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SOLUBILITY ENHANCEMENT OF POOR WATER SOLUBLE DRUG

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ABSTRACT

A success of formulation depends on how efficiently it makes the drug available at the site of action. Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. There are many techniques which are used to enhance the aqueous solubility. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for drugs. This is true for parenterally, topically and orally administered solutions. Hence various techniques are used for the improvement of the solubility of poorly water soluble drugs include hydro trophy, use of salt form, use of precipitation inhibitors, alteration of pH of the drug micro-environment, solvent deposition, precipitation pH adjustment, co-solvency,micellar solubilisation, super critical fluid techniques, solid dispersion, complexation, micro-emulsion, solid solution, eutectic mixture, selective adsorption on insoluble carriers, evaporative precipitation into aqueous solution, use of surfactants, use of amorphous, an hydrates, solvates and nanonisation.

INTRODUCTION

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitativeterms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and molefraction. Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueoussolubility.Solubility is the characteristic physical property referring to the ability of given substance, the solute, to dissolve in solvent. Almost More than 90% drugs are orally administered. Drug absorption, sufficient& reproducible bioavailability, pharmacokinetic profile of orallyadministereddrug substances is highly dependent on Solubility of that compound inaqueousmedium. More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active newchemical entities (NCEs) identified incombinatorialscreening programs employed by many pharmaceutical companies are poorlywater soluble. Drug absorption,sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today asone of the major challenges in oral delivery of new drug substances. Orally administered drugs ontheModel list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain. Of the130 orally administered drugs on the WHOlist61 could be classified withcertainty.84% of these belong to class I (highly soluble, highly permeable), 17%to class II (poorly soluble, highly permeable), 24(39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable).The rate and extent of absorption of class II & class Compounds is highly dependent on the bioavailability which ultimately depends on solubility. Due to this major reasonSolubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous

Solvent is a component whichforms major constituent of a solution &is capable to dissolve another substance to form a uniformly disperse mixture at the molecularlevel. Solute is a substance that present in small quantity & dissolves insolvent. The solubility of a solute is the maximum quantity of solute that can dissolvein certain quantity of solvent or quantity of solution at a specified temperature". In the other words,solubilitycan also define as the ability of one substance to form a solution with another substance.

S.no.	Descriptive terms	Parts of solvent required to dissolve one part of solute
1	Very soluble	Less than 1
2	freely soluble	More than 1 but less than 10
3	Soluble	More than 10 but less than 30
4	Sparingly soluble	More than 30 but less than 100
5	Slightly soluble	More than 100 but less than 1000
6	Very slightly soluble	More than 1000 but less than 10,000
7	Very very slightly soluble or practically Insoluble	More than 10,000

Solubilisation:

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute the 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.

Step 1: Holes opens in the solvent

Step 2: Molecules of the solid breaks away from the bulk Step 3: The freed solid molecule is integrated into the hole in the solvent.

Solubility-

The solubility depends on the physical form of the solid, the nature and composition of solvent medium, particle size, temperature, pressure, nature of the solute and solvent, molecular size polarity, polymorphs, rate of solution.

Techniques for Solubility Enhancement:A number of methodologies can be adapted to improve solubilization of poor water-soluble drugs and further to improve its bioavailability.

Hydro trophy:

Hydrotropic effect, the meaning is taken as the increase in saturation solubility of a substance in water by the addition of organic salts or also non-electrolytes, which of course must be physiologically compatible

The mode of action of the hydrotropic substances is thought to be due to either an associateformation, in low concentrations to aformation of molecular complexes or in higher concentrations to the water structure being influenced. These hydrotropic substances are able to increase the number of hydrogen bridges in the water clusters. This makes the water more hydrophobic &thus it is a better solvent for non-polar drug However, the use of hydrotropic substances such as sodium benzoate,nicotinamide,urea, caffeine, sorbitol, etc. is limited due to the following factors: Slight increase of saturation solubility with high concentration of excipients. (E.g. up to50%nicotinamidewith a triple increase in the saturation solubility)

Isotonicity is not reached. Individual effects of the excipients. Hydrotropicsolubilisation is one of them.Hydrotropy is a solubilisationphenomenon whereby addition of large amounts of second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium aciculate, urea,nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs. Hydrotropism are a class of amphiphilic molecules that cannot form well-organized structures, such as micelles, in water but do increase the aqueous solubility of organic molecules. Often strong synergistic effects are observed whenhydrotropism are added to aqueous surfactant or polymer solutions. A hydrotropic is a compound that solubilises hydrophobic compounds in aqueous solutions. Typically,hydrotropes consist of a hydrophilic part and hydrophobic part (like surfactants) but the hydrophobic part is generally too small to cause spontaneous self-aggregation.Hydrotropes do not have a criticalconcentration above which self-aggregation 'suddenly' starts to occur (as found for micelle-and vesicle-forming surfactants, which have a critical micelle concentration or CMC and a critical vesicle concentration, respectively Instead, some hydrotropesaggregate in a step-wise self-aggregation process, gradually increasing aggregation size. However, many hydrotropes donotseem to self-aggregate at all, unless asolubilisate has been added. Are in use industrially.Hydrotropes are used in detergent formulations to allow more.

Use of Salt Form:

Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pka value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water soluble than the parent drug. Salt formation isfrequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure. The ideal characteristics of a salt are that it ischemically stable, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution and exhibits good bioavailability) Potentially Useful Salts: Salt formation is one of the simplest chemical reactions, involving either a proton transfer or a neutralization reaction between an acid and a base. Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.

Complex Salt Formation:

Organic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubility than their corresponding inorganic salts. Acetic acid produced solubility higher than those observed with nay of the inorganic acids. Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum differenceof units between the pka value of the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water soluble than the parent drug. Salt Formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Aspirin, Theophylline, Barbiturates

Particle size reduction:

The solubility of a drug is intrinsically related to the particle size. Reduction of particle size of a drug by various means such as jet mill, rotor stator colloidal mill, ball mill, etc. leads to increase in surface area with enhanced dissolution. But limitation of this process includes thermal and physical stress on drug product that leads to degradation. Other disadvantages include limited opportunity to control important characteristics of final product such as shape, size, morphology, surface properties, and electrostatic charges. Also, amorphous region are thermodynamically unstable, susceptible to recrystallization on in hot and humid condition.

Nanosuspension technology:

Nanosuspension technology has been developed as a promising candidate for effective delivery of poor water-soluble drug. Nanosuspension is sub-micron colloidal dispersion of pure particles of drugs, which is stabilized by surfactants for either topical or oral use or parentral or pulmonary administration. In nanosuspension, particle size is usually less than one micron ranging between 200 and 600 nm.[5,6] Media milling, high pressure homogenization in water, high pressure homogenization in non-aqueous media and combination of precipitation and high pressure homogenization are the various method of preparation of nanosuspension.[7,8] Nanosuspension approaches have been employed for various drugs including tarazepide, atovaquone, amphotericin B, etc.

Surfactant:

The use of surfactant in enhancement of solubility of poorly soluble drug has been employed successfully.

Salt formation:

Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance and commercilation.

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 solubility.

Hydrotrophy:

Hydrotrophy is a solubilization phenomenon in which solubility of poorly water soluble drug is enhanced to many folds by using sodium benzoate, urea, sodium citrate, and sodium salicylate.

Rasool A.A. et al.,improve solubility of many drugs, i.e., diazepam, griseofulvin, testosterone, progesterone, and 17-estradiol in presence of nicotinamide and related compounds. All solubilities were found to increase in nonlinear fashion as a function of nicotinamide concentration.

Solid dispersion:

Chiou and Riegelman 1971[14] define solid dispersion as group of solid products consisting of at least two different components, generally, a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method.

Melting 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 forms6. 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. Such a technique was subsequently employed with some modification by Goldberg et al and

ChiouandRiegelman. The solidified masses were often found to require storage of 1 or more days in a desiccator at ambient temperatures for hardening and ease of powdering. Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37 or higher temperatures. 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 system7. A modification of the process involves spray congealing from a modified spray drier onto cold metal surface. Decomposition should be avoided and is affected by fusion time and rate of cooling. Another modification of the above method, wherein SD(s) of troglitazone-polyvinyl pyrrolidone (PVP) k 30 have been prepared by closed melting point method. This method involves controlled mixing of water content to physical mixtures oftroglitazone PVPK30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersion with 0% apparent crystallinity. Solvent Evaporation Method

The solvent based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic, and complete solvent removal from the product can be a lengthy process. Moreover subtle alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of solvents are generally required which can give rise to toxicological problems. This method has been used for a long time in the preparation of solid solutions or mixed crystals of organic or inorganic compounds9. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. Many investigators studied SD of meloxicam10, naproxen11, nimesulide12, carbamezipine13 and celecoxib14 using solvent evaporation technique. These findings suggest that the above-mentioned technique can be employed successfully for improvement. However, some disadvantages associated with this method are the higher cost of preparation, the difficulty in completely removing liquid solvent, the possible adverse effect of the supposedly negligible amount of the solvent on thechemical stability of the drug, the selection of a common volatile solvent, and the difficulty of reproducing crystal forms. In addition, a supersaturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties, as is discussed later. It must be emphasized that the suitability of the solvent method to prepare simple eutectics or partial solid solutions remains to be studied further because their final physical properties may be quite different from those obtained by the melting method7.

CONCLUSION

This article concludes that solubility of poorly water-soluble drugs is an important concept to reach into systemic circulation to show its pharmacological response. Dissolution is a rate limiting step for drug absorption of poorly water-soluble drugs. Experience with solid dispersion over the last 20-30 years indicates that this is a fruitful approach to increase the solubility of poorly water-soluble drugs. Increasing number of poorly water-soluble drug candidates as well as improvements in solid dispersion manufacturing methods strongly favour the role of solid dispersion in solubility enhancement of poorly water-soluble drugs.

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2.Solubility Enhancement – Eminent Role in Poorly Soluble Drugs

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