Review Article Sharma *et.al.*, 8(12): Dec., 2017:5679-5686]
CODEN (USA): IJPLCP **ISSN: 0976-7126**

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

A review on different techniques used for solubility enhancement of poorly water soluble drugs

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Abstract

Solubility of drug plays major role in the process of formulation development. Solubility is the amount of solute that goes in to the solvent to form solution at given conditions of temperature, pressure and pH. Low aqueous solubility is the major problem associated with poorly water soluble drugs. Water is always the solvent of choice for liquid pharmaceuticals formulations. Most of the drugs are weakly acidic or weakly basic with poor aqueous solubility. About 40% of the drugs from newly developed chemical entities currently being discovered are poorly water soluble. The biopharmaceutical classification system of drugs suggests low water solubility, poor dissolution, and low bioavailability of Class II and IV drugs. This review article explain the various techniques used to enhance solubility of poorly water soluble drugs such as complexation of drugs, use of cosolvents, preparation of polymeric fast dissolving film, solid dispersion techniques, polymeric micelles, emulsion formation, polymeric micelles, microemulsions, pharmaceutical salts, nanomorph technology, pro-drugs, particle size reduction technologies.

Key words: Solubility enhancement techniques, BCS class II & class IV drugs.

Introduction

Solubility of drugs plays major role in the process of formulation development and pharmacological performance of drugs inside the body. The solubility is expressed as a concentration, either by mass (g of solute/kg of solvent, g/dl (100ml) of solvent), molarity, molality, mole fraction, or other similar descriptions of concentration. The maximum equilibrium amount of solute that can dissolve per amount of solvent is the solubility of that solute in that solvent under the specified conditions.[1,2]

Modern fusion chemistry and screening techniques commonly used in drug discovery have increased the numbers of drug molecules with high molecular weight, higher lipophilicity, and poorer aqueous solubility. The Biopharmaceutical classification system (BCS) of drug substances based on its aqueous solubility and intestinal permeability has been shown in table-1.[3] Currently, 90% of the new chemical entities (NCEs) filling belong to the poorly water soluble BCS Class II and IV.

Poor aqueous solubility drug candidates often leads to poor absorption and bioavailability from the gastrointestinal (GI) tract, which presents the formulation scientists with considerable challenges when trying to deliver these drug molecules via oral route. The active drug must first dissolve in the GI fluids before it can diffuse through the GI tract membranes and then reach systemic circulation for drug absorption.

Table-1 Biopharmaceutical classification system of drugs with suitable examples.

Class I	Class II
• High permeability • High solubility Eg. Abacavir, Doxycycline, Metronidazole, Propranolol	• High permeability • Low solubility Eg. Felodipine, Carvedilol, Telmisartan, Tadalafil

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Class III	Class IV
• Low permeability • High solubility Eg. Atenolol, Captopril, Cloxacillin, Famotidine	• Low permeability • Low solubility Eg. Amphotericin, Furosemide, Methotrexate, Neomycin

TECHNIQUES/METHODS OF SOLUBILITY ENHANCEMENT

1. 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 spray drying, rely upon mechanical stress to disaggregate the active compounds.[4] The effect of particle size on solubility can be described by equation

$$\log \frac{S}{S_0} = \frac{2\ \gamma\ V}{2.303\ R\ T\ r}$$

Where, S_0 is the solubility of infinitely large particles, S is the solubility of fine particles, V is molar volume, r is the radius of the fine particle and D is the surface tension of the solid.

a) Micronization is a conventional technique used for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area; it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[5]

b) Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is 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 distributions of the solid particles in nanosuspensions are usually less than one micron with an average particle size ranging between 200-600nm.[6] Different methods utilized for preparation of nanosuspensions along with their merits and demerits are shown in table-2.

Table-2 Merits and demerits of methods of preparation of nanosuspension

Technology	Merits	Demerits
Precipitation	Simple, Ease of scale up	Growing of crystals needs to be limit by surfactant addition. Drug must be soluble at least in one solvent.
Emulsion/ Microemulsion Template	High drug solubilization Long shelf life. Ease of manufacture	Use of high amount of surfactant and stabilizers. Use of hazardous solvent in production.
High Pressure Homogenization	Applicable to most of drug Very dilute as well as highly concentrate. Aseptic production possible.	High number of homogenized cycle. Drug should be in micronized state. Possible contamination from metal ions coming off from the walls.
Media Milling	Applicable to the drugs that are poorly soluble in both aqueous and organic media. Little batch to batch variation. High flexibility in handling large quantities of drugs.	Contaminated with materials eroded from balls. Time consuming. Difficult to scale up. Prolonged milling may induce the formation of amorphous and instability.

2. Solid dispersion:

The term solid dispersion refers to a group of solid products consisting of at least two different compounds, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[7] Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. drug polymer miscibility and stability) pharmacokinetic (e.g. rate of absorption) constraints.[8] Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting-solvent method.

a) Melting Method

Melting method consisting of melting the drug within the carrier followed by cooling and pulverization of the obtained product. In the melting process, the molecular mobility of carrier is high enough to change the drugs incorporation.[8] A common adaptation to the melting phase consist of suspending the active drug in a previously melted carrier ,instead of using both drug and carrier in the melted state, reducing, therefore the process temperature.[9] To cool and solidifying the melted mixture, several processes such as ice bath agitation stainless steel thin layer spreading followed by a cold drought, solidification on petri dishes at room temperature inside a desiccators, spreading on plates placed over dry ice immersion in liquid nitrogen or stored in a desiccators were used. After cooling the mixture must be pulverized regarding its handling. However, use high temperatures, and the fact that several drugs can be degraded by melting process, can be a limitation of this method.[10]

b) Hot melt extrusion (HME)

It can be simply defined as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder.[11]

c) Solvent evaporation method

In solvent evaporation method we dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution.[12] Dissolve the drug (β-carotene and the carrier PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Commonly use solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some case cosolvant may use because large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. 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. The disadvantages of solvent method such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form.[13]

d) Dropping method

A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.[14]

3. Cosolvency:

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.[15]

4. Hydrotropy:

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of existing 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.[14]

5. Solubilisation by surfactants:

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilisation is very important in industrial and biological processes. The presence of surfactants may lower the surface tension

but increases solubility of drug within an organic solvent.

6. Fast dissolving film/strip:

Fast-dissolving film/strip is new drug delivery system for the oral delivery of the drugs. These are the most advanced forms of oral solid dosage forms due to more flexibility and comfort. It improves the efficacy of drugs by dissolving within a minute in oral cavity after the contact with saliva without chewing or necessitating water for administration. It gives quick dissolution, absorption and instant bioavailability of drugs due to high blood flow and permeability of buccal mucosa is 4-1000 times greater than that of skin.

7. High pressure homogenization (HPH):

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity. Homogenization can be performed in water or alternatively in nonaqueous media or water-reduced media. The particles are disintegrated by cavitations and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature. The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

8. pH adjustment:

Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.[16]

9. Supercritical fluid technology (SCF):

A supercritical fluid is a substance at a temperature and pressure above its critical point, where distinct liquid and gas phases do not exist. Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. Generally supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas anti-solvents recrystallisation (GAS).

a) Rapid expansion of supercritical solutions (RESS)

It is dissolved in a supercritical fluid (such as supercritical methanol) and then through a small nozzle, the solution is rapidly expanded into a region lower pressure and thus the solvent power of supercritical fluids decreases and the solute eventually precipitates. This technique is basically solvent free, so this is a clean technique. This modified process is used for the production of polymeric nanoparticles.[16]

b) Gas anti-solvents recrystallisation (GAS)

A liquid solvent is required in the process of GAS to dissolve the solute to be micronized; at the process conditions, because the solute is insoluble in the supercritical fluid, the liquid solvent should be completely miscible with the supercritical fluid (SC CO_2), e.g. methanol. The extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute. The SCF process can create nanoparticle of particles 5–2000nm in diameter.

10. Spray drying techniques:

a) Preparation of microparticles by spray drying

Spray dried particles consisted of active drug only and drug/suitable polymer in different ratios are prepared by dissolving the drug or drug/polymer mixture in ethanol/water solution. The solution is spray dried using Mini Spray Dryer. The formed microparticles are separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

b) Preparation of microparticles by spray chilling

Spray chilled particles are prepared by melting the drug or drug/suitable polymer mixture in different ratios at 90°C. The melt is kept at 90°C and atomised with a specially constructed pneumatic nozzle into air kept at 20°C. The particles are collected using cyclone separator and stored in a desiccator.[17]

11. Sonocrystallisation:

Recrystallization of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is sonocrystallisation. Sonocrystallisation utilizes

ultrasound power characterized by a frequency range of 20–100 kHz for inducing crystallization. Its not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz.[18]

12. Complexation:

a) 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 desiccator over fused calcium chloride.

b) 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 24hrs. The resultant product is pulverised and passed through sieve no. 80 and stored in dessicator over fused calcium chloride.[19]

c) **Co-precipitate method**

Active drug is dissolved in ethanol at room temperature 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 temperature for one hour and the solvent is evaporated. The resultant mass is pulverised and passed through sieve no. 80 and stored in a desiccator.[20]

13. Microemulsion:

Micro emulsion is known as a system of water, oil which is thermodynamically stable liquid solution. A micro emulsion can be divided of four component system such as internal phase, external phase, surfactant and cosurfactant, Non-ionic surfactant like labrafil and tweens with high hydrophile-lipophlie balances which are used to formation of oil-in water droplets during the production. In micro emulsion technique, many equipment are used such as water bath, stirring rod, volumetric flask and homogenizer. Micro emulsion is known as the isotropic, clear pre concentrate, thermodynamically stable translucent system which is containing a mixture of oil, hydrophilic solvent and hydrophilic surfactant dissolved in a poorly water soluble drug.[21]

14. Self emulsifying system:

SEDDS or SMEDDS are the important method to improve the solubility and bioavailability of poorly water soluble drug. SEDDS are define as isotropic mixture natural or synthetic oils, solid or liquid surfactant, or alternative, one or more hydrophilic solvent and co-solvent/surfactant.[22] SEDDS typically produce emulsions with a droplet size between 100–300nm while self-micro-emulsifying drug delivery systems (SMEDDS) form transparent micro-emulsions with a droplet size of less than 50 nm. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil−in−water (o/w) emulsions or micro-emulsions (SMEDDS). Self-emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture.

Composition of SEDDS: The composition of self emulsifying system is simple combination of drug, oils, surfactant and co surfactant or co-solvent. The self-emulsifying process depends on:

- The nature of the oil and surfactant
- The concentration of surfactant
- The temperature at which self-emulsification occurs.[23]

15. Neutralization:

Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β- Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.[24]

16. Cryogenic method:

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low-temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N_2, or, O_2, and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation.

17. Liquisolid technique:

The liquisolid technique is a novel concept where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained.[25]

18. Inclusion complexes:

It is formed by the inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes. Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrine and their derivatives commonly use in complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug.[26] Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation.[27,28] Solid inclusion complexes can be prepared by using following methods:

a) Kneading method

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

b) Lyophilisation/ Freeze drying technique

Lyophilisation/ freeze drying technique is considered as a suitable technique to get a porous, amorphous powder with high degree of interaction between drug & CD. This technique is suitable for thermo labile substances. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure is form.

c) Microwave irradiation method

In this technique the microwave irradiation reaction between drug and complexing agent takes place using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60ºC in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40ºC for 48 hrs. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product.

Conclusion

Several techniques discussed above can be used alone or in combination to enhance the solubility of the poorly water soluble drugs. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior. This review interpreted that enhancement of solubility of poorly water soluble drugs is an important concept to increase their gastrointestinal absorption, thus to improve their bioavailability and pharmacological responses.

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How to cite this article
Sharma P., Darwhekar G.N., Sharma P.K. and Shrivastava B. (2017). A review on different techniques used for solubility enhancement of poorly water soluble drugs. *Int. J. Pharm. Life Sci.*, 8(12):5679-5686.
Source of Support: Nil; Conflict of Interest: None declared

Received: 05.10.17; Revised: 16.11.17; Accepted: 01.12.17