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A COMPREHENSIVE REVIEW ON METHODS FOR ENHANCING THE SOLUBILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

The primary aim of this review was to improve the solubility and Bioavailability of BCS Class-II drugs because of their low solubility and dissolution rate. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Hence the class- II drugs require enhancement in solubility and dissolution rate in there formulation development particularly in solid dosage form such as in tablet and capsule. So because of this there are several methods and newer emerging technologies have been developed for increasing the solubility as well as bioavailability of class –II drugs. In this article review on literature on newer techniques or methods as well as recent research on formulation development of class- II drugs were done.

KEYWORDS: Bioavailability, Solubility, Lipophilicity, BCS.

INTRODUCTION

The important phenomenon and as a most of time discussed but a still or not a completely resolved issue, solubility or dissolution enhancement technique remains a most challengeable field for the researchers in the formulation design and developmental process. solubility and dissolution. These are the core concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine. As a result, recently more than 40% of new chemical compounds are fails before entering into the drug developmental process because of their non-optimal biopharmaceutical properties. These properties such as rate and extent of absorption, rate of distribution etc.

Hence, according to IUPAC, The solubility may be defined as, The analytical Composition of saturated solution expressed in terms of the proportion of a designated solute in a designated solvent is the solubility of that solute. It is expressed as a Concentration, Molality, Mole Fraction, Mole Ratio etc.

Solubility of a poorly water soluble drug is a frequently encountered challenge in screening studies of New Chemical Entities (NCE) as well as in formulation design and development. There are several methodologies can be developed to improve its bioavailability property. After administration of drugs by orally they are completely absorb but showed fair solubility in gastric medium and good bioavailability. But this bioavailability depends upon the several factors say as drug permeability through lipophilic Membranes. Hence at low concentration solubility is difficult to measure analytically. Therefore to ensure rapid and efficient formulation development a solubility classification for the selection of an appropriate formulation system for highly active compounds with good permeability was introduced. It was in August 2000, the U.S. FDA issued Guidance for Industry covering the Biopharmaceutical Classification System (BCS)

Classification: The BCS is a scientific framework for the classifying a drug substance on the basis of their equilibrium aqueous solubility as well as intestinal permeability. When combined with the *in vitro* dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, dissolution rate and intestinal permeability. These three factors are governing the rate and extent of oral drug absorption for immediate release solid oral dosage forms. The BCS defines four classes of drug substances on the basis of their solubility and permeability characteristics.

Biopharmaceutical classification system of drugs

BCS Class I	High solubility High permeability	B-blockers Propranolol, Metoprolol.
BCS Class II	Low solubility High permeability	NSAID's Ketoprofen, Antiepileptic Carbamazepine.
BCS Class III	High solubility Low permeability	B blockers Atenolol, H_2 Antagonist Ranitidine.
BCS Class IV	Low solubility Low permeability	Diuretics Hydrochlorothiazide, Furosemides.

Factors affecting solubilization

The solubility depends upon the nature and composition of solvent medium the physical form of solid as well as temperature and pressure of system.

1) Particle size

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

2) Temperature

As the temperature increases the solution process absorbs energy and the solubility will increases but if the solution process releases energy then the solubility will decrease with increasing temperature. A few solid solutes are less soluble in warm solutions. For example all gases, solubility decreases as the temperature of the solution increases.

3) Pressure

For solids and liquid solutes, changes in pressure have practically no effect on solubility but for gaseous solutes, an increase in pressure, increases solubility and a decrease in Pressure, decrease the solubility.

4) Nature of the Solute and Solvent

Strong solute-solvent attractions equate to greater solubility while weak solute-solvent attractions equate to lesser solubility.

5) Molecular size

The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround 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 branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

6) Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. So the polar solute molecules have a positive and a negative end to the molecule. 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. The other forces called London dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolar solvent a chance to solvate the solute molecules.

7) Polymorphs

Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

8) Rate of solution

The rate of solution is a measure of how fast substances dissolve in solvents. A various factors affecting rate of solution.

(a) Size of the particles

Breaking a solute into smaller pieces increases its surface area, when the total surface area of the solute particle is increased; the solute dissolves more rapidly because the action takes place only at the surface of each particle and hence increases its rate of solution.

(b) Temperature

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that dissolved but also increases the rate at which the solute will dissolve.

(c) Amount of solute already dissolved

When there is little solute already is in solution, dissolution takes place relatively very rapid. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

(d) Stirring

With liquid and solid solutes particles, stirring brings fresh portions of the solvent in contact with the solute and which results in increasing the rate of solution.

Techniques of Solubility and Bioavailability enhancement

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the recent approaches as well as newer techniques to improve the solubility are;

1) By using surfactant

A Conventional approach to solubilise a poorly soluble substance is to reduce the interfacial tension between the surface of the solute and solvent for better wetting salvation interaction. A Wide variety of surfactants like Tweens, spans, polyoxyethylene, glycerides, polyoxyethylene stearates and synthetic block copolymers etc. are very successful as excipient and carrier for dissolution enhancement.

2) pH Adjustment

Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase the water solubility behavior. Therefore as per the pH partition hypothesis and Handerson- Hesselbatch equation, ionization of a compound is dependent on the pH of media and pKa of drug. Also the change in the ionic compound can result to in –situ salt formation. Therefore this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in GIT.

3) Manipulation of solid state

From the stability and bioavailability aspects, the crystalline form of a drug is of pharmaceutical importance. Polymorphism (Existence of a drug substance in multiple crystalline forms) can cause variations in melting point, density, stability and drug solubility as these properties depend on the escaping tendency of the molecules from a particular crystalline structure. As a rule, for a drug that have the highest order of Crystallinity is the most stable form, exists in multiple polymorphic forms, i.e. with the least amount of free energy, and consequently, possesses the highest melting point and the least solubility. By controlling the crystallization process, amorphous or meta stable forms of drugs possessing high free energy can be forcibly created. They offer the advantage of higher solubility but suffer from stability issues unless stabilizers intended to inhibit crystal growth are incorporated in the formulation. A typical example for this is a high profile case involving polymorphism was withdrawal of Ritonavir (Norvir®) capsules from the market in 1998 because a less soluble (and consequently less bioavailable) polymorph was identified two years after the product was approved and marketed, causing a decrease in bioavailability of the drug. This incident sensitized the pharmaceutical industry to the critical importance of polymorphism and encouraged the inclusion of polymorph screening as a routine component of preformulation studies.

4) Self- Emulsifying drug delivery system

A self-emulsifying or self-micro emulsifying system is the concept of in situ formation of emulsion in the gastrointestinal tract. It is defined as the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophilic drug dissolution and absorption. So the ease of emulsification could be

associated with the ease of water penetrating into the various liquids crystalline or gel phases formed on the surface of the droplet. . The large quantity of surfactant in self-emulsifying formulations (30- 60%) irritates GIT. Most self- emulsifying systems are limited to administration in lipid filled soft or hard-shelled gelatine capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell .A Neoral® is an classical example of self microemulsfying drug delivery system (SMEDDS). Depending on the dose level, the relative bioavailability of cyclosporine A administered as Neoral® could be 174- 239% of the bioavailability of cyclosporine A from Sandimmune®, the originally marketed formulation. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long-term use due to the potential of causing diarrhoea.

Advantages

1) In relation to scale up and manufacture is that they form spontaneously upon mixing their components under mild agitation.
2) They are thermodynamically stable.

Disadvantages

1) It includes chemical instabilities of drugs and high surfactant concentrations.

5) Micro emulsion

A Micro emulsion is an optically clear, isotropic, thermo dynamically stable translucent system which contains, a mixture of oil, Hydrophilic surfactant and hydrophilic solvent in which the poorly water soluble drug dissolves. When comes in contact with water the formulation is spontaneously disperse or self emulsified to form a very clear emulsion of exceedingly small as well as uniform oil droplets containing the solubilized poorly soluble drug. These systems have been employed to increase the solubility at many temperature which are practically insoluble in water along with incorporation of proteins for oral, parenteral as well as percutaneous or transdermal use. These homogeneous systems can be prepared by using a wide range of surfactant concentration and oil to water ratio are of fluids of low viscosity. So for improving the solubility of drugs formulated as a micro emulsion various parameter play an important role such as Surfactants, Surfactant Mixtures and co –

surfactants. The surfactants like polyoxy ethylene for ex. Brij 35or sugar esters like Sorbitan mono oleate (Span 80), cationic or anionic like alkyl trimethyl ammonium bromide and sodium dodecyl sulphate or zwitter ionic such as phospholipids like lecithin because it exhibits excellent bio-compatibility.

6) Particle size reduction

Micronization or nanonization is one of the most potential approaches to improve the bioavailability of lipophilic drugs by means of reduction of the particle size to its submicron level. During the Preformulation studies of any formulation's particle size is an critical parameter which should be strictly controlled. To enhance the solubility the reduction in the particle size as a successful way but if it is in uncontrolled or un-optimized it can forms the recrystallization as well as re-aggregation of drug upon storage. Because of this a thorough study on the particle size and physical stability should be done. By using the conventional techniques size reduction to submicron range is not possible.

7) Supercritical Fluid Process (SCF)

Another novel nano-sizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve non-volatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. Super critical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. It is safe, environmental friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power Once the drug particles are solubilized within SCF, they may be recrystallized at

greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. The flexibility and precision offered by SCF processes allows Micronization of drug particles within narrow ranges of particle size, often to sub-micron levels. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application. These unique processing capabilities of SCFs, long recognized and applied in the food industry, have recently adapted to pharmaceutical applications. Current SCF processes have demonstrated the ability to create nano-particulate suspensions of particles 5- 2,000nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed anti-solvents process (PCA), solution enhanced dispersion by SCF (SEDS), supercritical anti-solvents processes (SAS) and aerosol supercritical extraction system (ASES).24

8) Complexation

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins are α, β, and ʎ-CD are composed of 6,7and 8 D-(+) glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups oriented outwards. Importantly cyclodextrins have a hydrophilic exterior and hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery. When the aqueous solubility of the pure drug is low then there is a greater relative solubility enhancement which is obtained through cyclodextrin complexation. There are certain forces which plays an imp role for the formation of complexation were attributed to-

1. The exclusion of high energy water from the cavity,
2. The release of ring strain particularly in the case of -CD,
3. Hydrogen and hydrophobic bindings
4. Van der Waal's interactions,

The most widely used native cyclodextrin is β- CD but its application in the pharmaceutical because of its low aqueous solubility (1.85 gm/100 ml, 250C), toxicity profile and low aqueous solubility of the formed complexes. Accordingly derivatives such as hydroxypropyl β-CD, and sulphobutylether- β-CD have been developed to produce more water soluble as well as less toxic entities. This is the most widely used method to enhance the water solubility and increase the stability of hydrophobic drugs by using cyclodextrins. By using following methods solid dispersion complexes can be prepared.

Kneading method

In this technique cyclodextrin (CD) is impregnated with water and forms a paste. After that drug is added and kneaded for specific period of time. The kneaded mixture is then added and dried and passed through sieve if required.

Lyophilization / Freeze drying technique

In this technique the solvent system from the solution is removed through a primary freezing and subsequent drying of the solution containing both drug and CD at reduced pressure. Thermo labile substances can be successfully made into complex form by this method.

Supercritical anti solvent technique

In this technique supercritical carbon dioxide is suggested as a new complexation medium due to its property of improved mass transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of the drug with CD in the solid state.

Advantages

1. It is a non-toxic Method.
2. Fast process, maintenance cost is very low with promising results.

Disadvantages

1) It requires high initial cost.

Microwave irradiation method

This technique uses the microwave irradiation reaction between the Complexing agent and Drug by using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water as well as organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time nearly about one to two minutes at 60˚ C in the

microwave oven. After the reaction is completed adequate amount of solvent mixture is added into the above solution or reaction mixture to remove the residual uncomplexed free drug and CD. Then the remaining precipitate is separated by using a Whatman's filter paper, and dried in vaccum oven at 400 C for 48hrs.

9) Hydrotrophy

It is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. It designate the increase in the solubility in water because of the presence of large amount of additives. In the point of Mechanism, it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase the solubility in given solvent are said to be "salt in" the solute and those salts which decrease the solubility known as "salt out" of the solute. There are several salts with large anions or cations which are very soluble in water resulted in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Whereas hydrotropic solutions does not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Specific examples may include Ethanol, aromatic alcohols like resorsinol, pyrogallol, catechol and b-napthols as well as salicylates, various alkaloids like caffeine and nicotine, ionic surfactants like diacides, SDS and dodecylated oxydibenzene.

10) Solid dispersion

The concept of solid dispersion was firstly proposed by Sekiguchi and obi, who investigated the generation and dissolution performance of eutectic, melts of a sulphonamide drug and a water soluble carrier in the early 1960. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which increases the dissolution of the drug. Solid dispersion technique can yield eutectic (Non- Molecular Label mixing) or solid solution. (Molecular –label Mixing) products. Eutectic dispersions are homogeneous dispersion of crystalline or amorphous drug in crystalline or amorphous carrier. Despite the promising aspect of dissolution enhancement and simplicity of concept, the solid dispersion technique has failed to take popularity because of Manufacturing, Scale Up- as well as Stability Problems. Solid dispersion is a useful pharmaceutical technique for increasing the dissolution of drug in dosage form. Some of the hydrophilic carriers which are used in the

pharmaceutical industry are polyvinyl pyrolidone, PEG, Plasdone, Tween 80, SLS etc. There are various technique used to enhance the aqueous solubility of hydrophobic drug such as Holt Melt method (Fusion Method),Solvent Evaporation Method, Hot Melt Extrusion.

Hot melt method (Fusion method)

In this method the physical mixture of a drug and water soluble carrier was heated directly upto its melting point. Then the melt mixture was cooled and solidified rapidly in an ice bath under the vigorous stirring. After that the final solid mass was crushed, pulverized and sieved, which can be compressed into tablets with the help of tablet excipient.

Solvent evaporation method

In this technique the drug and carrier was dissolved both in a common solvent and then evaporate the solvent under vaccum until to produce a solid solution. Many Investigators studied solid dispersion of Meloxicam 15, Nimusulide and Naproxen using a this technique

Hot melt extrusion

This is a essentially same as that of fusion method except that intense mixing of the components which is induced by the extruder. Just like as that of traditional fusion process, miscibility of drug and matrix can be a problem. Also for heat sensitive materials high shear forces high local temperature in the extruder**.**

11) 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. These are the mixtures of water and one or more water miscible solvents which is used to create a solution with enhanced solubility for the poorly water soluble compounds. Historically, 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 such as PEG 300, propylene glycol or ethanol. Various concentrations (5-40%) of the solid binary systems with polyethylene glycol 6000 were employed to increase solubility and dissolution of meloxicam. Co-solvency techniques have also found use in spray freezing of liquid like in diazole with polyvinyl alcohol, Polaxomer 407, and poly vinyl pyrrolidone K-15 in a micronized powder formulation. The pharmaceutical form is always liquid. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a

cosolvent approach. Co- Solvents can increase the solubility of poorly soluble compounds several thousand times compare to the aqueous solubility of the drug alone.

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.

12) Floating granules

Firstly, Patel Rajanikant et al. utilized a novel approach for the dissolution enhancement of ibuprofen (a weekly acidic, non-steroidal anti inflammatory drug) by preparing the floating formulation. The Drug having high permeability through stomach because it remains 99.9 % unionizes in the stomach (pKa of Ibuprofen - 4.43, pH of gastric fluid -1.2) and mostly permeable through stomach but due to its solubility limitation property it can't enter in to the systemic circulation and gastric empting time is 30 min to 2 hr. After this time ibuprofen goes in to small intestine where it is solubilized but can't permeate through its membrane. It was logically decided to design such formulations which retain in stomach for more than 2 hrs because the drug was not completely soluble within 2 hrs hence to dissolve completely in stomach region, this can be achieved by making floating dosage form. Floating ibuprofen granules were prepared by using the fusion method. Ibuprofen (200 mg divided in to 50 mg and 150 mg), gelucire 44/14 (350 mg melted) and ibuprofen (50 mg) added, dispersed with glass road for uniform distribution of drug into melted carrier, remaining 150 mg ibuprofen added into melted Gelucire 44/14, this whole dispersion added in to the melted gelucire 43/01. In optimized formulation, Granules remain floated for 3 hrs gave 100%drug release in 150 minute in stomach region where it remain in 99.9% unionize form and absorbed to systemic circulation.

13) Nano- Suspension

A pharmaceutical Nano-suspension is a biphasic system which consist of nano sized drug particles which is stabilized by using the surfactants for either oral or topical use or parenteral and for pulmonary administration. This technology has been developed as a promising candidate for the 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 nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. There are various methods which are used for

preparation of Nano-suspension such as Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in non aqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege).

Precipitation technique

In this technique the drug is dissolved in a solvent, which is then added in to non-solvent for precipitate of the crystals. The drugs such as Danazol, Naproxen etc are prepared by using this technique to improve their dissolution rate and oral bioavailability.

Nano –Crystals or nano systems (Media milling)

In this technique by using the high shear media mills nano-suspensions are prepared. Firstly the milling chamber charged with the milling media, water, drug and stabilizer which is rotated at a very high shear rate under controlled temperature for several days of time(at least 2-7 days). In that the milling Medium is composed of glass, Zirconium Oxide or Highly Cross- linked polystyrene resin.

14) Nano-Crystallization

The nano crystallization is the process in which decreasing of drug particles into the size range of 1-1000 nanometers. There are two distinct methods which are used for producing nanocrystals say as "bottom-up" and "top-down" development. In 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.

Milling

Nanoscale particles can be produced by using wet milling process. In ball mills, by using the Impact and attrition forces the particle is reduced. The most common models are a tumbling ball mill and a stirred media mill. The degradation of mill surfaces and subsequent suspension contamination are problems of this method.

High pressure homogenization

In high pressure homogenization, an aqueous dispersion of the crystalline drug particles is passed with high pressure through a narrow homogenization gap with a very high velocity.

Homogenization can be performed in water or alternatively in non aqueous media or water-reduced media. The particles are disintegrated by cavitations and shear forces. The static pressure exerted on the liquid causes the liquid to boil forming gas bubbles. When exiting from the gap, gas bubbles collapse under normal air pressure. This produces shock waves which make the crystals collide, leading to particle disintegration. A heat exchanger should be used when operating on temperature sensitive materials because high pressure homogenization causes increase in the sample temperature .The particle size obtained during the homogenization process depends primarily on the nature of the drug, the pressure applied and the number of homogenization cycles.

Precipitation

In the precipitation method, a dilute solution is first produced by dissolving the substance in a solvent. The solution with the drug is then injected into water, which acts as a bad solvent. At the time of injection, the water has to be stirred efficiently so that the substance will precipitate as nanocrystals. Nanocrystals can be removed from the solution by filtering and then dried in air.

15) Salt formation

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Of approximately 300 new chemical entities approved by the FDA during the 12 years from 1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form. The aqueous solubility of an acidic or basic drug as a function of pH dictates whether the compound will form suitable salts. The pH-solubility interrelationships also dictate what counter ions would be necessary to form salts, how easily the salts may dissociate into their free acid or base forms, what their dissolution behavior would be under different GI pH conditions, and whether solubility and dissolution rate of salts would be influenced by common ion.

16) Polymeric alteration

Different crystalline forms of a drug that may have different properties are known as Polymorphs. Polymorphs may differ in physicochemical properties such as physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolution

rate, morphology, density and biological activities as well as bioavailability. Amongst the stable, unstable and metastable crystalline polymorphs, metastable forms are associated with higher energy with increased surface area, subsequently solubility, bioavailability and efficacy. With regard to bioavailability, it is preferable to change drug from crystal forms into metastable or amorphous forms. However, the possibility of a conversion of the high energy amorphous or metastable polymorph into a low energy crystal form having low solubility cannot be ruled out during manufacture and storage. It is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions.

17) Co-grinding/Co-micronization

Co-grinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small amount of water is extremely effective to improve its apparent solubility with maintenance of drug crystallinity to some extent. Small particles produced by milling or micronization have increased surface area and expected to have enhanced dissolution rate. However, energy added to reduce particle size results in increased Van der Waal's interactions and electrostatic attraction between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate. Co-micronization of drugs by using excipients like microcrystalline cellulose can be used as an alternative to reduce or eliminate cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a reduction in particle-particle agglomeration or by reducing Van der Waal's interactions. Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of microcrystalline cellulose-Drug mixture.

18) Rapid expansion from Supercritical to Aqueous Solution (RESAS)

This process induces rapid nucleation of the supercritical fluid dissolved drugs and surfactants resulting in particle formation with a desirable size distribution in a very short time. The surfactants in the supercritical fluid stabilize the newly formed small particles and suppress any tendency of particle agglomeration or particle growth when spraying this solution (drug + surfactant + CO_2) into an aqueous solution containing a second surface modifier. The low solubility of poorly water soluble drugs and surfactants in supercritical

CO_2 and the high pressure required for these processes restrict the utility of this technology in pharmaceutical industry.

19) Evaporative precipitation into aqueous solution (EPAS)

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and the aqueous solution to optimize particle formation and stabilization. In EPAS, the surfactant migrates to the drug-water interface during particle formation, and the hydrophilic segment is oriented towards the aqueous continuous phase. The hydrophilic stabilizer on the surface inhibits crystallization of the growing particles and therefore facilitates dissolution rates.

20) Ultra-Rapid Freezing

Ultra-rapid freezing is a novel, cryogenic technology that creates nano-structured drug particles with greatly enhanced surface area. The technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions. This process involves freezing a dissolved drug in a aqueous of anhydrous polymer water solution onto the surface of a cryogenic substrate with a thermal conductivity (k) between 10 and 20 W/(m K), collecting the frozen particles and removing the solvent, resulting in highly porous, agglomerated particles. The polymer acts as a stabilizer acting as a crystal growth inhibitor. Because of rapid conductive heat transfer, resulting in high super-saturation and nucleation rates, the URF technology has the potential to create powders with superior physicochemical properties, similar to those produced by other rapid freezing technologies. As in other freezing technologies, the rapid freezing of the drug/polymer composition is decisive in preventing phase separation during freezing, allowing for the active to be molecularly dispersed with the polymer.[31] As with controlled precipitation, this process uses pharmaceutically acceptable solvents, excipients and conventional process equipment making it fast and scalable. Recrystallization of the drug is avoided by the inclusion of high glass-transition temperature (Tg) polymers such as PVP or HPMC. This technique is widely applicable to enhance in vivo absorption for the BCS class-II compounds.

21) Lipid-Based delivery systems

Lipid-based delivery systems like emulsions, microemulsions, liposomes, microspheres, solid-lipid nanoparticles, etc have ability to avoid resistant chemical and physical barriers to oral absorption and are most successful in enhancing the bioavailability of molecules that are poorly water-soluble but highly permeable drug molecules (BCS class II).

Some proposed mechanisms of action of lipid-based systems to enhance oral bioavailability of compounds include[57]:

1. Particle size reduction to molecular size yielding a solid-state solution within the carrier
2. Enhanced wetting of hydrophobic solids resulting in enhanced dissolution

- Increased rate of dissolution into aqueous environment from oil droplets of high surface area

1. Promotion of absorption via intrinsic lipid pathways
2. Enhanced thermodynamic activity via super-saturation of the aqueous environment of the gastrointestinal tract.

22) Cavitation & Melt Sono-Crystallization

Cavitation can be in general defined as the generation, subsequent growth and collapse of cavities resulting in very high energy densities of the order of 1 to 1018kW/m^3. Cavitation can occur at millions of locations in a reactor simultaneously and generate conditions of very high temperatures and pressures (few thousand atmospheres pressure and few thousand Kelvin temperature) locally, with the overall environment being that of ambient conditions. Thus, chemical reactions requiring stringent conditions can be effectively carried out using cavitation at ambient conditions. Moreover, free radicals are generated in the process due to the dissociation of vapours trapped in the cavitating bubbles, which results in either intensification of the chemical reactions or in the propagation of certain unexpected reactions. Cavitation also results in the generation of local turbulence and liquid micro-circulation (Acoustic streaming) in the reactor, enhancing the rates of transport processes.

CONCLUSION

The most important factor in the formulation development is the solubility of drug molecule. As it is it controls the formulation of the drug and therapeutic efficacy as well. For oral absorption the dissolution of the drug is an rate determining step therefore solubility is an important requirement for formulation and manufacturing of different dosage form of different drugs. This review focuses on various techniques involved in improvement or

enhancing the solubility. Based on their effectiveness as well as its safety with respect to biocompatibility of the excipients the choice of the method will differ. In concern with the orally administered drugs, the solubility is an one of the tare limiting parameter for achieving the desired concentration in the systemic circulation to get a Pharmacological response. Solubility enhancement is an very important.

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