WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 13, 265-282. Review Article ISSN 2277– 7105

SOLUBILITY ENHANCEMENT TECHNIQUES

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Article Received on
24 August 2020,

Revised on 13 Sept. 2020,
Accepted on 03 Oct. 2020,

DOI: 10.20959/wjpr202013-18931

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ABSTRACT

Solubility is the property of a solid, liquid, or gaseous chemical substances called solute to dissolve in a solid, liquid, or gaseous to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depend on the solvent used as well on temperature and pressure the extend of solubility of a substance in a specific solvent is measure as the saturation concentration. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining. Solubility is not to be confused with the ability may be dissolve or liquefy a substance only because of a chemical reaction. Aqueous solubility is the concentration of the aqueous phase, when the solution is in equilibrium with the pure compound in its usual phase. Solubility is based on the highest dose strength of an immediate release product. Various techniques have been used for the enhancement of solubility of poorly soluble drug which include physical and chemical modification of drug and other methods like particle size reduction, crystal engineering, salt formation use of surfactant and so forth. Solubility is the one of the important parameters to achieve desired concentration of drug in systemic circulation. Drug efficacy due to their poor solubility.

KEYWORDS: Solubility, Drugs, Crystallization, Hydrotrophy.

INTRODUCTION

Solubility is the property of a solid, liquid, or gaseous chemical substances called solute to dissolve in a solid, liquid, or gaseous to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depend on the solvent use as well on

temperature and pressure the extent of solubility of a substance in a specific solvent is measure as the saturation concentration where adding more solute does not increase its concentration in the solution.[1] The solvent is generally a liquid, which can be a pure substance or a mixture of two liquid. One may also speak of solid solution, but rarely of solution in a gas. The extend of solubility ranges widely, from infinity soluble (fully miscible) such as ethanol in water, to poorly soluble compounds.[2]

Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (eg, precipitation of solids). Solubility equilibrium occurs when two processes proceed at a constant rate.

Definition of solubility

Solubility is a chemical property referring to the ability for a given substance, the solute, to dissolve in a solvent. It is measured in terms of the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. Solubility is not to be confused with the ability may be dissolve or liquefy a substance, since these processes may occurs not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but dose dissolve in it by chemically reacting in zinc chloride and hydrogen, where zinc chloride is insoluble in hydrochloric acid. Solubility dose not also depend on particles size or other kinetic factors.[4]

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent solubility may be stated in unit of concentration, molality, mole fraction, mole ratio, and other units.[5]

Extensive use of solubility from different perspective has led to solubility being expressed in various manners. This is commonly expressed as a concentration, either by a mass (g of solute per kg of solvent, g per dL (100ml) of solvent), molality, mole fraction, or other similar description of concentration. The maximum equilibrium amount of solute that can dissolve per amount of solvent. The solubility of that solute in that solvent under the specified conditions.[6]

The advantage of expressing solubility in this manner is its simplicity, while the disadvantage is that it can strongly depend on the presence of other species in the solvent (eg, the common ion effect). Saturated solution of ionic compounds of relatively low solubility are sometime

description by solubility constants. It is a case of equilibrium process. It describes the balance between dissolve ions from the salt and undissolved salt. Similar to other equilibrium constants, temperature would affect the numerical value of solubility constant. The value of this constant is generally independent of the presence of other species in the solvent. The partition coefficient is a measure of differential solubility of a compound in a hydrophobic solvent and a hydrophilic solvent. The logarithm of these two values enables compounds to be ranked in terms of hydrophilicty. USP and BP classify the solubility regardless of the solvent used, just only in term of quantification and have defined the criteria as given in Table-1.[7,8]

Table 1.

Descriptive terms	**Approximate value of solvent in mililitre per gram 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 solution	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Insoluble	More than 10,000

Aqueous solubility is the concentration of the aqueous phase, when the solution is in equilibrium with the pure compound in its usua0l phase (gas, liquid or solid) at a specific temperature and pressure. We then speak of a saturated solution of the chemical, the concentration of which we will denote as CWs at. Whether an organic molecule “likes” or dislike” being surrounding by water molecule is one of the key factors in determining its environmental behavior. It is necessary, that we try to understand the molecular forces and interactions involved when an organic compound dissolves in water.

Once the solute occupies the cavity and is surrounded by water molecules, will be new attractive force between solute and solvent. These may be London Dispersion and dipole type force depending on the nature of the solute and their magnitude will depend on the factors such as size, polarity and potential H-bonding. Finally, the molecules in the salvation shell will form extra strong H-bonds to neighboring water molecules similar to those found in solid ice.[9]

Solubility can be expressed in precise or general terms. General terms include such

categorizations as ‘slightly soluble,‘soluble,‘insoluble.,Precist terms are expressed with units such as “g/L,’ ‘g/100 g,’ or ‘mg/ml. ’ The object is to provide a measure of how much solute will ultimately dissolve in a given quantity of solvent - a capacity. It is the resting point for the equilibrium between undissolved solute and solubilized solute. The extent to which cohesive. This capacity will often also be dependent on specific condition of temperature and atmospheric pressure as, solubility usually varies with change in these two parameters. Once the capacity of a solvent to dissolve any further solute is reached, further addition of solute will simply result in setting of the solute to the bottom of the container. Solution can be made that are super saturated by altering the temperature at which the solvent is added, and a concentration over the natural capacity at unaltered temperature of the solvent can be achieved.[10] The Biopharmaceutics Classification System (BCS) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. This system restricts the prediction using the parameters solubility and intestinal permeability.

Solubility is based on the highest-dose strength of an immediate release product. A drug is considered highly soluble when the highest dose strength is soluble in 250ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.[11]

Review of Literature

Solubility is the phenomena of dissolving of solute in solvent to give a homogenous system is one of the important parameter to achieve desired concentration of drug in systemic circulation for achieving a pharmacological response. Various techniques have been used for the enhancement of solubility of poorly soluble drug which include physical and chemical modification of drug and other methods like particle size reduction, crystal engineering, salt formation use of surfactant and so forth.

Selection of solubility improving method depends on drug property, site of absorption and required dosage form characteristics. Various technology adapted to prepare the inclusion complexes of poorly water soluble drug with cyclodextrins are verified desired. Thus this is required in the formation of tablet or capsule in date or modified release. Aqueous solubility is the concentration of the chemical in the aqueous phase, when the solution is in equilibrium with the pure compound in its usual phase. The solute occupied the cavity and is surrounded by water molecules, these will be new attractive forces between solute and solvent. These

may be London Dispersion and dipole type forces depending on the nature of the solute and their magnitude will depend on factors such as size polarity and potential H-bonding. These later two processes will be exothermic as new attractive forces are found. A different method of estimating activity coefficients is based on group contribution approach. In this case, the various enthalpic and entropic contributions for each functional group or structural unit of a molecule (interaction parameters) are summed over the entire molecule. A large number of the various interaction parameters are derived from experimental data and are incorporated into software applications that carry out the necessary calculations. UNIFAC does a good of estimating activity coefficients in nonaqueous solutions, whereas AQUAFAC (Aqueous Functional group Activity Coefficients) has been developed for aqueous solutions. If aqueous solubilities are not known, there are several approaches available for estimating them. Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. For orally administered drug solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drug but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drug. The solubility behavior of drug remain one of the most challenging aspects in formulation development. 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 development. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy due to their poor solubility and some drugs also show side effect due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. This is true for parenterally, topically and orally administered solutions. Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many fold with the use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like, it does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system etc.

Fairly soluble drug in gastrointestinal media exhibit complete oral absorption, and thus good bioavailability. About 40% of drugs are not soluble in water in practical and therefore are slowly absorbed, which results in insufficient and uneven bioavailability and GI toxicity.

Thus, most exigent phase of drug development of drug development practice particularly for oral dosage forms in the enhancement of drug solubility and thereby its oral bioavailability. Solubility, an important factor to achieve desired plasma level of the drug for pharmacological response, is the phenomenon of dissolution of solid in liquid phase resulting in a homogenous system. This review describes various traditional and novel methodologies proposed for solubility enhancement of simvastatin, and ultimately improvement in its bioavailability. For simvastatin, solubility is a crucial rate limiting factor to achieve its desired level in systemic circulation for pharmacological response.

Thus, problematic solubility of simvastain is a main challenge for its bioavailability enhancement; however, successful improvement essentially depends on the assortment of techniques. Among all the solubility enhancement techniques, solid dispersion method, in terma of ease and efficiency is most promising and routinely and employed techniques to resolve the solubility problem of simvastatin (Ghulam Murtaza, 2012).

Physical Modification

1. Importance of Solubility Enhancement:

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of doses form. As a result many of the generic drug companies inclined more to produce bioequivalent oral drug products.[12]

For most drugs the Pharmacological response can be directly to the plasma level. Thus the term bioavailability is define as the rate and extend (amount) of absorption of unchanged drug form its doses form. It can also defined as the rate and the extent to which the ingredients or active moiety is absorbed from the drug product and becomes available at the site of action. As per the definition of bioavailability, a drug with poor bioavailability is one with poor aqueous solubility, slow dissolution rate in biological fluids, poor solubility of dissolved drug at physiological pH, poor permeation through bio-membrane, extensive pre-systemic metabolism.[13]

The negative effect of compounds with low solubility include poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to increasing the development cost and time, burden shifted to patient (frequent high-dose administration).[14]

2. Techniques for Solubility Enhancement

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

Physical Modifications. Particle size reduction like micronization and nanosuspension, modification of the cocrystallization, drug dispersion, solid solutions and cryogenic techniques.

Miscellaneous Methods. Supercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

3. 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 large surface area allows greater interaction with the solvent which causes an increase in solubility.[15]

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. Micronized feno fibrate exhibited more than 10-fold increase in dissolution in at 30 minutes biorelevent media.[16,17]

3. Solid Dispersion

The concept of solid dispersion was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water soluble carrier in the early 1960s.[18] Solid dispersion represents a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drug 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 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 technique stop repare the solid dispersion of hydrophobic

drug to improve their aqueous solubility are listed here.[19-21]

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.

Hot-Melt Extrusion. Hot-melt extrusion is essentially the same as the fusion method exceptthat 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 then ext. processing step without grinding.[23]

4. Nanosuspension

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 distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600nm.[24,25] Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, highpressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high- Pressure homogenization.[26,27]

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 equipment; 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 miscible with antisolvent. Moreover, precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.[28] 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.[29,30]

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 resulting into breaking of micro particulate on and sized particles.[31]

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 cavitation 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.[32] 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.[33–35]

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 (homogenization). 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 particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.

5. Supercritical Fluid (SCF) novel nanosizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) a gas. At near-critical temperatures, SCFs, are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and that largely determine its solvent power.

SCF (usual carbondioxide), they may be recrystallized at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels. Current SCF processes have diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvent process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical antisolvent processes (SAS), rapid expansion of supercritical solutions. (RESS), antisolvent recrystallization (GAS), and aerosol supercritical extraction system (ASES).[36, 37]

6. Cryogenic Techniques

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating amorphous drug particles with high degree of porosity at very low temperature conditions. Cryogenic find 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, N2, Ar, O 2, and organic solvents). After cryogenic processing, drypowder can be obtained by various drying processes like sprayfreeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilization.[38–39]

Spray Freezing onto Cryogenic Fluids. Briggs and Maxvell invented the process of spray freezing onto cryogenic fluids. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol, or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the disperse ion of the aqueous solution.[40]

Spray Freezing into Cryogenic Liquids (SFL). The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid-liquid impingement between the automatized feed solution and cryogenic liquid to provide intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are

then lyophilized to obtain dry and free-flowing micronized powders.[41]

Spray Freezing into Vapor over Liquid (SFV/L). Freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability. During SFV/L the typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.[42]

7. Inclusion Complex Formation-Based Techniques

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs).These are oligosaccharides consisting of glucose monomers arranged in a donut.

Shaped ring having hydrophobic cavity and hydrophilic outer surface as illustrated. Three naturally occurring CDsareα-Cyclodextrin, β-Cyclodextrin,andγ-Cyclodextrin.[43] The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobiccavity provides a microenvironment for appropriately sized non-polarmolecules.

Based on the structure and properties of drug molecule it can form 1:1 or 1:2 drug cyclodextrin complex as illustrated. Various technologies adapted to prepare the inclusion complexes of poorly water soluble drugs with cyclodextrins are briefly described below.

Kneading Method. This method is based on impregnating the CDs with little amount of water or hydroalcoholic.

Lyophilization/Freeze-Drying Technique. Inordertogeta porous, amorphous powder with high degree of interaction between drug and CD, lyophilization/freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermolabile substances can be successfully made into complex form by this method. The limitations of this technique is the use of specialized equipment,

time consuming process, and yield poor flowing powdered product.

Lyophilization/freezedrying

Technique is considered as an alternative to solvent evaporation and involve molecular mixing of drug and Microwave Irradiation Method. This technique involves the microwave irradiation reaction between drug and complexing agent 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 60◦C 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 what man filter paper, and dried in vacuum oven at 40◦C. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction times and higher yield of the product.[45]

7. Micellar Solubilization

The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and the oldest method. 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 0.5-0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. 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.[11] Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroylmacroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved.[46,47] Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.[48]

8. Hydrotrophy

Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic

acids. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropicsalts”; a phenomenon known as “hydrotropism.”

The mechanism by which it improves solubility is more closely related to complexation. They have been reported to exhibit hydrotropic behaviour. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, αandβ-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylatedoxidibenzene. The aromatic hydrotropes with anionic head groups are mostly studied compounds. They are large in number because of isomerism and their effective hydrotrope action may be due to the availability of interactive pi (π) orbit (51).

9. 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 conditions of crystallization or on methods of comminution such as impact milling and fluid energy milling. The comminution techniques can produce particles which are highly heterogeneous, charged, and cohesive, with the potential to cause problems in downstream processing and product performance. Hence, crystal engineering techniques are developed for the controlled drugs to produce high purity powders with well- defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy.[58]

By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs. As a result, polymorphs for the same drug may differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions. A classic example of the importance of polymorphism on bioavailability is that of chloramphenicol palmitate suspensions. It was

shown that the stable polymorph of chloramphenicol palmitate produced low serum levels, whereas the metastable polymorph yielded much higher serum levels when the same dose was administered.[52]

CONCLUSION

Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. 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. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

REFERENCES

1. Limbachiya MI, Solubility enhancement techniques for poorly soluble drugs; A review. IJPRD, 2011; 4(4): 71-86.
2. M. Clugston and R. Fleming, Advanced Chemistry, Oxford Publishing, Oxford, UK, 1st edition, 2000.
3. P. B Myrdal and S. H, Yalkowsky, “Solubilization of drugs in aqueous media, ”in Encyclopedia of Pharmaceutical Technology, J. Swarbrik, Ed., p. 3311, Informa Health Care, New York, NY, USA, 3rd edition, 2007.
4. A. Martin, Solubility and Distribution Phenomena, Physical Pharmacy and Pharmaceutical Science, Lippincott Williams and Wilkins, 6thedition, 2011. “IUPAC gold book,” http:golgbook. iupac, org/S05740. html.
5. M. Aulton, “Dissolution and solubility, ” in Pharmaceutics: The Science of Dosageform Design, M. E. Aulton, Ed., p. 15, Churchill Livingstone, 2nd edition, 2002.
6. The United States Pharmacopia, USP 30-NF 25, 2007.
7. British Pharmacopia, 2009.
8. Environmental Organic Chemistry, R. P. Schwarzenbach; P. M. Gschwend; D. M. Imoden, 1998.

9. Sample pages from Remington Education: Physical Pharmacy, publishedby Pharmaceutical Press, 2016
10. G. L. Amidon, H. Lennernas, V. P. Shah, and J. R. Crison, "A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability," Pharmaceutical Research, 1995; 12(3): 413-420.
11. S. R. K. Yellela, "Pharmaceutical technologies for enhancing oral bioavailability ofpoorly soluble drugs," Journal of Bioequivalence and Bioavailability, 2010; 2: 28-36.
12. Savjani KT, Gajjar AK, Savjani JS. Drug Solubility: Importance and Enhancement Techniques. ISRN Pharmaceutics ArticalID195727, 2012; 1-10, doi: 10. 5402/2012/195727.
13. K. H. EdwardandD. Li, "Solubility," in Drug Like Properties: Concept, Structure, Design and Methods, fro.
14. N. Blagden, M. de Mstas, P. T. Gavan, and P. York, "Crystal engineering of active pharmaceutical ingredinets to improve solubility and dissolution rate, " Advanced Drug Delivery Reviews, 2007; 59(7): 617-630.
15. M. Vogt, K. Kunath, and J. B. Dressman, "Dissolution enhancement of fenofibrate by micronization, cogrinding and spray- drying: comparison with commerical preparations," European Journal of Pharmaceutical and Biopharmaceutics, 2008; 68(2): 283-288.
16. J. C. Chaumeil, "Micronization: a method of improving the bioavailability of poorly soluble drug," Method and Findings in Experimental and Clinical Pharmacology, 1998; 20(3): 211-215.
17. K. Sekiguchi and N. Obi, "Studies on absorption of eutectic mixtures. I. A. comparison of the behaviour of eutectic mixtures of sulfonamide and that of ordinary sulphathiazole in man," Chemical and Pharmaceutical Bulletin, 1976; 9: 866-872.
18. P. Gupta, V. K. Kakumanu, and A. K. Bansal, "Stability and solubility of celecoxib-PVP Amorphous dispersion: a molecular perspective," Pharmaceutical Reseaech, 2004; 21(10): 1762-1769.
19. A. M. Abdul- Fattah and H. N. Bhargava, "Preparation and in vitro evaluation of solid dispersionsofhalofantrine," International Journal of Pharmaceutics, 2002; 235: 1-2, 17-33.
20. S. Sinha, M. Ali, S. Baboota, A. Ahuja, A. Kumar, andJ. Ali, "Soliddispersionasanapproach for bioavailability enhancement of poorly water- soluble drug ritronavir," AAPS Pharm-SciTech, 2010; 11(2): 518-527.
21. "Nanosuspension drug delivery technology and application— nanotech— express pharma pulse. htm, "http://www. expresspharmapulse.com/.

22. R. H. Muller, C. Jacobs, and O. Kayer, “Nanosuspensions for the formulation of poorly soluble drugs, ” in Pharmaceutical Emulsion and Suspension, F. Nielloud and G Marti-Mestres, Eds., pp. 383–407, Marcel Dekker, New York, NY, USA, 2000.
23. R. A. Nash, “Suspensions, ” in Encyclopedia of Pharmaceutical Technology, J. Swarbrick and J. C. Boylan, Eds., 3: 2045–3032, Marcel Dekker, New York, NY, USA, 2nd edition, 2002.
24. K. P. R. Chowdary and B. L. R. Madhavi, “Novel drug delivery technologies for insoluble drugs,” Indian Drugs, 2005; 42(9): 557–564.
25. V. B. Patravale, A. A. Date, and R. M. Kulkarni, “Nanosuspensions: apromisingdrugdeliverystrategy,” JournalofPharmacy and Pharmacology, 2004; 56(7): 827–840.
26. R. H. Muller, B. H. L. Bohm, andJ. Grau, “Nanosuspensions:a formulation approach for poorly soluble andpo.
27. E. Merisko-Liversidge, G. G. Liversidge, and E. R. Cooper, “Nanosizing: a formulation approachforpoorly-water-solublecompounds,” European Journal of Pharmaceutical Sciences, 2003; 18(2): 113–120.
28. G. G. Liversidge and P. Conzentino, “Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats,” International Journal Pharmaceutics, 1995; 125(2): 309–313.
29. C. M. Keck and R. H. M ¨ uller, “Drug nanocrystals of poorly soluble drugs producedby high pressure homogenisation,” European Journal of Pharmaceutics and Biopharmaceutics, 2006; 62(1): 3–16.
30. P. Langguth, A. Hanafy, D. Frenzeletal., “Nanosuspensionformulations for low-soluble drugs: pharmacokinetic evaluation usingspironolactoneasmodelcompound,” Drug Development and Industrial Pharmacy, 2005; 31(3): 319–329.
31. C. Jacobs and R. H. M¨uller, “Production and characterization of a budesonide nanosuspension for pulmonary administration,” Pharmaceutical Research, 2002; 19(2): 189–194.
32. J. M¨oschwitzer, G. Achleitner, H. Pomper, and R. H. M¨uller, “Developmentofanintravenouslyinjectablechemicallystable aqueous omeprazole formulation using nanosuspension technology, ” European Journal of Pharmaceutics and Biopharmaceutics, 2004; 58(3): 615–619.
33. G. SunkaraandU. B. Kompella, “Drugdeliveryapplicationsof supercritical fluidtechnology,” Drug Delivery Technology, 2002; 2: 44–50.

34. L. Manna, M. Banchero, D. Sola, A. Ferri, S. Ronchetti, and S. Sicardi, "Impregnation of PVPmicroparticleswithketoprofen in the presence of supercritical CO2, " Journal of Supercritical Fluids, 2007; 42(3): 378–384.
35. H. Leuenberger, "Spray freeze-drying—the process of choice for low watersoluble drugs?" Journal of Nanoparticle Research, 2002; 4: 1-2, 111–119.
36. M. Mumenthaler and H. Leuenberger, "Atmospheric sprayfreeze drying: a suitable alternative in freeze-drying technology," International Journal of Pharmaceutics, 1991; 72(2): 97–110.
37. R. Q. Williams, "Process for production of nanoparticles and microparticles byspray freezing into liquid," US Patent no. 20030041602, 2003.
38. A. R. Briggs and T. J. Maxvell, "Process for preparing powder blends," US Patentno. 3721725, 1973.
39. T. L. Rogers, J. Hu, Z. Yu, K. P. Johnston, and R. O. Williams, "A novel particle engineering technology: spray-freezing into liquid," International Journal of Pharmaceutics, 2002; 242, no. 12, 93–100.
40. I. R. Buxton and J. M. Peach, "Process and apparatus for freezing a liquid medium, "US Patent no. 4470202, 1984.
41. "Cyclodextrins in pharmaceuticals: an overview," http://www. pharmainfo. net/pharma-student-magazine/cyclodextrins-pharmaceuticals-overview-0.
42. K. Uekama, F. Hirayama, and T. Irie, "Cyclodextrin drug carrier systems," Chemical Reviews, 98.
43. F. Cao, J. Guo, and Q. Ping, "The physicochemical characteristics of freeze-dried scutellarin- cyclodextrintetracomponent complexes," Drug Development andIndustrial Pharmacy, 2005; 31(8): 747–756.
44. X. Wen, F. Tan, Z. Jing, and Z. Liu, "Preparation and study the 1:2 inclusion complex of carvedilol with β-cyclodextrin," Journal of Pharmaceutical and Biomedical Analysis, 2004; 34(3): 517–523.
45. A. Martin, Physical Pharmacy, Willaims and Wilkins, Baltimore, Md, USA, 4th edition, 1993.
46. C. D. Rangel-Yagui, A. Pessoa, and L. C. Tavares, "Micellarsolubilization of drugs," Journal of Pharmacy and Pharmaceutical Sciences, 2005; 8(2): 147–163.
47. C. H. Hsu, Z. Cui, R. J. Mumper, and M. Jay, "Micellar solubilization of somepoorly soluble antidiabetic drugs," AAPS PharmSciTech, 2008; 9(2): 939–943.
48. A. A. Rasool, A. A. Hussain, and L. W. Dittert, "Solubility enhancement of somewater-

insoluble drugs in the presence of nicotinamide and related compounds," Journal of Pharmaceutical Sciences, 1991; 80(4): 387–393.

49. A. A. Badwan, L. K. El Khordagui, A. M. Saleh, and S. A. Khalil, "Thesolubilityofbenzodiazepinesinsodiumsalicylate solution and a proposed mechanism for hydrotropic solubilization," International Journal of Pharmaceutics, 1983; 13(1): 67–74.
50. A. J. Aguiar, J. Krc, A. W. Kinkel, and J. C. Samyn, "Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate, " Journal of Pharmaceutical Sciences, 1967; 56(7): 847–853. [47] http://www. nature. com/nrd/journal/v3/n12/fig tab/nrd1576F3. html.