Review Article

Advances in Solubility Enhancement Techniques

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Accepted on: 28-05-2013; **Finalized on:** 31-07-2013.

ABSTRACT

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. The major problem encountered with formulation development of new chemical entities as well as for the generic development is low aqueous solubility. It is seen that out of the total number of NCE (new chemical entities) developed, 40% seems to be practically insoluble in water. Thus solubility becomes the major challenge for a formulation scientist. For any drug to be absorbed it should be present in the solution form at the site of absorption. For enhancement of solubility there are various techniques that are used. These techniques include; Physical modifications techniques like media milling/ nanocrystal technology, cryogenic technology, supercritical fluid process, modification of the crystal habit, complexation, micellar technologies and chemical modifications. Other techniques like co-crystallization, co-solvency, hydrotrophy are used to increase the solubility of very soluble drugs like dolargin, loperamide, tubocurarine, doxorubicin, ibuprofen, griseofulvin, diazepam, naproxen, carbamazepine, nifedipine, phytosterol etc. Thus selection of solubility improving methods depends on drug property, site of absorption, and required dosage form characteristics.

Keywords: Co-crystallisation, cryogenic techniques, co-solvency, Particle size reduction, solid dispersion, solubility**.**

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. Solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[1]

A frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development is solubility. There are various methods which can be adapted to improve solubilization of poorly water soluble drug and to improve its bioavailability. Bioavailability is affected by several other factors like drug solubility in aqueous environment and drug permeability through lipophilic membranes being the important ones.

The solvent is generally a liquid which can be a pure substance or a mixture of two liquids. 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.[2] 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.

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.

Figure 1: Solubility criteria as per USP and BP

Descriptive term	Part of solvent required per part 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 Soluble	From 100 to 1000
Very Slightly Soluble	From 1000 to 10000
Practically insoluble	10,000 and over

If the solubility is expressed in this manner then the advantage is its simplicity and the disadvantage is that it can strongly depend on the presence of other species in the solvent (e.g. 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. As there are other equilibrium constants, temperature would affect the numerical value of stability constant. The theories given by Flory-Huggins, Hansen solubility and the Hildebrand solubility

parameters are empirical methods for prediction of solubility.

The other property such as partition co-efficient (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 Fig 1.[3,4] One of the main guide for predicting the intestinal drug absorption provided by the U.S. F.D.A. is the BCS classification. The two parameters restricted in this system are solubility and interstitial permeability.

The Biopharmaceutics Classification System has divided all the drugs in to four classes.

- 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

Importance of Solubility

The most convenient and commonly employed route of drug delivery is oral ingestion due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. Thus, many generic drug companies are inclined more to produce bioequivalent oral drug products.

The major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre systemic metabolism, and susceptibility to efflux mechanisms. The main cause for low bioavailability is attributed to poor solubility and low permeability. Solubility is an important aspect for other dosage forms like parenterals as well.[5] It is also important to achieve the desired pharmacological response.[6]

The drugs which are poorly soluble in water often require high doses in order to reach therapeutic plasma concentrations after oral administration. The major problem encountered with formulation development of new chemical entities as well as generic development is low aqueous solubility. For any drug to be absorbed it must be present in the form of an aqueous solution at the site of absorption. Water is mostly, the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

Amongst the new chemical entities being developed (NCE's) 40% are practically insoluble in water. The drugs which are administered orally it is a known fact that solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Thus, the problem of solubility is a major challenge for a formulation scientist. [7]

To improve the drug solubility and thereby increasing its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are various approaches enlisted in literature to enhance the solubility of a poorly water-soluble drug. The techniques or approaches to enhance solubility is selected on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability.

For BCS class 2 drugs especially, the bioavailability may be enhanced by increasing the solubility and certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The rate limiting step for the BCS class II drugs is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.

Procedure of Solubilisation[8]

Solubilisation process takes place as follows:

1. Breaking of intermolecular bonds in solute.
2. Separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

It basically occurs in three steps:

- Holes open in a solvent
- Molecules of the solid breaks away from the bulk
- The freed solid molecule is integrated into the hole in the solvent.

Factors affecting solubilisation

1. Particle size: Particle size is inversely proportional to solubility. As particle size decreases, surface area increases thus increasing the solubility of the solute in the solvent.
2. Temperature: Increase in temperature increases solubility.
3. Pressure: Solids and liquid solutes have no effect of pressure. But for gaseous solutes increase in pressure increases solubility and decrease in pressure decreases solubility.
4. Nature of solute and solvent: 1g of $PbCl_2$ dissolves in 100g of water and 200g of $ZnCl_2$ dissolves in water.

5. Molecular size: Solubility of the substance is decreased with increase in molecular size and molecular weight. In case of organic molecules, due to increase in branching the solubility increases.
6. Polarity: Polarity follows 'like begets like' phenomena. It is similar that polar solutes will dissolve in polar solvents only. Similarly, non-polar solutes will dissolve in non-polar solvents.
7. Polymorphs: Polymorphs can vary in melting point. Genereally polymorphs are made as the changes in the structure results in the change in its solubility.

Techniques of solubility and bioavailability enhancement [9]

The techniques of solubility enhancement are categorized as follows:

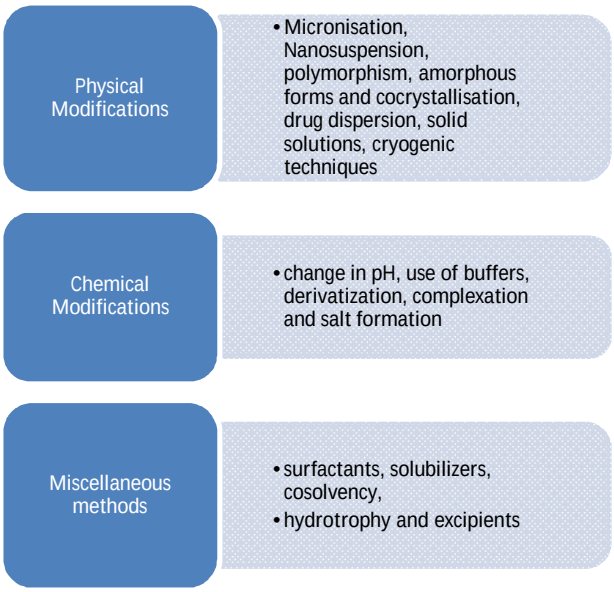

Figure 2: Techniques of solubility enhancement

These are the general techniques to enhance solubility.

PHYSICAL MODIFICATIONS

Solubility is a phenomenon which is related to particle size and surface area thus it becomes important to reduce the particle size of the drug thereby increasing its surface area and thus enhancing its solubility. There are conventional techniques to reduce the particle size, few of which includes comminution and spray drying. These techniques rely upon mechanical stress to disaggregate the active compound. However due to mechanical stress of communition and thermal stress of spray drying the drug substance may undergo degradation in both the cases and if thermo labile then spray drying would cause a problem. Thus using some of these conventional and traditional approaches solubility may not be enhanced up to the desired level.

Micronization is one of the traditional approaches required for particle size reduction. It aids in increasing the dissolution rate through increasing the surface area. Micronization is basically done using jet mill and rotor stator colloid mill. Micronisation was found to be useful in griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. For each of these drugs it was found to improve their digestive absorption, and consequently their bioavailability and clinical efficacy. Fenofibrate when micronized exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media.[10,11]

1) Solid Dispersions

Solid dispersion is one of the physical modification technique to enhance solubility. The types of approaches used to prepare solid dispersions includes:

- Hot-melt (fusion) method
- Solvent Evaporation
- Hot melt-extrusion

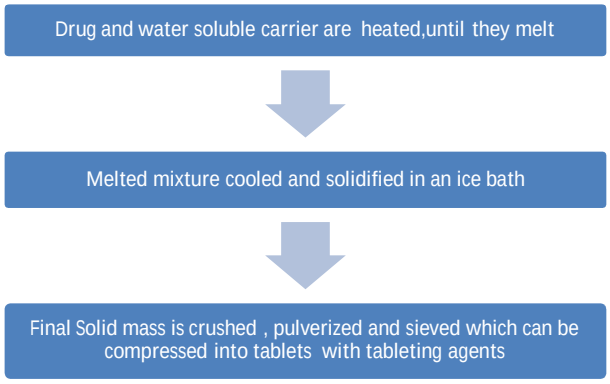

Figure 3: Hot-melt (fusion) method

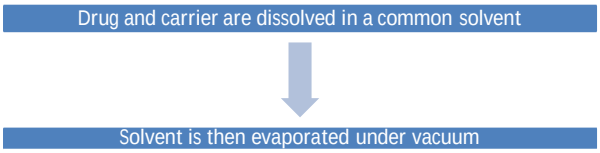

Figure 4: Solvent Evaporation Method

Tachibana and Nakamura produced a solid solution of the highly lipophilic *β*-carotene in the highly water soluble carrier povidone as they 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. Solid dispersion of meloxicam, naproxen, and nimesulide using solvent evaporation technique was studied by many investigators. No thermal decomposition of drug or carrier is one of the advantage of this method and disadvantage is higher cost of preparation and difficulty in completely removing the organic solvent.[9-12]

Example on significance of Solid dispersion

In one of the recent research conducted solubility of desloratadine was increased by solid dispersions in poloxamers. [13]

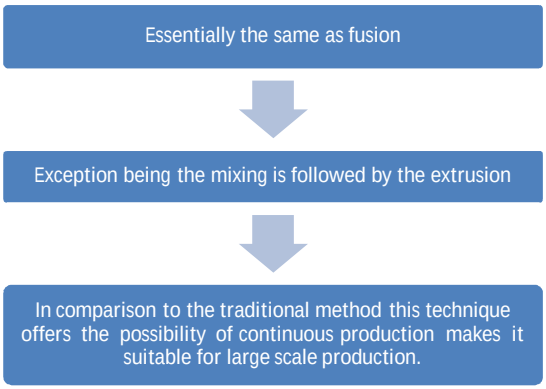

Figure 5: Hot-melt extrusion

2) Nanosuspension

This technology has been developed as a promising solubility enhancement technique for drugs that are both water and oil insoluble. The technique comprises of basically 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 ranges from 200nm and 600nm.There are various methods utilized to prepare nanosuspension and these includes media milling, high pressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of precipitation and high-pressure homogenization.

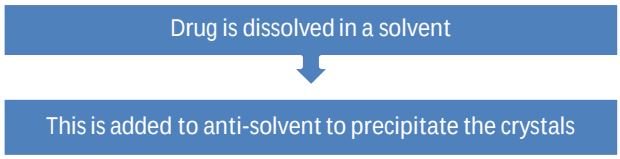

Figure 6: Precipitation technique

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. [14,15]

Media Milling

It uses 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 microparticulate drug to nanosized particles. [16]

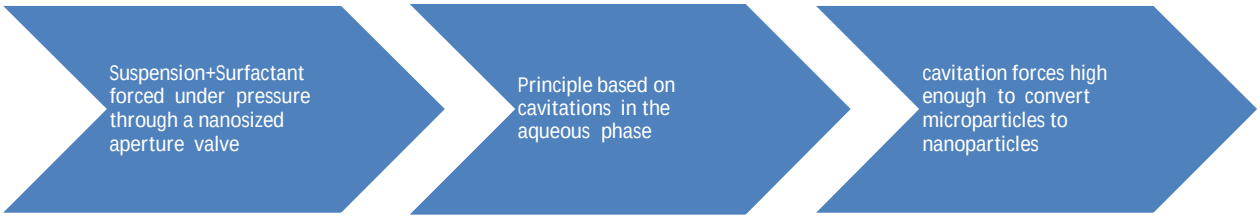

Figure 7: High-pressure homogenization

This technique was found to be useful in improving the dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole. [16-18]

Combined precipitation and homogenisation

The precipitated drug nanoparticles have a tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (homogenisation). They are in completely amorphous, partially amorphous or completely crystalline forms which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step. [10]

Example on significance of Nanosuspension

A nanosuspension of a herb Herpetrione (HPE) was prepared. Nanosuspension of HPE showed better invitro and invivo results as compared to the coarse HPE. The results revealed that particle size reduction could enhance HPE dissolution rate and absorption in gastrointestinal tract, and nanosuspension might be a good choice for oral delivery of poor bioavailability drug like HPE. [19]

Polymorphisim

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. Thus, crystal engineering techniques are developed for the controlled crystallization of drugs to produce high purity powders with well-defined particle size distribution, crystal habit, crystal form (crystalline or amorphous), surface nature, and surface energy. If the crystallizing conditions are modified or manipulated (by using different solvents or change in the stirring or adding other components to crystallizing drug solution), it then becomes possible to make crystals with different packing arrangement; Such crystals are called as polymorphs. Thus polymorphs for the same drug differ in their physicochemical properties

such as solubility, dissolution rate, melting point, and stability. [10]

Cocrystallisation

This is one of the new approach available for the enhancement of drug solubility. It includes application of co-crystals also referred as molecular complexes. If the solvent is an integral part of the network structure and forms at least two component crystals, then it may be termed as co-crystal. If the solvent does not participate directly in the network itself, as in open framework structures, then it is termed as clatharate (inclusion complex). A co-crystal may be defined as a crystalline material that consists of two or more molecular (and electrically neutral) species held together by non-covalent forces. These co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Three of the co-crystallising agents are classified as generally regarded as safe (GRAS) includes sachharin, nicotinamide, and acetic acid limiting the pharmaceutical applications.

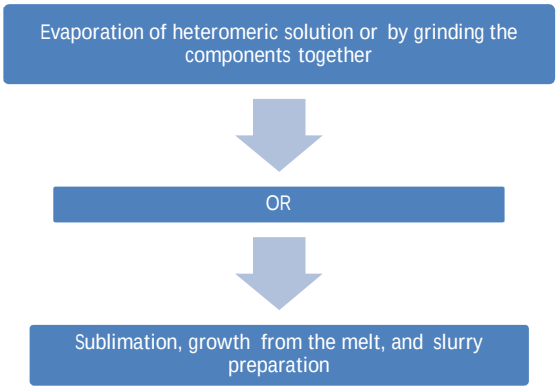

Figure 8: Preparation of co-crystals

More than 20 drugs till date have been reported including caffeine and glutaric acid polymorphic co-crystals.

Solid Solutions [20]

This is a binary system comprising of solid solute which is molecularly dispersed in a solid solvent. Since the 2 components crystallize together in a homogenous one phase system, solid solutions also called as molecular dispersions or mixed crystals or melts.

It can be classified by two way:

On the basis of the extent of the miscibility of the two components

- Continuous solid solution (isomorphous, unlimited, complete).
- Discontinuous solid solution (limited, restricted, partial, incomplete).

On the basis of the molecular size of two molecules of solid solution.

- Substitutional solid solution
- Interstitial solid solution

Continuous solid solution

In this type of solid solution the two components are miscible in the solid state in all proportions.

The total lattice energy of continuous solid solution at various compositions theoretically should be greater than that of bond between the different components at solid state.

Discontinuous solid solution

As opposite to continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solution. Each component is capable of dissolving the other component to a certain degree above the eutectic temperature. As the temperature decreases the solid solution regions becomes narrower.

Substitutional solid solution

Here the solid molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent and it can form a continuous or discontinuous solid solution. A decisive role is played by the size and the steric factor of the solute molecule in the formulation of solid solution, the size of the solute and the solvent molecule should be as close as possible. The drugs that have been made into these are anthracene – acenaphthene and ammonia-potassium thiocyanate.

Interstitial solid solution

This type of solid solution has the solute molecule occupying the interstitial space of the solvent lattice, usually forms only discontinuous solid solution. The size of the solute becomes critical as it has to fit into the interstices. The solid solutions of digitoxin, methyl testosterone, prednisolone acetate and hydrocortisone acetate in matrix of PEG-6000 is an example of this kind.

Super critical fluid

This has been used to decrease particle size. A super critical fluid is defined as non condensable fluid. These fluids have temperature and pressure greater than its critical temperature (Tc) and critical pressure (Tp). In this technique to increase the solubilisation, the pressure of the critical fluid is manipulated. Manipulation of the pressure of the critical fluid and its favorable characteristics of gases-high diffusivity, low viscosity and low surface tension may be imparted upon liquids to precisely control the solubilisation of a drug with a SCF. SCF's are highly compressible and it allows moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determines its solvent power. SCF's are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of fluid that largely determine its solvents power. [21]

CRYOGENIC TECHNIQUES

These techniques have been developed to create nano - structured amorphous drug particles with high degree of

porosity at very low temperature conditions so as to enhance the dissolution rate of drugs. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic and ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydro fluoro alkanes, N2, Ar, O2 and organic solvents).The dry powder after the cryogenic process can be obtained by various processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilization. [8]

The cryogenic techniques are of different types:

1. Spray freezing onto cryogenic fluids:

Drug and carrier (mannitol, maltose, lactose, inositol or dextran) is 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 dispersion of aqueous solution.

2. Spray freezing into cryogenic fluids (SFL):

It incorporates direct liquid – liquid impingement between the atomized feed solution and cryogenic liquid to provide more intense atomization into micro droplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry powder.

3. Spray freezing into vapor over liquid (SFV/L):

Freezing of drugs solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability .During SFV/L the atomized droplets 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.

4. Ultra-rapid freezing (URF):

Ultra rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drug solution to the solid surface of cryogenic substrate leading to instantaneous freezing and subsequent lyophilization for removal of solvent forms micronized drug powder with improved solubility.

5. High pressure homogenization:

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 particle cavitations forces are sufficiently high to convert the drug microparticles into nanoparticles.

CHEMICAL MODIFICATIONS

Change in pH

The organic solutes which are ionizable; changing the pH of the system may be the most effective means of increasing aqueous solubility. The solubility of an ionizable drug can be increased exponentially under proper conditions by adjusting the pH of the solution. A drug which is efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa.

Commercial products using pH adjustment: Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents.[11]

Buffers

Buffers are practically used to simply maintain the pH of the system over time. For pH solubilized drugs, another practical use of a buffer is to reduce or eliminate the potential for precipitation of the drug upon dilution. [20]

Selection of Buffer:

- In desired pH range the buffer must have adequate capacity.
- It must be biologically safe for the use intended.
- There should be no deleterious effect on the stability of the final product.
- It should permit the use of other excipients like flavoring or coloring agents.

A very small change in pH results in more drug going into the solution. So, by observing the pH solubility profile, it helps in selection of buffer for optimum pH range.

Buffers used in pharmaceutical preparations

Formulation	Buffers
Tablet and Capsules	Mg Carbonate; Sodium bicarbonate
Ointments and Creams	Citrate, acetate, phosphate
Ophthalmic	Boric acid, isotonic phosphate, citrate
Parenteral	Citrate, acetate, tartrate, glutamate

Solubilization with salts

The salts have improved solubility and dissolution characteristics in comparison to the original drug. The alkali metal salts of acidic drugs like penicillins and strong acid salts of basic drugs like atropine are more water-soluble than the parent drug. The factors which influence salt selection are physical and chemical properties of the salt, safety of counterion, therapeutic conditions and route of administration. [20]

Disadvantages:

- It is not feasible to form salts of neutral compounds**.**
- It may also be difficult to form salts of very weak bases or acids**.**
- The salt may be hygroscopic, exhibit polymorphism or has poor processing characteristics.

- The conversion of salt to free acid or base form of the drug on surface of solid dosage form that prevents or retards drug release.
- Precipitation of unionized drug in the GI milieu that has poor solubility.

Self-emulsifing drug delivery system

The concept of in situ formation of emulsion in the gastrointestinal tract is used by self-emulsifying drug delivery systems. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS), in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions or nano-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophillic drug dissolution and absorption. One of the advantage of this is in relation to scale up and manufacture that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. [11]

The concept of SMEDDS is known. There is a new concept of SNEDDS, self nano-emulsifying drug delivery system. One such research on Lacidipine (a calcium channel blocker) was done. This research had Lacidipine, surfactants that are reported as bioenhancers. The optimized formulation of LCDP showed a significant increase in dissolution rate compared to the drug suspension under the same conditions. The results proposed that the optimized SNEDDS formulation, containing bioenhancing surfactants, could be promising to improve oral absorption of LCDP. [22]

MISCELLANEOUS METHODS [11,19,23,25,27]

Surfactant/Micellar Solubilisation

Use of surfactant is basically a traditional approach to increase solubility. They reduce surface tension and improve dissolution of lipophilic drugs in aqueous medium; by improving wetting of solids and increasing rate of disintegration of solid into finer particles. These are also used to stabilize microemulsions and suspensions into which drugs are dissolved. Micellar solubilisation is used by antidiabetic drug like gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.

Hydrotropy

It's a solubilisation process, whereby addition of a large amount of a second solute, the hydrotropic agent results in an increase in the aqueous solubility of first solute. Hydrotropic agents are basically ionic organic salts, consists of alkali metal salts of various organic acids. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts"; a phenomenon known as "hydrotropism." Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drug compounds which exhibit hydrotropic behavior includes ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β-naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene. Hydrotropes with cationic hydrophilic group are rare, for example salts of aromatic amines, such as procaine hydrochloride.

Co-solvency

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents. Co-solvents are generally mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. This is one of the most widely used techniques because it is simple to produce and evaluate. Co-solvency has been utilized in different formulations including solids and liquids. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Poorly soluble compounds which are lipophillic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. Dimethyl sulfoxide (DMSO) and dimethyl acetoamide (DMA) have been widely used as co-solvents because of their large solubilization capacity for poorly soluble drugs and their relatively low toxicity. Advantages: Simple and rapid to formulate and produce. Disadvantages: As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered. Uncontrolled precipitation occurs upon dilution with aqueous media. Co-solvent products: Nimodipine Intravenous Injection Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK) are examples of co-solvent formulations.

CONCLUSION

Solubility is an essential pre-requisite. It can be said that, by solubility enhancement the bio-availability also increases and thus the absorption of the drug is more. For oral formulations of BCS class 2 and class 4 drugs increasing the solubility becomes an essential phenomena. Thus it can be concluded that all the above listed techniques provide aid in increasing the solubility and thereby increase its absorption. The current research trends in this area are improving the solubility aspects of 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.

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Source of Support: Nil, **Conflict of Interest:** None.