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A REVIEW ON ENHANCEMENT OF SOLUBILITY BY NOVEL TECHNIQUE

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ABSTRACT

Recent advances in formulation development aims to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. In recent decades, there have been numerous attempts to overcome the barriers like poorly soluble drugs and bioavailability. A number of techniques can be adapted to enhance solubilization of poor water soluble drug and further to improve its dissolution and bioavailability. Solubility is the important parameter to achieve desired concentration of drug in systemic circulation to be shown pharmacological response. Solubility and permeabilityis essential for the therapeutic effectiveness of the drug, poorly soluble drugs are often a challenging task for formulators in the industry conventional approaches for enhancement of solubility have limited suitability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Now nearly 40% of the new chemical entities (NCES) and about 90% of the drugs in development are identified by pharmaceutical industry screening programs have failed to be developed because of poor water-solubility, which form their formulation development difficult or even impossible. The purpose of writing this review on solubility enhancement of poorly soluble drugs, dissolution and bioavailability was to triggered the attention towards solubility, need to improve solubility factors affecting drug solubility enhancement and bioavailability.

KEYWORDS

Drug, Solubility enhancement, Dissolution, Bioavailability and New Chemical Entities (NCES).

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INTRODUCTON

Although the oral route of drug administration is the most common and preferred method of drug delivery due to patient convenience and ease of ingestion, but for many drugs and drug product it can be a inefficient mode of delivery for a number of reasons[1]. As a most discussed and know but still not completely resolved issue, solubility or dissolution enhancement remain a most vibrant field

for the researchers in formulation research and development[2]. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules in body fluid. Solubility and dissolution are the core concepts of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any new drug dosage form[3]. The solubility of a solute is the maximum quantity of solute that can dissolve easily in a certain quantity of solvent. When administered orally, a drug has to first dissolve in gastrointestinal fluids before it can be absorbed in to the blood and reach its site of action[4]. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for BCS class II substances, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. Therefore, uptake of poorly soluble drug cannot be completed within the time at absorption site due to slow dissolution rate and perhaps leading to prospect of gastric decomposition of drug due to longer GI residence time. In poorly soluble drugs have a two parameters[5]. First is its aqueous solubility of drug should be less than 100ug/ml and second is dose: solubility ratio. Dose to solubility ratio is a volume of gastrointestinal fluids necessary to dissolve the administered dose. Definition for different solubility terms are given in Table No.1.

The solubility of a substance is a maximum amount of solute that can dissolve in a known quantity of solvent at a given temperature which is in equilibrium with the solid solute. Solubility of substance depends on H-bond donor and acceptor properties of the molecule and also onsolvent and crystal lattice of molecule[6]. Effects of these factors can be well explained by equation.

S = f (Crystal packing energy + Cavitation energy + Solvation energy) ……..... (1)

Where crystal packing energy is energy require for breaking crystal lattice to interact solute molecules with the solvent molecules, cavitation energy is required to make cavity within the solvent and salvation energy is that the energy released after favorable interactions between solute and solvent[7].

Cavitation energy are often fulfilled by use of surfactants and crystal packing energy by amorphism or polymorphism of solute. Therefore along surface area, the saturation solubility may be a key think about the dissolution rate of drug. It depends on physiochemical properties of drug like, crystalline form, lipophilicity and pKa. Dissolution process consists of two consecutive stages 8:1. A artificial reaction leads to the liberation of solute molecules from the solid phase. Followed by transport of those molecules remote from the interface into the bulk of the liquid phase under the influence of diffusion or convection. The general rate of mass transport that happens during dissolution are going to be determined by the speed of slowest stage. In the absence of reaction between solute and solvent then the slowest stage is typically the diffusion of dissolved solute across the static boundary of layer of liquid that exist at a solid-liquid interface[8]. The dissolution rate of a solid during a liquid could also be described quantitatively by the Noyes-Whitney equation:

Dm/dt = ka (Cs - C)…… (2)

where, m is that the mass of solute that has passed into solution in time t, dm/dt represent the rate of dissolution, A is that the area of undissolved solid in association with the solvent, Cs is that the concentration of solute required to saturate the solvent at the experimental temperature, C is that the solute concentration at time t and ka is that the intrinsic dissolution rate or the dissolutionrateconstant[9]. Traditionally, nearly 40% of the new chemical entities (NCEs) identified by pharmaceutical industry screening programs have did not be developed due to poor water-solubility, which makes their formulation difficult or maybe impossible. Currently only 8% of new drug entity have both high solubility and permeability. The solubility of a solute is that the maximum quantity of solute which will dissolve during a certain quantity of solvent or quantity of solution at a specified temperature. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs[10,11].

Need to Improve Solubility

- Poorly water soluble drugs having significant challenges during formulation of dosage form designing due to their inadequate solubilization in gastrointestinal fluids.
- Drugs with poor water solubility can show performance constraint such as incomplete or variable absorption, slow onset of action and poor bioavailability.
- Drug effectiveness can vary from patient to patient and there can be a strong effect of food on drug absorption.
- Poor bioavailability leads to high dose.
- Inter and intra individual variability leads to inadequate therapy and or safety concern.
- In order to overcome problem associated with poorly water soluble drugs there is need to improve solubility, for which various solubilization techniques have been used.
- While selecting different solubilization technologies following factor should be considered. Bioavailability and dissolution rate: the technology must demonstrate to enhance dissolution and or bioavailability.
- It should not add substantial time or complexity to the development of poorly water soluble drugs and should be applicable to wide range of compounds with varying physical and chemical properties.
- Stability: The enhance material produced by the technology should be stable in terms of physical characteristics (particle size, morphology) and chemical properties (degradation) and consistent in regards to in vitro dissolution and in vivo bioavailability performance.
- Drug loading (ratio of drug to excipients) should be maximized for high dose drugs to minimize the size of the dosage form.
- Other considerations for the selection of an appropriate technology include the physical and chemical properties of the drug itself, along with its end use characteristics, such as dose and route of administration and therapeutic considerations.

FACTORS AFFECTING DRUGSOLUBILITY[12]

The solubility poorly soluble drugs depends on the physical form of the solid drug, the nature and composition of solvent medium as well as temperature and pressure of system.

Nature of the solute and solvent

There is a lot of difference in the solubility of two or more different substances on the basis of their natures. For example: In 100grams of water at room temperature only 1 gram of Lead (II) chloride can be dissolved where 200grams of Zinc chloride can be dissolved in same amount of water i.e. 100grams of water at same room temperature.

Particle size

The particle size of the solid drug substance influences the solubility because of a particle becomes smaller, the surface area to volume ratio increases. The larger surface area drug substance allows a greater interaction with the solvent.

The particle size of drug effect on solubility can be described by.

$\log S/S0 = 2 \gamma V /2.303 RTr$

Where,

S, is the solubility of infinitely large particles

S0, is the solubility of fine particles

V, is molar volume

R, is the radius of the fine particle

T, absolute temp in °K

R, universal gas constant

Molecular size

Molecular size will affect the solubility. The larger the molecule or the higher its molecular weight the substance is less soluble. Larger molecules are more difficult to encircle with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more subdivide will reduce the size (or volume) of the molecule and make it simple to solvate the molecules with solvent.

Temperature

Temperature will affect drug solubility. In the solution process solution absorbs temperature then the solubility of poor soluble drug will be increased as the temperature is increased. If in the solution

process solution releases energy then the solubility will decrease with increasing temperature. Generally, in the solution process an increase in the temperature of the solution increases the solubility of a solid solute. A few case solid solutes are less soluble in warm solvent or solution. For all gases, solubility decreases as the temperature of the solution increases.

Pressure

Pressure will also affect the solution process of drug solubility. For the gaseous solutes, an increase in pressure it will increases solubility and a decrease in pressure decrease the solubility. In the solids and liquid solutes, changes in pressure of solution have practically no effect on solubility of solute.

Polymorphs

Polymorphs will affect drug solubility. A solid material has a rigid form and a definite shape. The shape or habit of a crystal of a given solute substance may vary but the angles between the faces of crystal are always constant. A crystal of drug substance is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern of crystal is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is called polymorphism.

Polarity

Polarity of solute and solvent will affect to make solution. Generally a non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. In solution process if the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.

BIOAVAILABILITY

"Bioavailability means the rate and extent of active ingredient or active moiety is absorbed from systematic circulation or a drug product and becomes available at the site of action". The bioavailability of a drug is controlled by three principal factors. These variants are namely,

- Rate and extent of release of the drug from the administered dosage form
- Subsequent absorption from the solution state in systematic circulation.
- Biotransformation during the process of absorption.

The idea of permeability and solubility characteristics had been helpful to classify the drug under four classes prescribed by Biopharmaceutics Classification System (BCS).

Recently, a quantitative BCS has highlighted the importance of transit flow, in addition to solubility and permeability, on the drug absorption process. The BCS defines have the three dimensionless numbers- dose number (Do), dissolution number (DN) and absorption number (An) to characterize drug substances. These numbers are a combination of physicochemical properties of the drug and physiological parameters. The BCS has not only transformed the way scientists today approach drug delivery, but it has also revolutionized the development of new drug molecules and drug product[13].

In a Biopharmaceutics Classification System (BCS) a Class II drug will typically exhibit dissolution rate limited absorption and a Class IV drug will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical product development focus on improving the bioavailability of a Drug molecules in oral and systematic circulation. The Enhancing solubility and dissolution rate of poorly water-soluble drugs Enhancing permeability of poorly permeable drugs Formulation of solid dispersion in water-soluble carriers has been widely researched over the past four decades for solubility of poorly soluble drug and related bioavailability enhancement. In this article, the various techniques that can be used for solubility enhancement of BCS Class II drugs are discussed in this article with emphasis on the Co-solvents, Inclusion Complexes technique and its advantages[14].

TECHNIQUES OF SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

Classical and highly employed approaches to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs especially, BCS Class II drugs involve the solubilization by application of principles like pH adjustment, co-solvency, micro-emulsification, self-emulsification, micelles, liposomes and emulsions. Each method is dealing with some merits and demerits. Hence the decision of the method is a crucial step in the formulation process[15].

There are various techniques that help in increasing the solubility of drugs are as follows.

Chemical modifications

Salt formation
Solubilization
Co-crystallization
Co-solvency
Nanotechnology
Hydrotropy

Physical modifications

Particle size reduction

a) Conventional method
b) Micronization
c) Nanosuspension

Complexation

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

Solubilization by surfactants

Modification of the crystal habit

a) Polymorphs
b) Pseudo polymorphs

Solubilization by surfactants

a) Microemulsions
b) Self microemulsifying drug delivery system

Inclusion Complex Formulation Based Techniques

a) Kneading method
b) Lyophilization/ Freeze- drying Technique
c) Microwave irradiation method

Drug dispersion in carriers

a) Solid solutions
b) Solid dispersions

- Melting method
- Solvent methods
- Melting solvent method (melt evaporation)
- Melt extrusion methods
- Lyophilization techniques
- Melt agglomerations Process
- The use of surfactant
- Electrospinning

pH adjustment

Supercritical fluid process

Chemical modification

Salt formation

Salt formation is an effective method in solibility enhancement. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. Salt formation method measurely prefered in parenteral and other liquid formulations, as well as in solid dosage forms. Further as in solid dose sorts of some three hundred approved by the federal agency throughout the twelve years from 1995 to 2006 for selling, one hundred twenty were in salt forms16. In this count, out of the 101 approved salts of basic medication, 54 salts were prepared with acid, representing the hydrochloride acid was the predominant salt form the binary compound solubility of associate acidic or basic drug as a perform of pH scale dictates whether or not the compound can type appropriate salts. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts17. The pH and solubility of drug Interrogate also dictate what counter ions would be necessary to form salts, and how simply the salts may dissociate into their free acid or base forms, The dissolution behavior of drug would be under different GI pH conditions and whether solubility and dissolution rate of salts would be influenced by common ion18. For the formation of salt drug should have ionizable groups that will assist salt formation. The criteria used to select counter ion is as follows:

- Drug molecule should be the minimum difference of 2-3 pKa units between the drug and the counter ion.

- Counter ion should decrease crystal lattice forces.
- For this Techniques drug should be FDA approved or should have enough toxicological data to support the selection of the counter ion.
- The Salt formation technique has tremendous capability to enhance dissolution rate and bioavailability but it is catch with disadvantages like approval of salts is a tedious task and also not useful for neutral molecules.

Solubilization

The solubility of poorly soluble drug can also be improved by using various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap, Soluplus Povacoat, dendrimers, is improve the solubility of hydrophobic active pharmaceutical ingredient. In solubilization enhancement Sepitrap is a novel Solubilizer when Sepitrap Solubilizer used within 5 minutes, 80% of solubilizers are withdraw from Sepitrap TM. Sepitrap TM is a Microencapsulated solubilizer for solid dosage application. The ratio of sepitrap and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect solid characteristics and can be used without any formulation restriction[19].

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[20]. Its enhance the solubility of hydrophobes likely due to hydrophobic interactions, hydrogen bonding and electrostatic interaction between terminal functional groups of the dendrimers and hydrophobes. Most common dendrimers are polyamidoamine dendrimers poly propylene imine (PPI) dendrimers. Severa Literature suggests that PAMAM dendrimers are the most investigated dendrimers in solubilization. Poly (propylene) imine dendrimers (PPI) constitute an equally important family of dendrimers it is first reported by Brabander and Meijer.

Co-crystallization

Co-crystallization is a molecular complexation process to form co-crystals. Its alters the molecular interactions and is considered promising alternative to optimize drug solubility properties. Co-crystallization can be refined as a "multicomponent 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 the physical, chemical or physiological drawbacks of an active pharmaceutical ingredient. Mechanism of co solvency favors the dissolution of a non-polar solute by lowering the interfacial tension. The most appropriate co-crystal of drug can be selected using advance analytical techniques and rational physicochemical studies that include investigations of solubility and stability like XRD, DSC, XRPD, SSNMR. 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 cocrystals. Pharmaceutical Co-crystals basically consists of two components that are the API and the cocrystal former(s)[21].

Different techniques for co Crystallization

- Solvent evaporation
- Grinding
- Slurry Co - Crystallization
- Solvent drop grinding (Modification of Grinding)
- High throughput cocrystallization
- Hot melt extrusion
- Sonocrystallization Method.

Co Crystals Characterization Parameters

- Solubility
- Maximum wavelength
- Stability
- Intrinsic dissolution
- Bioavailability
- Melting Point

- Melt (Hot stage microscopy)
- Scanning Calorimetry (DSC)
- XRD
- Vibrational spectroscopy.

Co-solvents

Cosolvent system is a addition of a miscible solvents that is water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a nonpolar drug This process is called as a cosolvency and in cosolvency solvents used in combination to increase the solubility of the drugs are called as a cosolvents. In this system solvent reducing the interfacial tension between the for the most part aqueous solution and the hydrophobic solute. It is also called as a solvent blending. Using this Co-solvent technique formulations of poorly soluble drugs can be administered orally and parenterally[22]. Co solvents group have hydrogen bond donor and acceptor groups also small hydrocarbon regions. In this process hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self-association, co solvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus increasing solubility. Now a days, the water-soluble organic solvents are ethanol, glycerin polyethylene glycol 400 (PEG 400), propylene glycol. For example, Procardia (nifidipine) was developed by Pfizer contains glycerin, peppermint oil, PEG 400 and sodium saccharin in soft gelatin capsules. The water insoluble solvents include long-chain triglycerides the commonly used long-chain triglycerides is peppermint oil, peanut oil, soybean oil, olive oil, sesame oil, hydrogenated vegetable oil and soybean oil and medium-chain triglycerides are beeswax, oleic acid and d-α- tocopherol (vitamin E)[23].

Advantages

- Cosolvency approach every high drug concentrations of poorly soluble compounds can be dissolved.
- This approache of solubility enhancement can enhance the solubility of poorly soluble drug several thousand times compared to the aqueous solubility of the drug alone. By altering polarity of the solvent. The poor water solubility of weak electrolytes and nonpolar molecules can be improve.
- Cosolvencyis Simple and rapid method 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. This precipitates may be amorphous or crystalline and can vary in size. The drugs are extremely insoluble in water and do not readily redissolve after precipitation from the co-solvent mixture. In these situations, there is a potential risk for embolism and local adverse effects at the injection site.
- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

Nanotechnology

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. The methods of preparation like milling, high pressure homogenization, vacuum deposition and high temperature evaporation may be used[24].

Advantages of nanotechnology

It results in production of the nano or micro sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

Disadvantage of nanotechnology

The agglomeration problem is inherent and difficult to overcome.

Hydrotrophy

Hydrotrophyis a solubilization phenomenon where addition of a large amount of second solute results in an increase in the aqueous solubility of existing solute. Hydrotropic agents are basically ionic organic salts, reliable of alkali metal salts of various organic acids. The Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts". Aphenomenon 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 concentrated aqueous hydrotropic solutions of the sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate came to be observed to enhance the aqueous solubilities of many poorly water-soluble drugs. It was first observed by Neubergto describe the increase in the aqueous solubility of BCS Class 2 drug. Hydrotropic agents are a ionic organic salts. Hydrotropic solutions avoid to show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Apart from 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[25].

Physical modifications

Particle size reduction

The solubility of drug is related to drug particle size; as a particle becomes smaller, the surface area large. The larger surface area allows greater 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. Particle size reduction is a Conventional methods of solubility enhancement, Conventional method of particle size reduction, micronization, Nanosuspension this process mostly used in particle size reduction[26].

Advantages of particle size reduction

- It is efficient, reproducible, economic means of solubility enhancement.
- Allows rapid penetration of solvent.
- Increase the rate of solution in case of chemical substances, because reduction of particle size increases the surface area for the action of solvent.

Disadvantages of particle size reduction

- Due to high surface charge on discrete small particles, there is strong tendency for particle agglomeration.
- Physical, mechanical stress may induce degradation of active compound.
- Thermal stress which occurs during comminution may present problems in processing of thermosensitive agents.
- Developing solid dosage form with a high pay load without encouraging agglomeration and sterile intravenous formulation is technically challenging.

Conventional method of particle size reduction

Conventional method different mechanisms involved in conventional method of particle size reduction are cutting, compression, impact, attrition, combined impact and attrition. In this method comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Conventional method permit 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[27].

Micronization

It is a high energy particle size reduction technique that can convert coarse particles into particles of less than 5μ in diameter. Micronization increases the dissolution rate of drugs through increased

surface area, it does not increase equilibrium solubility. Micronization results in uniform and narrow particle size distribution essential for developing uniform dosage form. Noyes–Whitney postulations states that, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water soluble drug substances. The processes were applied to griseofulvin, progesterone, spironolactone diosmin and fenofibrate. For each drug, micronization improved their digestive absorption and consequently their bioavailability and clinical efficacy. Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes biorelevant media. Beside this micronization is a high energy process which causes disruptions in drug's crystal lattice[28].

Techniques for Micronization

- Jet milling or micronizer
- Controlled crystallization
- Rotor stator colloids mills
- Spray freezing in to liquid
- Microprecipitation and microcrystallization

Nanosuspension

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. Nanosuspensions made up of sub-micron colloidal dispersion of pure particles of drug and which are stabilized by surfactants. Nanosuspension technology is mainly applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical dosage form nanosuspension is biphasic systems consisting of nano sized drug particles in aqueous vehicle stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the undissolved solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600nm. Nanosuspension is produced by homogenization technology and wet milling technology[29].

Techniques for Nanosuspension

Precipitation Technique
Media Milling
High Pressure Homogenization
Combined Precipitation and Homogenization.

Complexation

Among all the solubility enhancement techniques, inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate and bioavailability of poorly water soluble drugs. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules[30]. The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers and Cyclodextrins. Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ Cyclodextrin. The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules.

Several technologies of Complexation adapted to prepare the inclusion complexes of poorly water soluble drugs with cyclodextrinsare as follow.

Kneading Method

This method is based on impregnating the cyclodextrins with small amount of water or any hydroalcoholic solutions to convert into a paste. Then drug is added to the above pulp and kneaded for a designated 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 method can be done by utilizing the extruders and other extruders machines. This is the most common and simple method used to prepare the inclusion complexes and it presents very low cost of production[31].

Two type of complex

Stacking complexes

Stacking complexes driven by association of non polar part of drug and complexes agent this results in exclusion of the non polar area from contact with water. Stacking can be homogeneous, but resulting solutionis clear.

Inclusion complexes

In this method complex formed by the inserting the nonpolar molecule, region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrine and their derivatives commonly used in complexation.

Solid ternary complexes can be formed with

Carboxylic acid - e.g. citric acid, tartaric acid

Water soluble polymer - e.g. Soluplus, Povacoat, Kollidon

Amino acid - e.g. Arginine, tryptophan, leucine, phenylalanine, methionine and isoleucine

Sugar alcohol - e.g. Mannitol

Ternary agent helps in binding of drug and with complexing agent. Most probably use of acidic ternary compound in case of basic drug or vice versa that is use of basic ternary compound with acidic drug is done to form solid ternary complex. Water soluble polymer may be used in specific concentration for example 0.5% or 1% by preparing its aqueous solution. Drug, B-CD and amino acid such as L- Lysine and Arginine ternary complexes may be prepared at 1:1:2 molar ratios, or weight ratio or other suitable ratio.

Physical mixture

In this the CDs or suitable polymer and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. It is simple trituration method.

Kneading method

This method is based on soaking the CDs or suitable polymer with little amount of water or hydro alcoholic solutions to converted 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 sieve.

Co-precipitate method

The required amount of drug is added in the solution of CDs or suitable polymer. The formed precipitate keep under magnetic agitation with controlled process parameters. The complex is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. This method is applicable to industry.

Solubilization by surfactants

Conventional approach to solubility enhancement of a poorly soluble substance by promoting wetting and reducing the surface tension between liquid and particle surface. Surfactants used in concentration below their critical micelle concentration (CMC) (CMC which is in the range of 0.05-0.10% for most surfactants), values from above CMC the drug entrapped in the micelle structure stall to partition in the dissolution fluid. Surfactants are molecules having with polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment couple to a polar group. The polar group can be a cationic, anionic, zwitterionic or nonionic in nature. Surfactants have also been used to improve miscibility between drug and polymer. This process of solubilization is of most importance in industrial and natural processes. A variety of surfactants like Polyglycolized glyceride, Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide)- poly (propylene oxide) like Poloxamers based micelles, Poly (beta benzyl-L-aspartate)-b-poly (ethylene oxide), Poly (caprolactone)-b-poly (ethylene oxide) etc are very successful as excipient and carrier for dissolution enhancement[32].

Modification of the crystal habit

Polymorphs

Polymorphism of solid particle describes the existence of a drug in two or more crystalline forms, each of which possesses a different space lattice arrangement but is chemically identical. If the crystallizing conditions are modified or manipulated. It then becomes possible to make crystals with different packing arrangement; such crystals are called as polymorphs. 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. Thus polymorphs for the same drug differ in their

physicochemical properties such as solubility, dissolution rate, melting point and stability[33].

There are two types of polymer

- Enantiomeric polymorph which is the crystal habit changed into another form by altering the temperature or pressure by reversibly.
- Monomeric polymorph, which is unstable at all temperature and pressure.

Pseudopolymorphs

The stochiometric type of latis where the solvent molecules are incorporated in the crystal lattice of the solid are called as the solvates. The solvates are crystals can exist in different crystalline forms called as Pseudopolymorphs. The surface area of drug available for dissolution is dependent on its particle size and wettability by luminal fluids. This particle size, is important in drug dissolution and dissolution rate, is dependent on the conditions of crystallization or on methods of atomize such as impact milling and fluid energy milling[34].

Solid solutions/dispersions

Solid dispersion (SD) has been widely used to enhance the solubility and the dissolution rate, solubility and oral or systamatic absorption of poorly water-soluble drugs. Drug dispersion has the 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 solid dispersion was first introduced to overcome the low bioavailability of lipophilic drugs by forming a eutectic mixture of drugs with water soluble carriers[35].

Methods of solid dispersion

- Melting method
- Solvent methods
- Melting solvent method (melt evaporation)
- Melt extrusion methods
- Lyophilization techniques
- Melt agglomerations Process
- The use of surfactant

pH adjustments

pH adjustment has a easy method of solubility enhancement by change the ionization behavior. The hydrophobic molecule can be protonated (base) or deprotonated (acid) and be dissolved in water by appeal a pH change. Ionizable compounds that are stable and soluble after pH adjustment are applicable. Poor water soluble drug molecules may potentially dissolve in water by applying a pH change. To enhance the solubility by this approach, the buffer capacity and tolerability of the selected pH are important to consider in dosage form. Solubilized excipients that may 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. According to pH-partition hypothesis and Handerson- Hesselbatch equation, ionization of a drug compound is dependent on the pH of media and pKa of drug. The change in the ionic medium can also result to in situ salt formation. Same time this method have a risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability and Tolerability and toxicity both local and systemic related with the use of a non physiological pH and extreme pH should be considered[36].

Super Critical Fluid (SCF) Technology

This Technology has a dissolved nonvolatile solvents, with the critical point of carbon dioxide. This live as a single phase above its critical temperature and pressure it has a safe, environmentally friendly and economical. The Super Critical Fluid process was developed and patented by the University of Brad ford. The use of a coaxial nozzle provides the drug in the organic solvent solution mixes with the compressed fluid CO2 (antisolvent) in the mixing chamber of the nozzle prior to dispersion and flows into a particle-formation vessel via a restricted orifice. Such nozzle accomplish the solution breakup through the impaction of the solution by a higher velocity fluid. The high velocity fluid produce high frictional surface forces, generate the solution to disintegrate into droplets. The density, transport properties i.e viscosity and diffusivity and other physical properties i.e dielectric constant and polarity vary

significant with small changes in operating temperature, pressure or both around the critical points in fluid. A wide range of materials has been prepared as carriers of microparticles and nanoparticles using this process. For this process used supercritical solvents are carbon dioxide, ethylene, nitrous oxide, ammonia, propylene, propane, n-pentane, ethanol and water. Several methods of Super Critical Fluid (SCF)processing have been developed to express precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvents processes (SAS). In another study, a significant decrease in the particle size is achieved by using the ultrasonic nozzle based supercritical antisolvent process[37].

Table No.1: Definition of Solubility (I. P.1996)

S.No	Definition	Parts of solvents required for one part of solute (in ml)
1	Very soluble	< 1
2	Freely soluble	1 - 10
3	Soluble	10 - 30
4	Sparingly soluble	30 - 100
5	Slightly soluble	100 -1000
6	Very slightly soluble	1000 - 10,000
7	Insoluble	> 10,000

Table No.2: Biopharmaceutics Classification System (BCS)

Class I	Class II
High solubility	Low solubility
High permeability	High permeability
Class III	**Class IV**
High solubility	Low solubility
Low permeability	Low permeability

CONCLUSION

For BCS class II drugs, enhancing solubility would be very efficient for increasing bioavailability. Developments of newly synthesized compounds are frequently stopped because of solubility issues. Solubility of drug can be enhanced by many techniques and each technique will increase certain drug solubility by a number of bunch. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. There are many other sources of applications used to enhance solubility. These techniques are micellar solubilization, super critical fluid process, crystal modification, amorphization, spray freezing, use of surfactants, salt formation and several others techniques. It is necessary to use one of these techniques and the ones mentioned above to increase the solubility of drugs because the bioavailability is affected by low solubility. Each technique has advantages and disadvantages, which is important when deciding the appropriate method for the drug selection. It is imperative that the correct technique is chosen in order to decrease the possibility of errors. A better understanding of how to increase the solubility of drugs with different methods has been developed by academic and industrial research and this science will lead to development of efficient formulation for poorly soluble drugs.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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