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A Concise Review on Methods of Solubility Enhancement

Godase CB, Babar AL, and Gopal AB*

Department of Pharmacy, Arvind Gavali College of Pharmacy, India

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*Corresponding author: Godase B, Department of Pharmacy, Arvind Gavali College of Pharmacy, India
E-mail: godasecb@gmail.com

Abstract

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. More than 40% of new chemical entities developed in pharmaceutical industry are lipophillic and fail to reach the market due to their poor water solubility. The solubility behavior of drug is the major challenge for formulation scientist. The present review is devoted to increase the solubility of poorly water-soluble drugs.

Keywords: Solubility; Formulation; Drug; Supersaturated; Biopharmaceutics

Introduction

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable.

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. Solubility does not also depend on particle size or other kinetic factors; given enough time, even large particles will eventually dissolve. 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 units of concentration, molality, mole fraction, mole ratio, and other units.

Extensive use of solubility from different perspective has led to solubility being expressed in various manners. It is commonly expressed as a concentration, either by mass (gm of solute per kg of solvent, gm per dL (100 mL) 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.

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 (e.g., the common ion effect). Saturated solutions of ionic compounds of relatively low solubility are sometimes described by solubility constants. It is a case of equilibrium process. It describes the balance between dissolved ions from the salt and undissolved salt, its 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 Flory-Huggins solution theory is a theoretical model describing the solubility of polymers. The Hansen Solubility Parameters and the Hildebrand solubility parameters are empirical methods for the prediction of solubility. It is also possible to predict solubility from other physical constants such as the enthalpy of fusion. The partition coefficient (Log P) is a measure of differential solubility of a compound in a hydrophobic solvent (octanol) and a hydrophilic solvent (water). The logarithm of these two values enables compounds to be ranked in terms of hydrophilicity (or hydrophobicity). USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in Table 1. 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. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are incredibly important, since 85% of the most sold drugs in the USA and Europe are orally administered. All drugs have been divided into four classes [1-10].

Table 1: **BSC Classification**

BCS Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Techniques for solubility enhancement

1. Chemical Modifications.
2. Physical Modifications:
   a) Particle size reduction.
   b) Modification of the crystal habit.
   c) Complexation.
   d) Inclusion Complex Formulation Based Techniques.
   e) Solubilization by surfactants.
   f) Drug dispersion in carriers.
   g) pH adjustment.
3. Supercritical fluid process.
4. Liquisolid technique.
5. Polymeric alteration.

Methods

Methods of Solubility enhancement

When the solubility in substances in aqueous media is limited, formulation strategies are required early in the drug discovery and they remain of critical importance for lead substance selection and commercial drug product development. Various techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs which include as following:

Chemical modifications

a) Salt Formation.
b) Co-crystallization.
c) Co-solvency.
d) Hydrotropy.
e) Use of novel solubilizer.
f) Nanotechnology.

Physical modification

Particle size reduction

a) Conventional method.
b) Micronization.
c) Nanosuspension.

Modification of the crystal habit

a) Polymorphs.
b) Pseudo polymorphs.

Complexation

a) Physical mixture.
b) Kneading method.
c) Co-precipitate method.

Inclusion complex formulation-based techniques

a) Kneading method.
b) Lyophilization/ freeze- drying technique.
c) Microwave irradiation method.

Solubilization by surfactants

a) Microemulsions.
b) Self microemulsifying drug delivery system.

Drug dispersion in carriers

Solid dispersions

I. Fusion Process.
II. Solvent method.
III. Fusion solvent method.
IV. Spray drying.
V. Lyophilization (Spray Freeze Drying Method).
VI. Hot melt extrusion.
VII. Dropping method.
VIII. pH adjustment.
IX. Supercritical fluid process.
X. Liquisolid technique.
XI. Polymeric alteration.

Chemical modifications

Salt formation

Many a times an API cannot be formulated in its pure form due to various issues of instability, thus they are converted to solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of them imparts a different physiochemical property and affects performance characteristics stability, bioavailability, purification and manufacturability of the drug in their own better way. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. Salts are formed when a compound is ionized in solution. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilised in peanut oil.

Co-crystallization

Co-crystallization alters the molecular interactions and is considered promising alternative to optimize drug properties. A more refined definition of a co-crystal can be “multi-component crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule. Co-crystallization overcomes various physical, chemical or physiological drawbacks of an API. Mechanism of co solvency favours the dissolution of a non-polar solute by lowering the interfacial tension. The most appropriate co- crystal can be selected using analytical techniques and rational physicochemical studies that include investigations of solubility and stability. The only difference between solvates and cocrystals is the physical state of the components. If one of the components is liquid and the other is solid then it is termed as solvates but on the other hand if both exists in solid form then they are termed as co crystals. Pharmaceutical Co-crystals basically consists of two components that are the API and the co-crystal former(s).

Different techniques for co crystallization

1. Solvent evaporation.
2. Grinding.
3. Slurry Co – Crystallization.
4. Solvent drop grinding (Modification of Grinding).
5. High throughput co-crystallization.
6. Hot melt extrusion.
7. Sonocrystallization Method.

Co-crystals characterization parameters

1. Solubility.
2. Maximum wavelength.
3. Stability.
4. Intrinsic dissolution.
5. Bioavailability.
6. Melting Point.

7. Melt (Hot stage microscopy).
8. Scanning Calorimetry (DSC).
9. XRD.
10. Vibrational spectroscopy.

Co-solvency

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as co solvency and the solvent used in combination are known as co solvent. Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly known as solvent blending. There is a dramatic change in the solubility of drugs by addition of organic co-solvent into the water. The cosolvents are having hydrogen acceptor or donor groups with a small hydrocarbon region. The hydrophobic hydrocarbon region usually interferes with the hydrogen bonding network of water which consequently reduces the intermolecular attraction of water while the hydrophilic hydrogen bonds ensures water solubility.

Hydrotropy

The term Hydrotropy was coined by Carl Neuberg in 1916 but the practical implications were introduced as late as 1976 by Thoma and coworkers. In this method by adding large amount of secondary solute increase the aqueous solubility of water insoluble drug (Table 2).

Table 2: **Classification of hydrotropes.**

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate
Aromatic cationics	PABA, Procaine hydrochloride, Caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

Mechanism of action of hydrotropes

Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. The hydrophilicity increase by anionic group and the ring system interacts with the solute to be dissolved. The mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium alginate, sodium benzoate, etc.

Hydrotropes with cationic hydrophilic group are rare, for example salts of aromatic amines, such as procaine hydrochloride. Besides enhancing the solubilization of compounds in water, they are known to exhibit influences on surfactant aggregation leading to micelle formation, phase manifestation of multicomponent systems with reference to nanodispersions and conductance percolation, clouding of surfactants and polymers, and so forth.

Use of novel solubilizer

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap, Soluplus Povacoat, dendrimers, is improve the solubility of hydrophobic API.

Sepitrap as novel Solubilizer: In less than 5 minutes, 80 % of solubilizers are desorbed from SepitrapTM (Microencapsulated solubilizer for solid dosage application) and therefore is available to solubilize the drug substance. The ratio of sepitrap and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect tablets characteristics and can be used without any formulation constraints.

Dendrimers act as solubilizing agents to host both hydrophilic and hydrophobic drugs and are known for their three dimensional, monodispersed, highly branched, macromolecular nano- scopic architecture with number of reactive end groups obtained by reiterative sequence of reactions. Dendrimers are considered as static unimolecular micelles and their micellar structure remains stable at even higher concentrations of solvents. Micelle-like behaviour of dendrimers resulted into their application to solubilize hydrophobic drugs. Dendrimers enhance the solubility of hydrophobes probably due to hydrophobic interactions, hydrogen bonding and electrostatic interaction between terminal functional groups of the dendrimers and hydrophobes. Most common dendrimers are polyamidoamine (PAMAM) dendrimers polypropyleneimine (PPI) dendrimers. Literature suggests that PAMAM dendrimers are the most investigated dendrimers in solubilization. Poly (propylene)imine dendrimers (PPI) constitute an equally important family of dendrimers reported first by Brabander and Meijer. These dendrimers closely resemble PAMAM dendrimers (except repeating units).

Nanotechnology

It refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation [23-26]. The methods of preparation like milling, high pressure homogenization, vacuum deposition, and high temperature evaporation may be used.

Physical modifications

Particle size reduction

Solubility of drug is often intrinsically related to drug particle size. As particle size become smaller, surface area to volume ratio increases. Larger surface area allows grater interaction with the solvent which causes an increase in solubility. The bioavailability of poorly soluble drugs is often related to drug particle size. Increased surface area by reducing particle size improves the dissolution properties and allows a wider range of formulation approaches and delivery technologies.

Conventional method of particle size reduction

Different mechanisms involved in conventional method of particle size reduction are cutting, compression, impact, attrition, combined impact and attrition. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an economic, reproducible, and efficient means of solubility improvement. However, the mechanical forces natural to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also considered when processing thermo sensitive or unstable active agents. Only by using traditional methods of solubility enhancement it is not possible to increase the solubility of poorly soluble drugs up to desirable level.

Micronization

It is a high energy particle size reduction technique that can convert coarse particles into particles of less than 5μ in diameter Micronization results in uniform and narrow particle size distribution essential for developing uniform dosage form. As micronization occurs surface area increases with decreasing particle size and solubility increases. The properties of the micronized drug substance such as particle size, size distribution, shape, surface properties, and agglomeration behavior and powder flow are affected by the type of micronization technique used. Mechanical communition, spray drying and supercritical fluid (SCF) technology are the most commonly employed techniques for production of micronized drug particles. According to the Noyes–Whitney postulations, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water-soluble drug substances.

Techniques for micronization

a) Jet milling /fluid energy mill or micronizer.
b) Rotor stator colloids mills.
c) Microprecipitation & microcrystallization.
d) Controlled crystallization.
e) Supercritical fluid technology.
f) Spray freezing into liquid.

Nanosuspension

Nanosuspension technology is important tool for solubility enhancement of poorly soluble drug. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is between 200 and 600 nm. In nanosuspension the particle size of drug reduces which increase the surface area and therefore the dissolution rate and solubility increases which enhance bioavailability. Basically, Nanosuspension is submicron colloidal dispersion of pure particles of drug which is stabilized by surfactants. Nanosuspension technology can also be applicable for drugs which are insoluble in both water and organic solvents.

Methods for preparation of nanosuspension:

There are two important methods for preparation of nanosuspension is

1. Bottom up technology.
2. Top down technology.

In bottom up technology the drug is dissolved in a solvent, which is then added to nonsolvent that causes precipitation of the fine drug particles. Precipitation technique is not applicable to drugs which are poorly soluble in aqueous and non-aqueous media. In case of top down techniques various methods include:

A. High pressure homogenization (dissocubes/nanopure).

- a) Combined precipitation and homogenization (Nanoedege).
- b) Nanojet technology.
- B. Milling techniques
- a) Media milling (Nanocrystals)
- b) Dry co-grinding.
- C. Emulsion solvent diffusion method.
- D. Super critical fluid method.

Modification of the crystal habit

Modification of the crystal habit polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability, etc. Broadly polymorphs can be classified as enantiotropes and monotropes basd on thermodynamics properties.

Polymorph

Polymorphs exist in

- a) Stable form- shows low aqueous solubility.
- b) Metastable form- shows high aqueous solubility.

e.g.: The polymorphic form III of riboflavin is 20 times more water soluble than the form I.

Pseudopolymorphs

Pseudopolymorphs, i.e., co-crystals are also studied along with polymorphism, which are solid crystalline materials comprising two or more molecules or atoms in the same crystal lattice. Co- crystals are also generally characterized as hydrates (solvent trapped), solvates (solvent present), and clathrates (molecules trapped). The first co-crystals reported were the co-crystals of hydroquinone and quinone in 1844 by Friedrich Wöhle. Co-crystals directly affect the solid-state properties in terms of solubility and bioavailability. Co-crystals are frequently designed for pharmaceutical formulations and many pharmaceutical products like tropomyosin and troponin, have been already designed by virtue of the co-crystal phenomenon.

Complexation

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

Technique of complexation physical mixture

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

Kneading method

Active drug with suitable polymer in different ratios is added to the mortar and triturated with small quantity of ethanol to prepare slurry. Slowly the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at 250C for 24hrs. The resultant product is pulverized and passed through sieve no. 80 and stored in dessicator over fused calcium chloride.

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 pulverized and passed through sieve no. 80 and stored in desiccators.

Inclusion complex formulation-based techniques

Inclusion complexes are formed by the lodging of the nonpolar molecule or nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). Commonly used host molecules are cyclodextrins. The cavity of host must be large enough to accommodate the guest and small enough to eliminate water, Solid inclusion complexes are prepared by various methods such as kneading method co-precipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method.

Techniques of inclusion complex method

Kneading method

This method is based on impregnating the CDs with little amount of water or hydroalcoholic solutions to convert 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 a sieve if required. In laboratory scale, kneading can be achieved by using a mortar and pestle. In large scale, kneading can be done by utilizing the extruders and other machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production.

Lyophilization/freeze-drying technique

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 CDs or suitable polymer at reduced pressure. Lyophilization is mainly dependent on unique properties of water and its role as solvent, gas, diluents, plasticizer, and stabilizer. It is an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent.

Microwave irradiation method

It 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 is separated by Whatman filter paper, and dried in vacuum oven at 40 °c for 48 hrs.

Solubilization by surfactants

Surfactants are molecules with 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 nonionic. When small polar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is of most importance in industrial and natural processes. The addition of surfactants decreases the surface tension and increase the solubility of the drug by increasing the dissolution of lipophilic drugs in aqueous medium. The surfactants are also used to stabilize drug suspensions. When the concentration of surfactants more than their critical micelle concentration(CMC), which is in the range of 0.05– 0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles and is known as micellization and predominantly results in elevated solubility of poorly soluble drugs.

Microemulsions

A micro emulsion is an optically clear pre-concentrate, isotropic, thermo dynamically stable transparent, translucent system, containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water-soluble drug. The criteria for the selection of surfactant are HLB and non-toxicity. On contact with water, the formulations self emulsifies and forms a very clear emulsion of small and uniform oil droplets containing the solubilized poorly soluble drug. Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral. Oil-in-water (o/w) microemulsion is the most suitable formulation, which is expected to increase the solubility by dissolving compounds with low water solubility into an oil phase. They can also enhance oral bioavailability by reducing the droplet size (< 100 nm), and hence increase the rate of absorption due to surfactant-induced permeability changes.

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. SEDDSs typically produce emulsions with a droplet size between 100–300 nm while self-micro- emulsifying drug delivery systems (SMEDDSs) 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.

Drug dispersion in carriers

Solid dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water- soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), Plasdone- S630. Surfactants like

Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion. The solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) and ritonavir with gelucire.

Applications of solid dispersions

It is possible that such a technique be used:

a) To obtain a homogeneous distribution of a minute amount of drug in solid state.
b) To stabilize the unstable drug.
c) To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
d) To formulate a fast release primary dose in a sustained released dosage form.
e) To reduce pre systemic inactivation of drugs like morphine and progesterone.
f) To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
g) To convert polymorphs in a given system into isomorphous, solid.

Hot melt method (fusion method)

The main advantages of this direct melting method is its simplicity and economy. The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system.

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of the drug and carrier.

Solvent evaporation method

Tachibana and Nakamura were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water-soluble carrier povidone. Many investigators studied solid dispersion of meloxicam, naproxen, and nimesulide using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poorly water-soluble drugs.

Fusion-solvent method

Carrier(s) is/are melted, and the drug(s) is/are incorporated in the form of a solution. If the carrier can hold a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Method is useful for drugs with high melting points or that are thermolabile.

Spray drying

The carrier and the active ingredient are dissolved, suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates, and solid dispersion is formed quickly.

Lyophilization (Spray Freeze Drying Method)

This method has been successfully developed to prepare solid dispersions at ambient temperature and avoid the heating during the preparation of thermosensitive drugs; spray freeze drying (SFD). SFD technology involves the atomization of a feed liquid containing poorly water-soluble or insoluble APIs and excipients directly into a cryogenic liquid at ambient temperature to produce a frozen micronized powder that is subsequently dried. This process offers a variety of advantages compared to traditional technologies for solid dispersions, including amorphous structure and high surface area.

Hot-melt extrusion

A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active ingredients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through heated screws, it is transformed into its “fluid like state”. This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drug that are somewhat thermolabile to be processed.

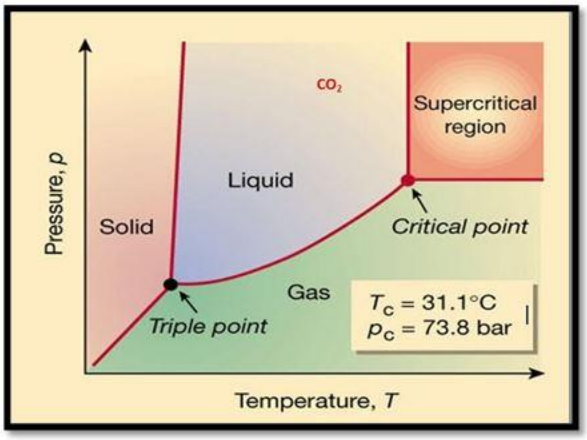

***Figure 1:* Phase diagram of super critical fluid.**

Dropping method

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

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.

Supercritical fluid process

Super critical fluid is fluid which exists as single fluid above its critical temperature and pressure. SCF shows the properties of both a liquid and a gas above its critical condition. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be re-crystallized at greatly reduced particle sizes (Figure 1).

Liquisolid technique

In liquisolid technique liquid may be transfer into free flowing, readily compressible and apparently dry powder by simple blending with selected carrier and coating material. The liquid portion which can be liquid drug, drug suspension or drug solution in a suitable non-volatile liquid vehicle can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The acceptable flowing and compressible powder form of liquid medication is liquisolid compact. The liquisolid is newer and promising approach because of simple manufacturing process, low production coast, and applicable for industry due to good flow and compact property of liquisolid formulation. When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface (Table 3).

Table 3:* *Components of liquisolid system.

Component	Examples
Non-Volatile	Polyethylene Glycol 200, Poly Ethylene Glycol 300, Poly
Liquids	Ethylene Glycol 400, Glycerine, Propylene Glycol, fixed oils.
Carrier Materials	Microcrystalline Cellulose PH 101, Microcrystalline Cellulose PH 200, Lactose, Methyl Cellulose, Ethyl Cellulose, Starch1500, Ethocel, Eudragit RL, Eudragit RS 12, HPMC K4M, HPMC, K100M, Xanthum Gum, Guar gum
Coating	Aerosil 200, Silica (Cab-O-Sil M5), Syloid 244FP, and Colloidal
Materials	Silicon Dioxide.
Disintegrants	Sodium Starch Glycolate (Explotab, Primogel), Croscarmellose Sodium, Cross Polyvinyl Pyrrolidine, Pregelatized Starch.
Glidant	Talc
Lubricant	Magnesium stearate

Classification of liquisolid system

Classification based on type of liquid medication contain there in

1. Powdered drug solutions.
2. Powdered drug suspensions.
3. Powdered liquid drugs.

Polymeric alteration

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may vary in physicochemical properties such as physical and chemical stability, melting point, vapour pressure, shelf-life, dissolution rate, morphology, density, biological activities intrinsic solubility, and bioavailability. Amongst the stable, unstable, and metastable crystalline polymorphs, metastable forms are related with higher energy with increased surface area, solubility, bioavailability and efficacy. About bioavailability, it is favoured to change drug from crystal forms into metastable or amorphous forms over its shelf-life under a variety of real-world storage conditions [11-22].

Conclusion

The various techniques enlisted in this article are used in combination for solubility enhancement of poorly water-soluble drugs, but the solubility improvement mainly depends on the selection of proper method. The selection of suitable method for solubility enhancement is depends on drug properties like melting point, solubility, chemical nature, physical nature, pharmacokinetic behaviour and so on. The article concludes that solubility of poorly water-soluble drugs is an important concept to reach into systemic circulation to show its pharmacological response.

Summary

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.

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