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REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT:

Absorption process is develop in biological system to getting required organic and inorganic chemicals in to systemic circulation and maintain bioavailability. The bioavailability issue can be due to insufficient solubility or permeability. Most compounds face the solubility problems. Hence, with the advancement of chemical science, the need of development of pharmaceutical technologies is also increasing and it depend upon drug to drug. The drug exhibit very poor aqueous solubility the rate at which drug dissolve in gastro intestinal tract and exhibit rate limiting step. Oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effect On the basis of solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in the Class II and Class IV of the BCS system. To improve solubility and bioavailability of poorly soluble drug we use various methods or techniques. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

KEY WORDS: Bioavailability, Novel methods, Solubility, BCS Class.

INTRODUCTION:

The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble such as ethanol in water to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining. Solubility equilibrium occurs when the two processes proceed at a constant rate.

Under certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio and other units. Extensive use of solubility from different perspective has led to solubility being expressed in various manners. It is commonly expressed as a concentration, either by mass (gm of solute per kg of solvent, g per (100 mL) of solvent, molarity, molality, mole fraction, or other similar descriptions of concentration. The maximum equilibrium amount of solute that can dissolve per amount of solvent.

Very soluble Less than 1

- Freely soluble From 1 to 10
- Soluble From 10 to 30
- Sparingly soluble From 30 to 100
- Slightly soluble From 100 to 1000
- Very slightly soluble From 1000 to 10,000
- Practically insoluble 10,000 and over

Solubility is a crucial pre-formulation attribute that regulates the targeted drug concentration in the systemic circulation. The bulk of newly discovered chemical entities have low solubility, which leads to low bioavailability [4]. The drug's solubility is a crucial characteristic since it influences the drug's release, absorption, rate of dissolution, and ultimately its bioavailability. Therefore, processing is required to enhance the medication's water solubility and dissolution

BCS Classification System The US Food and Drug Administration (FDA) created the Biopharmaceutics Classification System (BCS). categorizes pharmaceuticals into four classes according on their solubility and permeability characteristics. Low solubility causes a soluble obstacle in Classes II and IV of the system, where the medication absorption process's rate-limiting phase is dissolution. The drugs are categorized by the Biopharmaceutical Classification System (BCS) according to their intestinal permeability and intrinsic solubility. Good intestinal permeability and solubility contribute to a drug's high bioavailability. The bioavailability of drugs with low solubility and permeability is dependent on their solubility and permeability, respectively. The majority of medications in the pharmaceutical industry today have poor solubility. Poor solubility has been effectively addressed by a number of solubility enhancement strategies.

Table 1 BCS Classification System of drugs

Sr. No.	BCS Class	Solubility	Permeability	Example
1	Class I	High	High	Metoprolol, Amlodipine
2	Class II	Low	High	Ibuprofen, Naproxen
3	Class III	High	Low	Cimetidine, Ranitidine
4	Class IV	Low	Low	Furosemide, Nelfinavir

Importance of Solubility:

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products .However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystolic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role for other dosage forms like parenteral formulations. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.

Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist.

The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II(low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the

gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS classII drugs .

Techniques for Solubility Enhancement

Solubility improvement techniques can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

Physical Modifications:

Particle size reduction like micronization and nano suspension, modification of the crystal habit like polymorphs, amorphous form and co- crystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

Micronization

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. Compared several techniques for improving the dissolution of fenofibrate, a poorly soluble drug and particle size reduction was realized by jet milling (micronization; co-grinding with lactose, polyvinyl pyrrolidone or sodium lauryl sulphate) and by media milling using a bead mill (nanosizing) with subsequent spray-drying. Supersaturated solutions were generated by Nano sizing combined with spray-drying, this process converted fenofibrate to the amorphous state. Fenofibrate drug products commercially available on the German and French markets dissolved similarly to crude or micronized fenofibrate, but significantly slower than the cog round or spray dried fenofibrate mixtures. The results suggest that cogrinding and spray-drying are powerful techniques for the preparation of rapidly dissolving formulations of fenofibrate, and could potentially lead to improvements in the bioavailability of oral fenofibrate products.

Eg. Microspheares of nicardipine hydrochloride (NCH)-loaded for delivery over a 12-hr period. Microspheres containing Eudragit RS and L with different ratios were prepared by solvent evaporation method. The change in the diameters of microspheres with time in simulated intestinal fluid (pH 7.5) at 37°C has been studied. Release of NCH from microspheres increased with Eudragit L amount, but no controlled-release pattern was observed. Q values ≥18.88 caused a slow initial release followed by an accelerated release. Microspheres with an Eudragit RS-L ratio of 1:5.7, Q value of 38.71, and drug release rate of 0.155% min-1 exhibited a remarkable delayed time for erosion to begin (120 min). Thus, microspheres prepared from this formulation may provide an effective enteric dosage form, releasing NCH at a predetermined rate. This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask.

Nanoionisation

It's a process whereby the drug powder is converted to Nano crystals of size 200-600nm, e.g. Amphotericin B. The main production technologies currently in use to produce drug Nano crystals yield as a product a dispersion of drug Nano crystals in a liquid , typically water (called Nano suspension). There are three basic technologies currently in use to prepare nanoparticles:

i. Pearl milling.

ii. Homogenization in water (wet milling as in a colloid mill).

iii. Homogenization in non aqueous media or in water with water-miscible liquids.

Prepared megestrol acetate (MA) nanoparticles via a liquid precipitation technique. The as-prepared MA particles had a mean size of 208 nm, and 90% of the particles were distributed in the range of 100−300 nm, whereas the raw MA had a mean particle size of about 3.02 μm, ranging widely from 0.2 μm to 30 μm. The freeze-dried MA nanoparticles exhibited improved wettability as demonstrated by the contact angle measurement result proving that particles were covered by a hydrophilic layer. In dissolution rate tests, the nanoparticles achieved 100% drug dissolution within 5 min, while the raw MA did not dissolve completely after 120 min, suggesting that the dissolution property of MA nano particles was significantly enhanced.

Supercritical Fluid Recrystallization

Supercritical fluids (e.g. carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure, allowing it to assume the properties of both liquid and a gas. At near-critical temperatures, SCFs are highly 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 are solubilized within SCF , they may be recrystallization at greatly reduced particle sizes. The best example of this is carbon dioxide. SCF are highly compressible at critical temperatures and allows alteration in density and mass transport characteristics which determines its solvent power due to moderate changes in pressure. As the drug gets solubilized within SCF they can be recrystallized with reduced particle size. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via sSCF technologies for particle size reduction.

Spray freezing into liquid and lyophilization

This technique was develop and patented by the university of Texas in 2013 by dow chemical company. This technique involve atomizing and aqueous, organic , aqueous –organic co- solvent solution, aqueous organic emulsion and suspension containing a drug and pharmaceutical excipients directly in to compress gas eg. Helium , propane , ethane or cryogenic liquid using the acetonitrile as the solvent then the drug loading capacity is increased and the drying time is decreased the dissolution rate is remarkable enhanced from SFL powder.

Use of surfactants

Surfactants are very useful as absorption enhancers and enhance both dissolution rate as well as permeability of drug. They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles. Seedhar N. et al[15], studied solubility enhancement of antimicrobial drug enrofloxacin using a series of co-solvents and surfactants. Aqueous solubility of enrofloxacin could be increased up to 26 times. Co-solvents alone produced only small increase in solubility. However, the combined effect of co-solvents and buffer was synergistic and a large increase in solubility could be attained. Ionic surfactants were found to be much better solubilizing agents than non-ionic surfactant. Amongst ionic surfactants, solubility was found to be very high in anionic surfactant, sodium dodecyl sulphate as compared to the cationic surfactant, acetyl trim ethyl ammonium bromide. Up to 3.8 mg/ml **.**

Use of salt forms: Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water-soluble than the parent drug.

Use of precipitation inhibitors

A significant increase in free drug concentration above equilibrium solubility results in super saturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC,PVP,PVA,PEG etc.

Co precipitation method

Active drug is dissolved in ethanol at room temperature and suitable polymer is dissolved in distilled water. Different molar ratios of active drug and suitable polymers are mixed respectively. The mixture is stirred at room temperature for one hour and the solvent is evaporated. The resultant mass is pulverized and passed through sieve no. 80 and stored in desiccators. In precipitation technique the drug is dissolved in a solvent, which is then added to antisolvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipment's; but the challenge is the addition of the growing drug crystals to avoid formation of micro particles. The limitation of this precipitation technique is that the drug needs to be soluble in at least one solvent and this solvent needs to be miscible with antisolvent. Moreover, precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and non-aqueous media[6]. Nano suspension of Danazol and Naproxen have been prepared by precipitation technique to improve their dissolution rate and oral bioavailability. The size reduction of naproxen was also associated with an apparent increase in the rate of absorption by approximately 4-fold[7.8.]

Spray drying

The drug is dissolve in the suitable solvent and required stoichiometric amount of carrier material like B – cyclodextrin is dissolve in water solution then mixed by sonication method or other method to make a clear

solution. Evaporation of drug and polymer solution in different ratio is carried out by using spray dryer. The solutions are prepared by dissolving drug in methanol and polymer in distilled water and mix both solutions, which produces a clear solution. The solvent evaporated by using evaporator. The spray dried mixture of drug with polymer is obtained in 20–30 min.

Alteration of pH of the drug microenvironment

This can be achieved in two ways- in situ salt formation, and addition of buffers in to the formulation e.g. buffered aspirin tablets .

Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition hypothesis and Henderson- Hesselbatch equation the ionization of a compound is dependent upon the pH of media and pKa of drug, The salt formation is infeasible for unionized compounds. And formation of salts may also converse to respective acid or base forms in the GI tract.

Use of a morphs, anhydrates, solvates and metastable polymorphs

Depending upon the internal structure of the solid drug, proper drug selection with greater solubility is important. Depending upon the internal structure of the solid drug, selection of proper excipient with drug they show grater solubility is important . Amorphous form are more stable then metastable polymorphous, anhydrates are more soluble then hydrates and solvates are more soluble then non solvents.

Eutectic Mixtures

In this system fusion are done. Eutectic method melting process are done by using the differ solute and solvents they show complete miscibility. Eutectic melts differ then the solid solutions in that the fused melt of solute –solvent show complete miscibility but negligible solid-solid solubility, i.e. such systems are basically intimately blended physical mixture of two crystalline components.

Use Of Co solvent:

Co solvents system can increase the water solubility of a drug significantly. It is mixture of the miscible solvent often used to solubilized lipophilic drug but the choices of biocompatible solvents are limited, such as to glycerin, propylene glycol, dimethylsulfoxide, ethanol and N, N dimethylformamide etc. Etman et al.[26] studied solubility of etodolac in four different co-solvents; ethanol, propylene glycol, polyethelene glycol 400, and glycerol, three sugars sucrose, sorbitol and mannitol, two hydrotropic salts; sodium benzoate, sodium salicylate, and two enhancers; Tween 80, Brij 58. Based on the solubility data, a trial has been done to propose a formulation (100 mg/3ml) for parenteral use in an aqueous solvent blend and formulation was tested physically for color, turbidity, and precipitation.

Self Emulsification

In the absence of external phase water mixture of oil, surfactant and co surfactant one or more hydrophilic solvent and co- solvent forms a transparent isotropic solution that is known as self-emulsification drug delivery system that form O/W emulsion or micro emulsion spontaneously upon dilution in aqueous phase and is used improving the lipophilic drug dissolution and absorption .

The self-emulsification process is specific to the nature of the oil/surfactant pair, surfactant concentration, oil/surfactant ratio and temperature in that self-emulsification occurs. In the self-emulsification could be associated with the ease of water penetrating into the various liquids crystalline or gel phases which form on the surface of the droplet.

A few parameters have been consider to characterize the self-emulsifying performance including the rate of emulsification, the emulsion size distribution and the charge of resulting droplets. Among them, emulsion droplet size is considered to be a decisive factor in self-emulsification dispersion performance, since it determines the rate and extent of drug release and absorption. In addition, positively charged emulsion droplets could be obtained by incorporation of a small amount of cationic lipid into such system. The oral bioavailability of progesterone was significantly enhanced in rats by forming positively charged emulsion in comparison to the corresponding negatively charged formulation.

The advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously under mild agitation and they are thermodynamically stable .There are drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.of water-insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles.

Therapeutic effectiveness of a drug depends upon the bioavailability therefore it ultimately depends upon the solubility and dissolution rate of drug molecules. These solubility and dissolution rate are important parameters to achieve desired concentration of drug in systemic circulation.

Melt-granulation technique

In this technique the powder drug is efficiently agglomerated by the use of melted binder which can be molten liquid a solid or a solid that melt during the process usually in high shear mixture where the product temperature are raised higher then the melting point of the binder either by heating the jacket or when the impeller speed is high by the heating technique no water and organic solvent are needed there is no drying step so the process is environmentally safe.

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