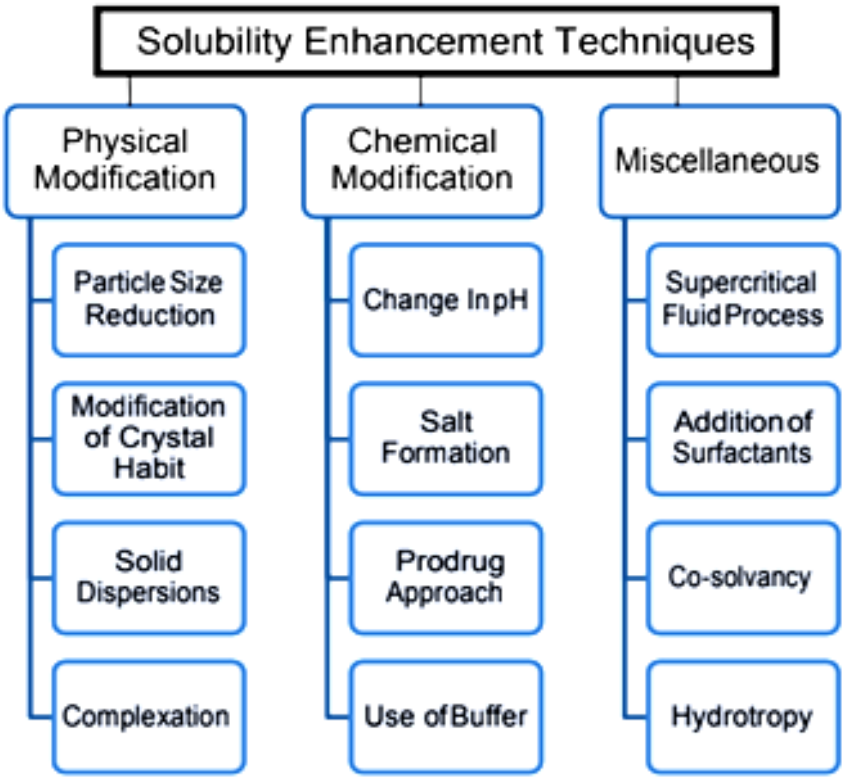

Fig. 1: Techniques used to enhance solubility of poorly soluble drugs

Physical Modification : Among various techniques for solubility enhancement, physical modifications ofdrug product such as reduction of particle size and modifying crystal habit are commonapproaches to increase drug solubility.

Modifications Chemical : Change of ph, use of buffer, derivatization, complexation, and salt formation. Miscellaneous Methods Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

Microniazation

Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubilityand dissolution velocity of the drug. Micronization technique is used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Particle size reduction methods include recrystallization of the solute particles from solutions using liquid antisolvents, along with labor intensive techniques like crushing, milling, grinding, freeze drying and spray-drying. The rapid expansion of supercritical solutions (RESS) is an alternative technique for the micronization of particles using supercritical carbon dioxide to quickly and naturally reduce the particle sizes of various drugs.

Nanosuspension :

Nanosuspension are sub micron colloidal dispersions of pure particles of drug which are stabilized by surfactants. Increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient.

Various particle technologies, from conventional size reduction methods to recent novel methods that can be used for formulating drugs with poor aqueous solubility as

Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction .

Techniques For the Production of Nano-Suspensions :

Wet Milling :

Active drug in the presence of surfactant is defragmented by milling.

Table 2: Particle technologies to improve the solubility of some drugs

Particle Technologies	Method	Example Drugs
Mechanical Micronization	Jet milling Ball milling	Cilostazol , Ibuprofen Danazol, Carbamazepine, Dipyridamole, Indomethacin
Particle size reduction by novel particle engineering	Cryogenic spraying process	Danazol,carbamazepine,Glibenclamide
	Spray drying, *in situ* salt formation solidification with polymers	Nimodipine, Dexibuprofen , Curcumin , I buprofen
Complexation with cyclodextrins	Freeze drying . vaccum evaporation, kneading	Celecoib, Clotrimazole, Bifonazole
Polymeric micelles	Dialysis, freeze drying	Paclitaxel, Etoposide, Ecetaxel , Amphotericin-B

Other technique involves the spraying of drug solution in volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation results in precipitation of drug in thepresence of surfactant. Drying of Nano-Suspension can be done by lyophilisation and spray drying.

Homogenization :

Drug particles are reduced under high pressure and high velocity by applying of shear force. By this phenomenon drugs particles get dispersed. Homogenization depends on pressure and nature of drug. Three types of homogenizersare used in pharmaceutical and biotechnology industries conventional homogenizer,sonicators and high shear fluid processors.

Novel Techniques :

Although conventional size reduction techniques are convenient and simple, they are sometimes undesired and unfavourable depending upon the types of drug substancesand the particles to be micronized. Conventional methods of size reduction are usuallyknown to have certaintypical disadvantages of being less efficient due to high energyrequirement, posing threats of thermal and chemical degradation of drugs and the endproducts being not uniform in the particle size distribution.

To overcome theselimitations and to specifically control the particle properties, several particle engineeringtechniques have been developed as an alternative and are utilized to produce the requiredparticle size and carefully control the particle properties. These novel particle engineering technologies such as cryogenic engineering technologies such as cryogenic spray processes is the novel method of producing nano size drug particles as an attempt to reduce particle size and enhance solubility, dissolution and hence the bioavailability of drugs with poor aqueous solubility.

Jet milling

A fluid jet mill uses the energy of the fluid (high pressure air) to achieve ultra fine grinding of pharmaceutical powders. It has several advantages of being a dry process, size reduction of micron-sized particles with narrow size distributions, absence of contamination and is suitable for heat sensitive drugs. In a study conducted by Jinno etall the in vitro dissolution rate of a poorly soluble drug cilostazol was improved by milling and a moderate enhancement of bioavailability was observed in absorption fromcilostazol suspension produced by jet milling.As the jet pressure increases, more amount of MnBi phase decomposes into Bi and Mn phases. The weight fraction of MnBi phase decreases from 81%, for the starting powder, to 43% by increasing the milling pressure to a high value of 80 psi. Particle size decreases rapidly to about 1 µm on jet milling and even though the average particle size does not change noticeably with further increase of milling pressure, the particle size distribution appears to be different. Moderate milling pressure has resulted in powders with narrow particle size distribution, low decomposition of MnBi phase and smooth demagnetization curves.

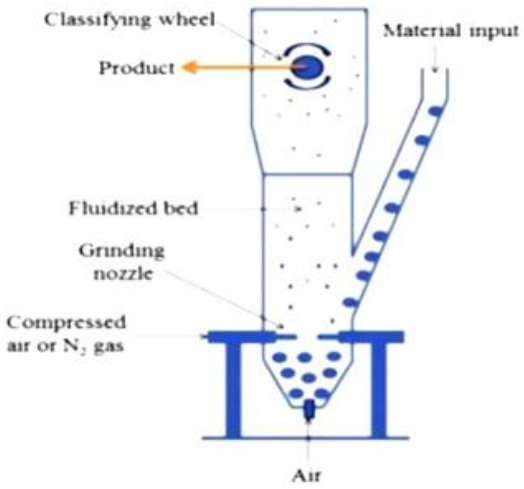

Fig. 2: Fluidized bed elements

Ball milling

A pharmaceutical ball mill is usually a cylindrical crushing device that is used for grinding of pharmaceutical powders by rotation around a horizontal axis. The device is partially filled with the material to be ground plus the grinding medium usually ceramic balls, flint pebbles or stainless steel balls. Back in 1995, Liversidge and Cundy reported that ball milling could be used for preparing nanoparticulate formulation of a poorly water soluble drug, danazol, which showed enhanced bioavailability in beagle dogs whencompared to that of aqueous suspension of conventional danazolparticles . Ball millingtechnique for size reduction is also essential in preparing amorphous powders of drugs ifmilled together with polymeric compounds as suggested by Patterson et al. in 2006. Preparing amorphous form is an essential approach to improve dissolution of drugs sincethe amorphous state are more readily soluble than the crystalline form because of higherGibbs free energy in the amorphous form . In their work, Patterson et al. used threepoorly water soluble drugs (carbamazepine, dipyridamole and indomethacin) with apolymer polyvinyl pyrrolidone K30 (PVP K30) at a 1:2 drug polymer ratio to prepareglass solutions of the drugs. The glass solution was referred to an amorphous solid inwhich the solute (drug) was dispersed in the solid solvent (polymer) on a molecular level. Use of a ball mill to prepare the glass solutions was found to be effective in producing asingle homogenous amorphous phase, and the dissolution rates were also found to behigher when compared to the glass solutions of the same drugs prepared by spray drying.

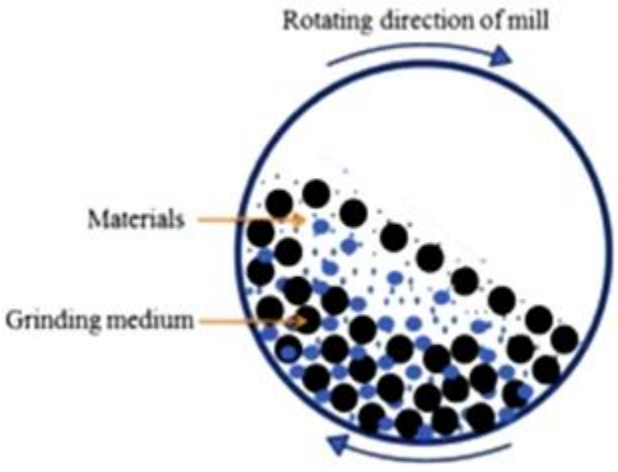

Fig. 3 Ball Mill

High pressure homogenization

High pressure homogenization (HPH), a top down technology, is a widely used technique for preparing nanosuspensions of drugs with poor water solubility. Its use hasbeen reported to improve the dissolution rate and bioavailability of several poorly watersoluble drugs such as spironolactone, budesonide and omeprazole by effective sizereduction to the nanosizerange . HPH has also been known to overcome the drawbacksof conventional size reducing methods such as amorphization, polymorph transformationand metal contamination due to high mechanical energy associated with conventionalmilling processes. Due to this reason, HPH is particularly advantageous for comminutionof drug particles. In HPH, the solid to be comminuted is first dispersed in a suitable fluidand then forced under pressure through a nanosized aperture valve of a high pressurehomogenizer, which is essentially a bottleneck through which the suspension passes witha high velocity, and then suddenly experiences a sudden pressure drop, turbulent flowconditions and cavitation phenomena . Thus comminution of particles is achieved bycollision of particles with each other, collision with the homogenizer and by cavitationand the two factors that influence homogenization in this process are the pressure dropand the number of passes across the homogenizer.

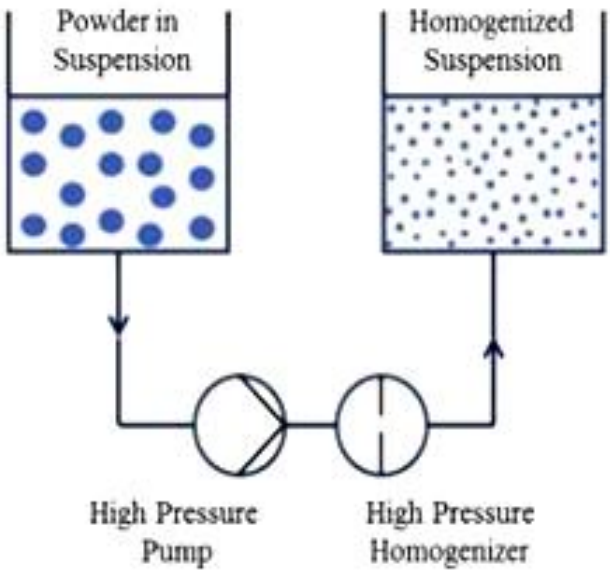

Fig. 4: High Pressure Homogenizer

Modification of Crystal Habit or Crystal Engineering:

The surface area of drug available for dissolution is dependent on its particle size and ability to be wetted by luminal fluids. This particle size, Which is critical to drug dissolution rate, is dependent on the condition of crystallization or an methods of communication such as impact milling and fluid energy milling.(16) Particles produced by communication technique are highly charged, non uniform and can produce agglomerates. Hence, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powder with well defined particle size distribution.

Pharmaceutical Co-Crystals :

A Co-Crystal may be defined as a crystalline compound that consist of two or more molecular species held together by non-covalent bond. Only three Co-crystalizing agents are considered as safe. Saccharin, Nicotinamide and Acetic Acid (16). Example :Carbanazepineasccharin co-crystal was shown to be superior to crystal forms of carbamazepine alone in terms of stability, dissolution, suspension stability and oral absorption profile.

Solid Dispersions :

Solid Dispersion (SD) Technology is the science of dispersing one or more active ingredients in an inert matrix in t solid dispersions were first described by sekiguchi andobi in 1961 in which they used concept of eutectic mixtures (17). It refers to a group of asolid products consisting of at least two components, a hydrophilic matrix and ahydrophobic drug. The matrix can be either crystalline or amorphous; basically amorphous is having good solubility than crystalline substance because no energy isrequired to break up the crystal lattice of a drug during dissolution process. Drug solubility and wet ability may be increased by surrounding hydrophilic carriers.

Types of Solid Disper

Based on their molecular arrangement, four different types of solid dispersions can distinguished. They are described below.

1. Eutectics
2. Amorphous precipitations in crystalline matrix
3. Solid solutions

a. Continuous solid solutions

b. Discontinuous solid solutions

c. Substitutional solid solutions

d. Interstitial solid solutions

e. Glass suspensions and solutions

Eutectic Mixtures

Eutectic mixtures are formed by the drug and polymer is miscible in their molten state,but on cooling, they crystallize as two distinct components with negligible miscibility. Inthis type of solid dispersion a drug .

Amorphous precipitation in crystalline matrix

In this type within the amorphous solvent the solute molecules are dispersed irregularlyand molecularly. In earlier studies other carriers were used in this type of dispersion suchas urea and sugars (sucrose, galactose and dextrose). But now a day's cellulosederivatives and organic polymers are used (PVP, PEG etc). To plasticize the polymervarious solute molecules are used. The reduction in glass transition temperature is due tosolutes which are used to mould the polymer.

Solid solutions:

In a solid solution the two components are crystallize together in a homogeneous onephase system. The particle size of the drug in the solid solutions is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, the solid solutions may beclassified as continuous or discontinuous

Chemical Modifications:

1. **Change in pH :**

The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastro intestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization (17). Poorly water soluble drugs with the parts of the molecule that can be protonated (Base) ordeprotonated (Acid) may potentially be dissolved in water by applying a pH change Hadjustment can in principle be used for both oral and parenteral administration (17). Ionised form of

drug is responsible for solubility in water. Since, Most drugs are weak Electrolytes their degree of ionisation depends upon the pH of the biological fluid.

Pro Drug Approach:

Salt information is limited to molecules with ionisable groups, however pro drugs may be formed with any organic molecule having a chemically reactive functional group,Pro drugs are synthetic derivatives (e.g. Esters and amide) of drug molecules that mayhave intrinsic pharmacological activity but usually must undergo some transformationIn-vivo to liberate the active drug molecule. Through the formation of pro drug, a varietyof side chains or functional groups may be added to improve the biological orpharmaceutical properties of compound . In 1980, Amidon suggested the making ofwater soluble pro drugs by the addition of specific amino acids that are the substrates for enzymes located in intestinal brush border. Using the lysine ester pro drug of estrone, potential increase in absorption rate was found in vivo using perfused rat intestines.

CONCLUSION:

Solubility if drug is one of the important factors that governs the formulation development particularly for the rate and extent of drug to be absorbed. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. These techniques along or in combination can be used to enhance the solubility of drug and thereby bioavailability. Proper selection of solubility enhancement method is the key to ensure the goals of good formulation.

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