CODEN (USA): IJPB07 ISSN: 2320-9267
Indian Journal of Pharmaceutical and Biological Research (IJPBR)
Journal homepage: www.ijpbr.in

Review Article DOI: https://doi.org/10.30750/ijpbr.7.2.2

Solubility Enhancement Techniques for Poorly Soluble Pharmaceuticals: A Review

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ARTICLE INFO:

Article history:
Received: 18 March 2019
Received in revised form:
20 May 2019
Accepted: 30 May 2019
Available online: 30 June 2019

Keywords:
Solubility,
Bioavailability,
Dissolution rate.

ABSTRACT

Among newly discovered chemical entities about 40% drugs are hydrophobic which are failed to reach market due to their low aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response.Drug efficacy can be limited due to poor aqueous solubility and some drugs also show side effects like gastric irritation, peptic ulcers,due to their poor solubility**.** Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes challenging. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the new formulation development.

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. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[1]

Solubility occurs under dynamic equilibrium, whichmeans that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs whennthe 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 Solubility and permeability is the deciding factor for the *in-vivo* absorption of the drug, these can be altered or modified by enhancement techniques.[3]

According to IUPAC, solubility may be defined as "the analytical composition of a saturated solution, expressed in terms of the proportion of a designated solute in a designated solvent, is the solubility of that solute.[4]

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes being the important ones. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellarsolubilization, hydrotropy, etc. Actually, only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.[5]

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10

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Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

PROCESS OF SOLUBILIZATION

The process of solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.[12] Solubilization process occurs into three steps (Figure 1).[6]

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.

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.

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. 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.

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 solubilities of these two substances is the result of differences in their nature.

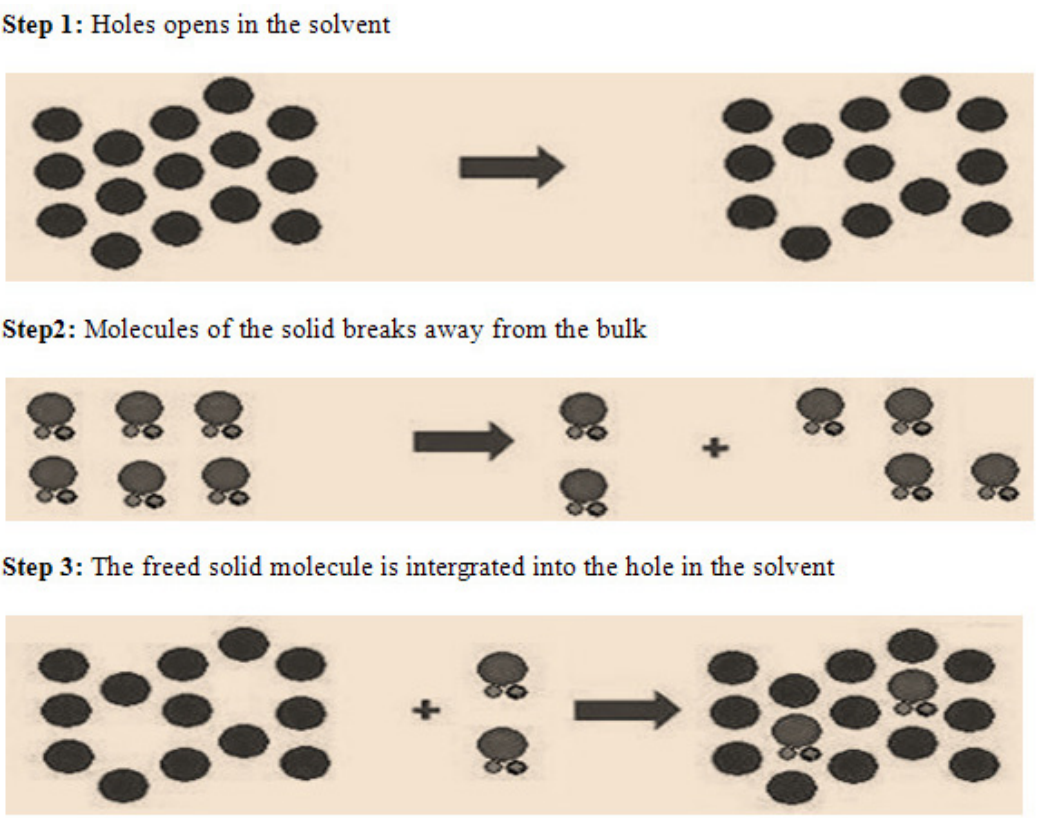

Figure 1: Process of solubilization

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 tosolvate 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 .

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.[9]

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.[7]

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

Physical Modifications.

Particle size reduction like micronization and nanosuspension ,modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and 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, hydrotrophy, and novel excipients.[2]

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 a greater interaction with the solvent which cause increase in solubility.

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during scomminution and spray drying is also a concern when processing thermosensitive or unstable active compounds. Also, this traditional methods are often incapable of reducing the particle size of nearly insoluble drugs (< 0.1 mg/mL).

Micronization is another conventional technique for the particle size reduction. Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility.[5] Decreasing the particle size of these drugs which cause increase in surface area, improves their rate of dissolution. 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.

These processes were applied to griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. For each drug, micronization improved their digestive absorption, and consequently their bioavailability and clinical efficacy.[8]

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 increases 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 pay load

without encouraging agglomeration may be technically challenging.

- Technically, development of sterile intravenous formulations is even more challenging.[5]

SOLID DISPERSION

Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (povidone, PVP), polyethylene glycols (PEGs), Plasdone- S630. Surfactants like tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion. The solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) and ritonavir with gelucire.

Various techniques to prepare the solid dispersion of hydrophobic drugs with an aim to improve their aqueous solubility are listed here .

Hot-Melt Method (Fusion Method)

The main advantages of this direct melting method is its simplicity and economy. In this method, the physical mixture of a drug and a water-soluble carrier are heated directly until the two melts. The melted mixture is then cooled and solidified rapidly in an ice bath with vrigorous stirring. The final solid mass is then crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agents. The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system . An important requisite for the formation of solid dispersion by the hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of both the drug and the carrier.

Solvent Evaporation Method

Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water soluble carrier povidone. The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents. However, the disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing the organic solvent (a regulatory perspective), the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the selection of a common volatile solvent, and the difficulty in reproducing crystal forms .

Hot-Melt Extrusion

Hot-melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.[2]

COMPLEXATION

Physical Mixture

Active drug with suitable polymer in different ratios mixed in a mortar for about one hour with constant trituration. The mixture is passed through sieve no. 80 and stored in dessicator over fused calcium chloride.

Kneading Method

Active drug with suitable polymer in different ratios is added to the mortar and triturated with small quantity of ethanol to prepare a slurry. Slowly the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at 25°C for 24 hours. The resultant product is pulverised and passed through sieve no. 80 and stored in dessicator over fused calcium chloride.[10]

Co-Precipitate Method

Active drug is dissolved in ethanol at room temprature and suitable polymer is dissolved in distilled water. Different molar ratios of active drug and suitable polymers are mixed respectively. The mixture is stirred at room temprature for one hour and the solvent is evaporated. The resultant mass is pulverised and passed through sieve no. 80 and stored in a desiccators.[9]

COLSOLVENTS

Cosolvent system is a mixture of miscible solvents often used to solubilize lipophilic drugs. Currently, the water-soluble organic solvents are polyethylene glycol 400

(PEG 400), ethanol, propylene glycol, and glycerin. For example, procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400, and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides (i.e., peanut oil, corn oil, soybean oil, sesame oil, olive oil, peppermint oil, hydrogenated vegetable oil, and hydrogenated soybean oil), medium-chain triglycerides (Miglyol 812), beeswax, d-α- tocopherol (vitamin E) and oleic acid. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil.[10]

Co-solvency techniques have also found use in spray freezing of liquidlike in danazol with polyvinyl alcohol, poloxamer 407, and poly vinyl pyrrolidone K-15 in a micronized powder formulation. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophillic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Co-solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Very high drug concentrations of poorly soluble compounds can be dissolved compared to other solubilization approaches. Though co-solvency has been highly utilized in the design of many different formulations, it has found its main use in parenteral dosage forms because of theirritating effects of most surfactants and the low toxicity of many co-solvents, and because of the relatively greater ability of co-solvents tosolubilise nonpolar drugs. The most frequently used low toxicity co-solvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol. The use of co-solvents is a highly effective technique to enhance the solubility of poorly soluble drugs .

Co-solvents may be combined with other solubilization techniques and pH adjustment to further increase solubility of poorly soluble compounds.[6]

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.[5]

HYDROTROPY

Hydrotropy describes the increase in the solubility of a less soluble solute by the addition of fair concentrations of alkali metal salts of various organic acids. Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. Essentially the anionic group increases the hydrophilicity and the ring system interacts with the solute to be dissolved.[11] Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water soluble drugs.[12]

SUPERCRITICAL FLUID (SCF) PROCESS

The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that super critical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used super critical fluid. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.[13-16] An SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility, and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently been adapted to pharmaceutical applications. Commonly used supercritical

solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n pentane, ethanol, ammonia, and water.[5]

MANIPULATION OF SOLID STATE

From the stability and bioavailability aspects, the crystalline form of a drug is of pharmaceutical importance. Polymorphism (existence of a drug substance in multiple crystalline forms) can cause variations in melting point, density, stability, and drug solubility as these properties depend on the escaping tendency of the molecules from a particular crystalline structure.[17-21] As a rule, for a drug that have the highest order of crystallinity is the most stable form, exists in multiple polymorphic forms, i.e., with the least amount of free energy, and, consequently, possesses the highest melting point and the least solubility. By controlling the crystallization process, amorphous or meta stable forms of drugs possessing high free energy can be forcibly created. They offer the dvantage of higher solubility but suffer from stability issues unless stabilizers intended to inhibit crystal growth are incorporated in the formulation. A high profile case involving polymorphism was withdrawal of ritonavir (Norvir®) capsules from the market in 1998 because a less soluble (and consequently less bioavailable) polymorph was identified two years after the product was approved and marketed, causing a decrease in bioavailability of the drug.[22-26] This incident sensitized the pharmaceutical industry to the critical importance of polymorphism and encouraged the inclusion of polymorph screening as a routine component of preformulation studies.[7]

NANOSUSPENSION

Nanosuspension technology has been developed as a promisingcandidate for efficient delivery of hydrophobic drugs.This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspensionis a biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nano suspensionsis usually less than one micron with an average particle size ranging between 200 and 600 nm .

Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, high pressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high-Pressure homogenization.

Precipitation Technique

In precipitation technique the drug is dissolved in a solvent, which is then added to antisolvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments; but the challenge is the addition of the growing drug crystals to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be iscible with antisolvent. Moreover, precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueousmedia .Nanosuspension of Danazol and Naproxen have been prepared by precipitation technique to improve their dissolution rate and oral bioavailability. The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately 4-fold.

Media Milling

The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug, and stabilizer is rotated at a very high-shear rate under controlled temperatures for several days (at least 2–7 days). The milling medium is composed of glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug esulting into breaking of microparticulate drug to nanosized particles.

High Pressure Homogenization

High-pressure homogenization has been used to prepare nanosuspension of many poorly water soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitations forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The concern with this method is the need for small sample particles before loading and the fact that many cycles of homogenization are required. Dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole have been improved by reducing their particle size by high pressure homogenization.

Combined Precipitation and Homogenization

The precipitated drug nanoparticles have a tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (homogenisation). They are in completely amorphous, partially amorphous or completely crystalline forms which create problems in long term stability as well as in bioavailability, so the precipitated particlesuspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.[27-32]

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Cite this article: **Jyoti Gupta, Anjana Devi.** Solubility enhancement techniques for poorly soluble pharmaceuticals: a review. **Indian J. Pharm. Biol. Res. 2019;7(2):9-16.**