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REVIEW ARTICLE ON SOLUBILITY ENHANCEMENT TECHNIQUES FOR POORLY SOLUBLE DRUGS

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ABSTRACT

A drug administered in solution form immediately available for absorption. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug . Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques.

Keywords: Dissolution, permeability, solubility.

INTRODUCTION

Solubility: The term ‘Solubility’ is defined as maximum amount of solute that can be dissolved in a given amount of solvent to form a homogenous system at specified temperature. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity , molality , volume fraction, mole fraction. The pharmacopoeia lists solubility in terms of number of millilitres of solvent required to dissolve 1g of solute. The indian pharmacopoeia provides general terms to describe a given range. These descriptive terms are given as:

Definition	**Part of solvent required for one part of solute**
Very soluble	< 1
Freely soluble	1 - 10
Soluble	10 - 30
Sparingly soluble	30 – 100
Slightly soluble	100 - 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

IMPORTANCE OF SOLUBILITY

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Hence various techniques are used for the improvement of the solubility of poorly water-soluble drugs.

Solubility of drug is largely due to, Polarity of the solvents, that is, to its dipole moment. A polar solvent dissolves ionic solutes and other polar substances.

2. The ability of solute to form hydrogen bond with solvent.

3. Also depends on the ratio of the polar to non polar groups of the molecule. As the length of a non-polar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases. Straight chain monohydric alcohols, aldehyde , ketones , and acids with more than four or five carbons cannot enter into the hydrogen bonded structure of water and hence are only slightly soluble.

When additional polar groups are present in the molecule, as found in tartaric acid,propylene glycol, glycerin, water solubility increases greatly. Branching of the carbon chain reduces the non-polar effect and leads to increased water solubility. Tertiary butyl alcohol is miscible in all proportions with water, where as n-butyl alcohol is slightly dissolved.

Techniques Of Solubility Enhancement

I. Physical Modifications A. Particle size reduction a. Micronization c.Sonocrystalisation b. Nanosuspension d.Supercritical fluid process

B. Modification of the crystal habit a. Polymorphs b. Pseudopolymorphs

C. Drug dispersion in carriers a. Eutectic mixtures b. Solid dispersions c. Solid solutions D. Complexation a. Use of complexing agents E. Solubilization by surfactants a. Microemulsions 11

II. Chemical Modifications a. Change in the pH b. Use of buffer c. Derivatization

III. Other methods Co- crystallisation Co-solvency Hydrotrophy Solubilizing agents Solvent deposition Selective adsorption on insoluble carrier Using soluble prodrug Functional polymer technology Precipatation Porous microparticle technology Nanotechnology approaches

Particle size reduction

A. Particle size reduction: Particle size reduction can be achieved by a.Micronization b.nanosuspension c.Sonocrystalisation d.Supercritical fluid process a. Micronization: Micronization increases the dissolution rate of drugs through increased surface area. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug . The process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods (fluid energy or jet mill).The process is also called micro-milling. Colloidal mill

B. Nanosuspension : A pharmaceutical nanosuspension is biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs . This technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed . Nanosuspension approach has been employed drugs like paclitaxel,tarazepide,amphotericin B which are still on research stage.

Techniques for the production of nanosuspensions : a) Homogenization. b) Wet milling. Homogenization: The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles. Wet milling: Active drug in the presence of surfactant is defragmented by milling.

Other techniques for reduction of the particle size

Other techniques for reduction of the particle size 1 . Sonocrystallisation 2 . Supercritical fluid process

1. Sonocrystallisation: The novel approach for particle size reduction on the basis of crystallisation by using ultrasound is Sonocrystallisation . Sonocrystallisation utilizes ultrasound power for inducing crystallisation . It not only enhances the nucleation rate but also an effective means of size reduction and controlling size distribution of the active pharmaceutical ingredients. Most applications use ultrasound in the range 20 kHz-5 MHz 16

2. Supercritical fluid process: Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense noncondensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). A SCF process allows micronisation of drug particles within narrow range of particle size, often to sub-micron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5 to 2,000 nm in diameter .

The most widely employed methods of SCF processing for micronized particles are. 1. rapid expansion of supercritical solutions (RESS) 2. and gas antisolvents recrystallisation (GAS) both of which are employed by the pharmaceutical industry using carbon dioxide (CO2) . due to its favourable processing characteristics like its low critical temperature(Tc = 31.1 o C) and pressure (Pc = 73.8 bar). 19.

Modification of the crystal habit:

B. Modification of the crystal habit: Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, one polymorphs form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes . Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area. T he anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates.

Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug. Amorphous > Metastable polymorph >Stable polymorph

C.Drug dispersion in carriers

C.Drug dispersion in carriers: The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the 1.Hotmelt method. 2.solvent evaporation method. 3.Hotmelt extrusion method.

1. Hot melt method: Sekiguchi and Obi,used a hot melt method to prepare solid dispersion. Sulphathiazole and urea were melted together and then cooled in an ice bath. The resultant solid mass was then milled to reduce the particle size. Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process.

2. Solvent Evaporation Method: An important prerequisite for the manufacture of a solid dispersion using the solvent method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying. Temperatures used for solvent evaporation generally lie in the range 23-65 o C. These techniques have problems such as negative effects of the solvents on the environment and high cost of production , hot melt extrusion method is preferred in preparing solid solutions.

3.Hot-melt Extrusion: Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient . The process has been useful in the preparation of solid dispersions in a single step .

D. Complexation: Complexation is the reversible association between two or more molecules to form a nonbonded entity with a well defined stiochiometry . Complexation relies on relatively weak forces such as vanderwaal forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents and a partial list can be found in table.

Inclusion complexation: Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules

are cyclodextrins . Cyclodextrins are non- reducing,crystalline , water soluble, cyclic, oligosaccharides. Cyclodextrins consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α- Cyclodextrin , β- Cyclodextrin , and γ- Cyclodextrin . The internal surface of cavity is hydrophobic and external is hydrophilic, this is due to the arrangement of hydroxyl group within the molecule .

Staching complexation: Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stached complexes can be homogeneous or mixed. The former is known as self association and latter as complexation.

E. Solubilization by surfactants

E. Solubilization by surfactants: Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or nonionic. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent Microemulsion : A microemulsion is a four-component system composed of external phase, internal phase, surfactant and cosurfactant . The addition of surfactant, which is predominately soluble in the internal phase unlike the cosurfactant , results in the formation of an optically clear, isotropic, thermodynamically stable emulsion. It is termed as microemulsion because of the internal phase is <0.1 micron droplet diameter.

The formation of microemulsion is spontaneous and does not involve the input of external energy as in case of coarse emulsions. The surfactant and the cosurfactant alternate each other and form a mixed film at the interface, which contributes to the stability of the microemulsion . Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hyrophile-lipophile balances are often used to ensure immediate formation of oil-in-water droplets during production. Advantages of microemulsion over coarse emulsion ,It’s ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, enhanced penetration through the biological membranes, increased bioavailability and less inter- and intra-individual variability in drug pharmacokinetics.

B. CHEMICAL MODIFICATIONS By change of pH: For organic solutes that are ionizable,changing the pH of the system is the simplest and most effective means of increasing aqueous solubility . 2) Use of buffer: Buffer maintains the pH of the solution overtime and it reduces or eliminate the potential for precipitation upon dilution. On dilution pH alteration occurs that decrease solubility . Change of pH by 1 fold increase solubility by 10 fold If it changes by one pH unit ,that decrease ionization of the drug and solubility decreases by 10 fold.

3) Derivatization: It is a technique used in chemistry which transforms a chemical compound into a product of similar chemical structure, called derivative. Derivatives have different solubility as that of adduct. It is used for quantification of adduct formation of esters and amides via acyl chlorides.

III. Other methods Co- crystallisation Co-solvency Hydrotrophy Solubilizing agents Solvent deposition Selective adsorption on insoluble carrier Using soluble prodrug Functional polymer technology Precipatation Porous microparticle technology Nanotechnology approaches

1.Co-crystallization: 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. Co-crystals are more stable, particularly as the co-crystallizing agents are solids at room temperature. Only three of the co-crystallizing agents are classified as generally recognised as safe (GRAS) it includes saccharin, nicotinamide and acetic acid limiting the pharmaceutical applications. Co-crystals can be prepared by evaporation of a heteromeric solution or by grinding the components together. Another technique for the preparation of co-crystals includes sublimation, growth from the melt, and slurry preparation.

2. Cosolvency: The solubilisation of drugs in co-solvents is an another technique for improving the solubility of poorly soluble drug. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency . Solvent used to increase solubility known as cosolvent . Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending.

SOME PERANTRALPRODUCT THAT CONTAIN COSOLVENT 36 PRODUCT COSOLVENT Diazepam (Valium) 10% ethanol + propyline glycol Digoxin (Lanolin) 10% ethanol + propyline glycol Epinephrine(susphrin) 32.5% glycerin

3. Hydrotrophy: 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 (sodium benzoate, sodium acetate, sodium alginate, and urea) . 4. Solubilizing agents: The solubility of poorly soluble drug can also be improved by various solubilizing materials. PEG 400 is improving the solubility of hydrochlorthiazide85. Modified gum karaya (MGK), a recently developed excipient was evaluated as carrier for dissolution enhancement of poorly soluble drug, nimodipine .

5. Solvent deposition: In this method,the poorly aqueous soluble drug such as Nifedipine is dissolved in an organic solvent like alcohol and deposited on an inert , hydrophylic,solid matrix such as starch or microcrystalline cellulose and evoporation of solvent is done. 6.Selective adsorption on insoluble carriers: A highly active adsorbent such as inorganic clays like Bentonite can enhance the dissolution rate of poorly water-soluble drugs such as griseofulvin,indomethacin and prednisone by maintaining the concentration gradient at its maximum. 2 reasons suggested for rapid release of drugs from the surface of clays :- 1. weak physical bonding between adsorbate and adsorbent. 2. hydration and swelling of the clay in the aqueous media.

7. Use of soluble prodrug: The most common prodrug stratergy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. Example : prodrug of established drugs has been successfully used to improve water solubility of corticosteroids benzodiazepines. 8.Functional Polymer Technology : Functional polymer enhaces the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal,which is the main barrier to rapid dissolution in aqueous media. The dissolution rate of poorly soluble , ionizable drug like cationic,anionic and amphoteric actives can be enhanced by this technology. Applied to heat sensitive materials and oils also.

9. Precipitation: In this method, the poorly aqueous soluble drug such as cyclosporine is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nano size particles. The product so prepared is also called as

hydrosol. 10. Porous microparticle technology: The poorly water soluble drug is embedded in a microparticle having a porous, water soluble,sponge like matrix,dissolves wetting the drug and leaving a suspension of rapidly dissolving drug particles. These drug particles provide large surface area for increased dissolution rate . This is the core technology applied as HDDSTM(Hydrophobic Drug Delivery System).

11. Nanotechnology approaches: For many new chemical enteties of very low solubility, oral bioavailability enhancement by micronization is not sufficeint because micronized product has a tendency of agglomeration,which leads to decreased effective surface area for dissolution . Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less . NANOCRYSTAL: Size: 1-1000 nm Crystalline material with dimensions measured in nanometers. There are two distinct methods used for producing nanocrystals . 1 . bottom-up. 2. top-down . The top-down methods (i.e. Milling and High pressure homogenization) start 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), 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 .
Other novel Nanotechnology approaches: Nanocrystal technology Nanoedge technology Nanopure technology Nnocochelate technology

APPLICATION OF SOLUBILITY

APPLICATION OF SOLUBILITY Solubility is of fundamental importance in a large number of scientific disciplines and practical applications, to the use of medicines, and the transport of pollutants. Solubility is represents a fundamental concept in fields of research such as chemistry,physics , food science, pharmaceutical, and biological sciences. The

solubility of a substance becomes specially important in the pharmaceutical field because it often represents a major factor that controls the bioavailability of a drug substance.

Solubility is commonly used to describe the substance, to indicate a substance's polarity,to help to distinguish it from other substances, and as a guide to applications of the substance. Solubility of a substance is useful when separating mixtures. Moreover, solubility and solubility-related properties can also provide important information regarding the structure of drug substances, and in their range of possible intermolecular interactions.

CONCLUSION

Conclusion A drug administered in solution form immediately available for absorption. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs . Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug . Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques.

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