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Review Article

Advanced Solubility Enhancement Techniques for Poorly Soluble Drugs

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Abstract

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 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. Solubility of drug is an important physicochemical property because it affects bioavailability of a drug candidate, rate of drug release from dosage form and its dissolution into dissolution medium and consequently the therapeutic efficacy of the pharmaceutical product. About 90% of the drug candidates used today in pharmaceutical industry has poor water solubility. The active ingredient cannot reach its molecular target in the body if it remains undissolved in the gastro intestinal fluid and ultimately excreted unchanged from body which simply means any drug that do not dissolve will not perform its desired function therefore solubility is a critical a critical issue for a drug molecule if it has to survive in the pharmaceutical development process. Therefore different solubilization technologies that solve this problem by increasing the solubility of poorly soluble drugs are important for pharmaceutical industry as they are opening the pathway for the development of more effective dosage forms. This review is intended to highlight the role of solubility enhancement techniques in the formulation development of poorly soluble drugs and discussed the recent advanced technologies used in solubility enhancement.

Keywords: solubility, particle size reduction, crystal engineering, solid dispersions.

Introduction

International union of pure and applied chemistry defined solubility as an analytical composition of a saturated solution comprising a specified solute in a desired solvent. But more appropriately in simple and quantitative terms solubility can be expressed as ability of the given substance (solute) to dissolve in a solvent. Qualitatively it is defined as an interaction between two substances (solute and solvent) resulting in formation of homogenous dispersion. The solubility of a given drug substance can be expressed in the ranges of very soluble to practically insoluble. A compound is said to be insoluble when less than 0.1gram of it is soluble in 100ml of the specified solvent [1]. For poorly soluble or very poorly soluble compounds, insoluble term is often used. Most of the pharmaceutical drug molecules as estimated, approximately 40 per cent which are currently available in the market and 90 per cent of compounds used in drug delivery systems have solubility problem which creates problem in reproducible absorption from gastrointestinal track, ultimately affecting the bioavailability, as well as safety and efficacy of product. As per FDA, a drug is considered highly soluble when the highest dose strength of it is soluble in 250 ml or lesser amount water over a pH range of 1 to 7.5. The volume 250 ml was estimated on the bases of bioequivalence study protocol which prescribe drug to be administered to fasting individual with a glass of water. Problems arising from low aqueous solubility:

·Precipitation of drug during serial dilution in buffer, biochemical assays, functional assays and cell -base assays

·Reduced target-specificity of a drug

·Low dissolution rate and bioavailability of drug

·Drug absorption and distribution.

A drug must be able to reach its target site in effective concentrations for which adequate, solubility of a compound is desired in body fluids therefore solubility of a compound is related to its pharmacologic potency and its permeability. A lower micro molar aqueous solubility can be acceptable only for extremely potent and/or permeable compounds. Low aqueous solubility is the major problem involved in the formulation development of new chemical entities as well as for the generic development. It has been found that more than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. Solubility issue is a major problem for formulation scientist to develop a new drug delivery system. Any drug to be absorbed must be present in the form of solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, prodrug formation solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics [2].The Present review summarized some of the advanced technologies used in the solubility enhancement of poorly soluble drugs along with mechanism involved and importance of solubility analysis at preformulation studies.

Bio-pharmaceutical classification system (BCS)

Bio pharmaceutical classification is a system used for the classification of drug substances depending upon their aqueous solubility and intestinal permeability. The main purpose of this is to increase the efficiency of drug development process and to formulate a rational drug delivery system. As per this system, drug substances are classified into four classes depending upon their solubility and permeability characteristics. Considerably large amount of drug candidates (approximately 70 per cent) fall into class II, and according to BCS, bioavailability for this class of drugs may be enhanced by increasing the solubility as drug release from dosage form and dissolution rate in GI tract are the only rate limiting steps in absorption. Other class of drugs i.e. I, III and IV occupy 5 per cent and 20 per cent approximately [3].

Class I — high soluble and high permeable

Class II— low soluble and high permeable

Class III — high soluble and low permeable

Class IV— low soluble and low permeable

Need for Solubility Enhancement

Most of the drug molecules synthesised today are poorly water soluble and therefore creating problems in all aspects of formulation development, drug administration process, therapeutic effectiveness and so the financial calculations. Rational and cost effective formulation of a dosage form without any market issues, maintaining the image and standard of a product as well as company are the main objectives of any industry. So thinking from this view of point, the pharma industry always tries to overcome all the issues related to quality and efficacy of products. Low bioavailability due to poor solubility results into decreased therapeutic effectiveness of drug along with patient-to-patient variability (both inter and intra) and side effects. Hence, research approaches to overcome solubility issues play significant role in the process of drug development, so that more and more compounds can be converted into rational dosage forms, along with improvement in efficacy, safety and reduction in cost. Need for solubility enhancement is more in case of solid dosage forms like tablets and capsules, as oral route is most convenient and commonly used route for drug administration [4].

Mechanism of solubilisation

The basic mechanism of drug solubility involves breaking of intermolecular or inters ionic bonds between solute molecules thereby creating sufficient space for solvent molecule to enter into the solute molecules and promote wetting of particles to provide interaction between solute and solvent necessary for solubilisation. Various steps involved in the drug solubilisation are summarized in Figure 1.

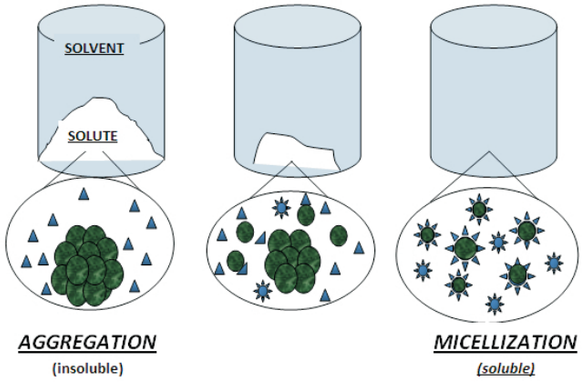

Figure 1: Mechanism of drug solubility

Solubility Analysis in Preformulation

Solubility analysis in early formulation level focuses on solute-solvent system to be chosen for development of new dosage form and choice of analytical method. Preformulation solubility analysis involves determination of pKa value, intrinsic solubility, temperature dependent solubility, pH solubility profile, dissolution and intrinsic dissolution rate.The various analytical techniques used for the determination of solubility includes HPLC analysis, spectrophotometric technique, Gas chromatography, fluorescence spectroscopy. Solubility values of distilled water, 0.9% NaCl, 0.01 M HCl, 0.1 M HCl, and 0.1 M NaCl (which were kept at room temperature and at pH 7.4) were used in the early development. Solubility determination is generally carried out at two temperatures 4 ºC and 37 ºC, 4 ºC ensure good stability and 37 ºC simulates body temperature.

Techniques used for solubility enhancement

Various techniques can be used for the solubility enhancement of poorly soluble drugs. These techniques can be categorised in physical, chemical and miscellaneous modifications in drug molecules. Physical modification consists of reduction in particle size, modification of crystal structure, preparation of solid dispersion. Chemical modification involves pH change, use of buffer, salt formation etc. Miscellaneous techniques include use of adjuvant like surface active agents, solubilising agents, adjuvant, natural and synthetic polymers. Use of polymers as a solubilising excipient is one of the popular method for the solubility enhancement of poorly soluble drugs. Selection of solubility enhancement method depends on:

·Physicochemical properties of drug molecule

·Site of absorption required

·Characteristics of dosage form selected.

Physical modification - Physical modification in drug molecule can be done by particle size reduction like micronization and formulation of nano suspension and micro emulsion, modification of the crystal structure like polymorphs, amorphous form and co crystallization, dispersing drug in carriers like PEG 4000, urea, mannitol etc which form eutectic mixtures, solid dispersions, solid solution and formation inclusion compounds with cyclodextrine.

Chemical methods - Change of pH, use of buffering agents, derivatization, complex formation and salt formation. Derivatization helps in solubility enhancement by transforming the lesser soluble chemical into a more soluble one by adding more hydrophilic groups.

Miscellaneous methods

·Supercritical fluid,

·Use of additives (eg. surfactant, solubilising agents)

·Co solvency

·Hydrotrophy

·Novel solubilising excipient

·Solvent deposition

·Selective adsorption on insoluble carriers

·Use of soluble prodrugs

·Micro particle technology

·Nanotechnology approach [5]

Advanced Technologies - Some of the advanced techniques innovated for the purpose of solubility and bioavailability enhancement in drug are mentioned below:

Spray dried dispersion (SDD)

Spray dried dispersion technology is one of the most powerful formulation approach used to enhance the bioavailability for

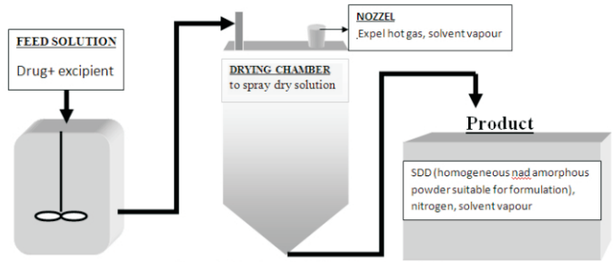

Figure 2: Overview of solid dry dispersion technology

compounds having low solubility. An SDD is a single-phase, amorphous molecular dispersion prepared by dispersing the drug in a polymeric matrix such as hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate to form a solid solution with the compound molecularly "dissolved" in a solid matrix. In this technique as the name indicates, SDDs are obtained by dissolving drug and polymer in an organic solvent and then the resulting solution is spray-drying. The formulation and process conditions are chosen so that the

solvent rapidly evaporates from the droplets so that no time is given for phase separation or crystallization. In addition to their proven performance in enhancing solubility, SDDs have showed long-term stability of product, scale-up and excellent manufacturability a process overview of spray dried technique is demonstrated in Figure 2 [6].

Hot melt extrusion (HME)

Hot melt extrusion is one of the most effective techniques used in pharmaceutical manufacturing of variety of dosage forms. Effective delivery of numbers of BCS class II compounds having low solubility can be done by formulating amorphous dispersions made by hot-melt extrusion (HME). Drug dissolution rate and bioavailability of a poorly soluble drug can be enhanced using this technique by dispersing the drug candidate into hydrophilic excipient this involves the melting of a drug substance with an appropriate polymeric excipient in a co-rotating twin-screw extruder. Additionally excipient, such as surfactants, may be added to aid in the extrusion process and to improve dissolution performance upon administration. When cooled, the product obtained form extrusion or the extrudate generally consists of a single-phase amorphous glassy matrix that can be milled to the desired particle size and can be compressed into traditional tablet or filled into capsule dosage forms [7]. A process design of hot melt extrusion technique is given in Figure 3.

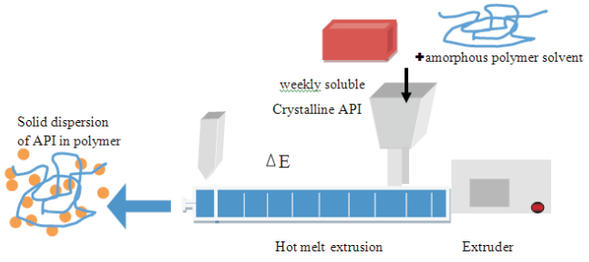

Figure 3: Over view of Hot melt extrusion technique

Solid Nano Crystalline Dispersion (SNCD)

The drug crystals which are embedded in a polymer-rich matrix constitute the solid nano crystalline dispersion. In this technique the drug solution with polymer such as hydroxypropyl methyl acetate succinate was spray dried to form a spray dried amorphous solid dispersion and then exposed to controlled temperature and humidity to form submicron, high-energy crystals from amorphous dispersions. They can be formed through crystallization of the drug in a spray-dried dispersion (SDD) under controlled conditions of temperature and humidity that favour high nucleation rates over crystal growth. SNCDs have two important advantages:

· The drug nanocrystals enhances dissolution rate of poorly soluble drug due to high energy nature.

·Increased stability of the drug form and allows higher drug-loading.

Thus, it is possible to attain both good performance and good stability of drug with

SNCDs. Process overview of solid nano crystalline dispersion is given in Figure 4.

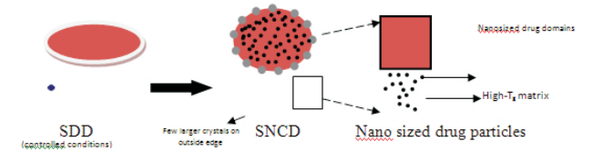

Figure 4: Process overview of solid nano crystalline dispersion

SNCDs are best used in cases where any of the following apply:

·In case of improved stability is needed relative to amorphous drug forms because a high drug-loading is required or because the amorphous drug has a low glass-transition-temperature (Tg);

·In case of improved chemical stability (relative to an amorphous drug form) is needed; or

·Small crystals sufficiently meet pharmacokinetic (PK) targets as they have higher dissolution rate [8].

Spray-dried nano adsorbate technology (SDNAD)

Spray-dried nano adsorbate technology, or SDNAD, consists of a solid amorphous dispersion adsorbed on the surface of a high surface-area insoluble material, such as fumed silica and silicon dioxide. The dispersion so formed has increased surface area relative to normal dispersion of particles, leading to rapid dissolution of the drug, resulting in improved bioavailability relative to crystalline drug. Solid nano adsorbents are made by conventional spray-drying process. During the process, the drug and polymer are dissolved in a solvent, while the high surface-area insoluble material is suspended in the spray solution. The suspension is then spray-dried to form solid particles having the solid nano adsorbents. The final product can then be formulated into solid dosage forms, such as tablets and capsules for immediate- or modified-release, depending on the desired therapeutic profile [9]. SDNAs have advantages for formulating mixtures of drugs, mixtures of drug and surfactants, liquid/lipid formulations, and semi-solid formulations. Some of the advantages of SDNAs include:

·Improved physical stability as compared to pure amorphous form of drug

·Stabilization of drugs that rapidly crystallize

·Increased bioavailability relative to crystalline drug or large amorphous particles

·Increased dissolution rate of drug relative to crystalline drug

·Used for liquid and semi-solid drug formulations

·SDNAs are used for forming solid dosage forms and combination products.

Co-crystallization

Co crystallization is one of the new approaches available for the enhancement of drug solubility. It includes application of co-crystals which are also referred as molecular complexes. Co crystals are the crystalline structures comprising of two components which may be atoms, molecules or ions held together by hydrogen bonding, ionic and van der Waals interaction. If the solvent is an integral part of the crystalline structure, then it may be termed as co-crystal. If the solvent does not participate in the network and remains in open framework structures, then it is termed as clatharate (inclusion complex). This co -crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Three of the co-crystallising agents that are classified as generally regarded as safe (GRAS) includes saccharin, nicotinamide, and acetic acid [10]. Another example of synthetic compound include cyanoximes as an effective co crystallising agent, it has solubility in wide range of solvents and therefore used for solution based co crystal synthesis. Co crystallisations alter many physical properties of drug molecule such as solubility, stability, dissolution and bioavailability without altering the chemical composition of drug. Some of the examples of drugs available in market as co crystals include: atropine, ketoprofen, atenolol, loratadine, omeprazole and cetrizine.

Cryogenic technique

Cryogenic spray processes are novel techniques that can be used to increase the solubility and therefore to enhance the dissolution rate and bioavailability of poorly soluble drugs by producing nanostructure amorphous drug particles with high degree of porosity at very low

temperatures. These cryogenic processes are followed by various drying processes like spray drying, freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilisation to produce dry free flowing porous powder particles. There are several types of cryogenic spray techniques like: spray freezing onto cryogenic fluids, spray freezing into cryogenic liquids (SFL), spray freezing into vapour over liquid and ultra-rapid freezing to produce smaller drug particles with improved wet ability and solubility [11].

Spray freezing onto cryogenic fluids

In this technique, first the drug and the carrier such as mannitol, maltose, lactose, inositol, or dextran are dissolved in water and sprayed over the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to facilitate the dispersion of drug in the aqueous solution [12].

Spray freezing into cryogenic liquids (SFL)

In this technique direct liquid-liquid interaction between the sprayed feed solution and cryogenic liquid is done to provide intense atomization into micro droplets and consequently significantly faster freezing rates. The frozen particles are then freeze dried to obtain dry and free-flowing micronized particles with enhanced solubility and dissolution rate [13].

Spray Freezing into Vapour over Liquid (SFV/L)

In this technique at first, freezing of drug solutions in cryogenic fluid vapours such as carbon dioxide, nitrous oxide, and helium is done with subsequent removal of frozen solvent to produces fine drug particles having high wet ability which enhances solubility. During spray freezing over cryogenic liquid the atomized droplets typically begins to freeze in the vapour phase before they come in contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, thus fine drug particles may nucleate and grow.

Ultra-rapid freezing (URF)

The most novel cryogenic technology used for solubility enhancement is ultra-rapid freezing. This technology creates drug particles having nano size range with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leads to instantaneous freezing and subsequent lyophilisation (for removal of solvent) forms of micronized drug powder with improved solubility. Ultra rapid freezing prevents the phase separation and the crystallization of the pharmaceutical ingredients [14].

Super critical fluid technology

Particle size reduction using supercritical fluid (SCF) processes is a novel nanosizing and solubilisation technology whose application has increased in recent years. 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 a gas. At near critical temperatures, supercritical fluids are highly compressible allowing moderate changes in pressure density and mass transport characteristics of the fluid that largely determine its solvent power. Once the drug particles are solubilised within the supercritical usually carbon dioxide, they may be re crystallised at greatly reduced particle sizes. The flexibility and precision offered by super critical fluid processes allows micronization of drug particles within narrow ranges of particle size, often to submicron levels. Current supercritical fluid processes have demonstrated the ability to create nano particulate suspensions of particles 5–2,000nm in diameter showing enhancement in solubility and dissolution rate of poorly soluble drug particles [15, 16].

Liquid solid technology

Though solid dispersion and particle size reduction are key technologies used for polymer-based solubility-enhancing excipient, an increasing number of scientific research studies are also focusing on the use of this technology. This technology involves the conversion of the insoluble drug particles in liquid form, to a free-flowing and compressible powder following the addition of a polymer excipient such as polymethacrylate. Liquid solid technology can be used for a wide range of API and has a relatively low operating cost. It is potentially safe and efficacious method used for oral drug delivery. However, it is not suitable for drug formulations that carry high dosage levels of API [17, 18]. Basic mechanism involved in the liquid solid technology for the solubility enhancement and increased drug release is increased surface area leading to improved wetting properties which increase the aqueous solubility.

Porous micro particle technology

Porous micro particle technology involve embedding of poorly drug soluble particles into micro particles having porous sponge like matrix that enhances wetting of particle leaving a suspension of rapidly dissolving drug particles these particle large surface area required for increased solubility and dissolution rate.

Nano technology

Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. Two important nano technologies used in recent days are formation of nano crystals and nanomorphs.

Nanocrystal Size of 1-1000 nm crystalline material with dimensions measured in nanometers are referred as nano crystals There are two distinct methods used for producing nanocrystals bottom-up and top-down. The top-down methods involves milling and high pressure homogenization with milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods i.e. Precipitation and Cryo -vacuum method where nanoscale materials are chemically composed from atomic and molecular components.

Nanomorph The nanomorph technology is to convert drug substances with low water-solubility from a coarse crystalline state into amorphous nanoparticles. A suspension of drug substance in solvent is fed into a chamber, where it is rapidly mixed with another solvent. Immediately the drug substance suspension is converted into a true molecular solution. The admixture of an aqueous solution of a polymer induces precipitation of the drug substance. The polymer keeps the drug substance particles in their nanoparticulate state and prevents them from aggregation or growth. Using this technology the coarse crystalline drug substances are transformed into a nanodispersed amorphous state, without any physical milling or grinding procedures. It leads to the preparation of amorphous nanoparticles [19].

Polymers used in Solubility Enhancement

Commercially available polymers used for the solubility enhancement with their composition, properties and applications are summarized in Table 1.

Table 1: Commercially available polymers and their stated details

Trade name	Composition	Properties	Applications	Ref.
Soluplus®	Polyvinyl caprolactum-polyvinyl acetate-polyethylene glycol graft copolymer	Free flowing granules, white to slightly yellowish, practically no taste.	Solubilizer in aqueous media for oral formulations	[20,21]
Kolliphor™ TPGS	d-α tocopheryl polyethylene glycol 1000 succinate	Non ionic surfactant with amphiphilic character, white to light brown.	Solubilizer, stabilizer, drug permeability enhancer, antioxidant and emulsion vehicle	[22,23]
Kolliphor™ HS 15	Mixture of polyglycol mono -and di ester of 12 hydroxy stearic acid derivative	Yellowish white paste, waxy, freely soluble in water and ethanol, insoluble in liquid paraffin	Solubilzer for fat soluble vitamins, used in parenteral formulations, self emulsifying and nano emulsifying drug delivery systems	[24,25]
Kolliphor™ RH 40	Mixture of tri hydroxystearate ester of ethoxylated glycol with small amount of polyethylene glycol tri hydroxy stearate.	White yellowish paste, tasteless and odourless, soluble in water, ethanol, chloroform and carbon tetrachloride.	Used in the formulation of aqueous solution of fat soluble vitamins for oral and topical applications, as solubilizer in combination with co solvents in self emulsifying drug delivery systems and taste masking agent	[26,27]
Kolliphor™ EL/ELP	Glycerol polyethylene glycol ricinoleate	Pale yellow oily liquid that is clear at temperature above 26º C , faint but characteristic odour	Solubilizer and emulsifying agent	[28,29]
Poloxamers	Non-ionic poly ethylene oxide (PEO) and poly propylene oxide (PPO) copolymers.	Liquid, pasty or solid at room temperature.	Surfactant, emulsifying agent, solubilising agent, dispersing agent	[30]
Kollidon®17PF	Polyvinyl pyrrolidone	White free flowing powder with characteristic odour.	Solubilising agent, dispersing agent, crystallisation inhibitor, pore former in solid oral dosage form	[31,32]

Conclusion

Therapeutic solubility of a drug molecule depends upon its bioavailability and ultimately over the drug solubility therefore it is an important parameter to obtain the desired concentration of drug at site of absorption to have desired therapeutic response. For the formulation of oral dosage forms of poorly soluble drugs solubility becomes an essential phenomenon. Thus it can be concluded that all the above listed techniques provide aid in increasing the solubility and thereby increase its absorption because the low aqueous solubility is the major problem encountered in formulation of dosage form of new chemical entity. The current research trends in this area are improving the solubility aspects of various hydrophobic and lipophilic drugs. Hence we can thereby conclude that widening the horizons of research trends in the area of solubility enhancement would be fruitful for the development of new dosage forms.

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Conflicts of interest

The authors confirm that this article content has no conflict of interest.

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