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Review On Solubility Enhancement Technique

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ABSTRACT:

The absorption process is developed in biological systems to deliver necessary organic and inorganic substances into systemic circulation while maintaining bioavailability. Bioavailability issues might be caused by insufficient solubility or permeability. Most chemicals have solubility difficulties. As a result, as chemical science advances, so does the necessity for the creation of pharmaceutical technologies, which vary depending on the medicine. The medicine has relatively low water solubility, which means that it dissolves slowly in the gastrointestinal tract. The oral route is the most desirable and preferred method of giving medicinal medicines because of their systemic effect. Drugs are categorized into four classes according on their solubility under the BCS classification. Various strategies are employed to increase the solubility of poorly soluble medications, including physical and chemical alterations of the drug, as well as additional methods such as particle size reduction, crystal engineering, salt creation, solid dispersion, surfactant application, and complexation. The choice of solubility-improving technology is determined by the drug's properties, absorption site, and dose form requirements.

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

INTRODUCTION:

The solvent is often a liquid, which might be a single chemical or a combination of two liquids. Solid solution is also used, but gas solution is less common. The degree of solubility varies greatly, ranging from infinitely soluble (ethanol in water) to poorly soluble (silver chloride in water). The term insoluble is frequently used to describe chemicals that are poorly or very poorly soluble. Solubility occurs in dynamic equilibrium, which means that it is the outcome of two opposing processes: dissolution and phase joining. Solubility equilibrium occurs when the two processes proceed at the same rate.

Under some conditions, equilibrium solubility can be exceeded to produce a so-called supersaturated solution, which is metastable. Solubility should not be confused with the ability to dissolve or liquefy a substance, as these processes can occur due to both dissolution and a chemical reaction. Solubility is defined by IUPAC as the analytical composition of a saturated solution expressed as a proportion of a specific solute in a particular solvent. Solubility can be expressed in terms of concentration, molality, mole fraction, mole ratio, and other units. The widespread use of solubility from many perspectives has resulted in solubility being stated in several ways. It is often stated 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 concentration-related terms. The maximum amount of solute that can dissolve in a given 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 an important pre-formulation parameter that controls the targeted drug concentration in the systemic circulation. The majority of newly discovered chemical entities have limited solubility, resulting in low bioavailability [4]. The drug's solubility is an important property since it determines its release, absorption, rate of dissolution, and, ultimately, bioavailability. Thus, processing is necessary to improve the medication's water solubility and dissolution.

BCS Classification System The Biopharmaceutics Classification System (BCS) was designed by the United States Food and Drug Administration (FDA). Pharmaceuticals are classified into four types based on their solubility and permeability characteristics. Low solubility creates a soluble impediment in the system's Classes II and IV, where dissolution is the rate-limiting step of the medicine absorption process. The Biopharmaceutical Classification System (BCS) categorizes medications based on intestinal permeability and intrinsic solubility. A drug's bioavailability is enhanced by good intestinal permeability and solubility. Drugs with low solubility and permeability have varying degrees of bioavailability. The bulk of drugs in the pharmaceutical business today are poorly soluble. Several ways for improving solubility have effectively addressed poor solubility.

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 widely used mode of drug delivery because to its ease of administration, high patient compliance, cost effectiveness, lack of sterility requirements, and flexibility in dosage form design. As a result, many generic medication companies are more likely to develop bioequivalent oral drug formulations.However, the main issue in designing oral dose forms is their low bioavailability. Oral bioavailability is determined by various parameters, including water solubility, drug permeability, dissolving rate, first-pass metabolism, presystolic metabolism, and sensitivity to efflux mechanisms. The most common causes of low oral bioavailability are poor solubility and low permeability. Other dosage forms, such as parenteral formulations, rely heavily on solubility as well. Solubility is a crucial criterion for attaining the desired concentration of drug in systemic circulation and the required pharmacological reaction. Poorly water soluble medicines frequently require high dosages to achieve therapeutic plasma concentrations following oral administration. Low water solubility is a serious issue in the formulation creation of novel chemical entities and generic drugs. Any medicine that will be absorbed must be present in the form of an aqueous solution at the absorption site. Water is the preferred solvent for liquid medicinal compositions. Most medications are either weakly acidic or weakly basic, with little water solubility. More than 40% of novel chemical entities (NCEs) generated in the pharmaceutical sector are practically insoluble in water. These poorly water soluble medicines have sluggish drug absorption, resulting in low and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered medicines, solubility is the most critical rate-limiting factor in achieving the appropriate concentration in systemic circulation for pharmacological response. The problem of solubility is a significant barrier for formulation scientists.

The increase of drug solubility and hence oral bioavailability remains one of the most difficult parts of the drug development process, particularly for oral-drug delivery systems. There are various ways available and documented in the literature for increasing the solubility of weakly water-soluble medicines. The approaches are chosen based on specific criteria such as the qualities of the medicine under consideration, the nature of the excipients to be used, and the nature of the planned dosage form. Poor solubility and slow dissolution rate of weakly water soluble medicines in aqueous gastrointestinal fluids frequently result in limited bioavailability. The bioavailability of drugs classified as class II (low solubility and high permeability) by the BCS may be increased by enhancing the drug's solubility and dissolution rate in gastrointestinal fluids.

Techniques for Solubility Enhancement

There are three types of solubility improvement techniques: physical modification, chemical alteration of the medicinal ingredient, and others.

Physical Modifications:

Particle size reduction methods such as micronization and nano suspension, crystal habit modification such as polymorphs, amorphous forms, and co-crystallization, drug dispersion in carriers such as eutectic mixtures, solid dispersions, solid solutions, and cryogenic procedures.

Micronization

The procedure entails reducing the size of solid drug particles to 1 to 10 microns, which is often accomplished using spray drying or attrition processes (fluid energy or jet mill). The method is also known as micro-milling. Several techniques for improving the dissolution of fenofibrate, a poorly soluble drug, were compared, and particle size reduction was achieved by jet milling (micronization; co-grinding with lactose, polyvinyl pyrrolidone, or sodium lauryl sulphate) and media milling using a bead mill (nanosizing) with subsequent spray drying. Supersaturated solutions were created by combining nanosizing with spray-drying, which transformed fenofibrate to an amorphous state. Fenofibrate medication preparations commercially available in Germany and France dissolved similarly to crude or micronized fenofibrate, but much slower than cog round or spray dried fenofibrate mixes. The findings indicate that cogrinding and spray-drying are effective procedures for creating rapidly dissolving fenofibrate formulations, which may lead to improved bioavailability of oral fenofibrate products.

Eg. Nicardipine hydrochloride (NCH) microspheres are loaded for 12-hour administration. Solvent evaporation was used to create microspheres containing Eudragit RS and L at varying ratios. The diameters of microspheres were measured over time in simulated intestinal fluid (pH 7.5) at 37°C. The release of NCH from microspheres increased with Eudragit L quantity, but no controlled-release pattern was detected. Q values ≥18.88 resulted in a slower initial release, followed by an accelerated release. Microspheres with a Eudragit RS-L ratio of 1:5.7, Q value of 38.71, and drug release rate of 0.155% min-1 had a much longer time for erosion to commence (120 minutes). Thus, microspheres made from this mixture may serve as an effective enteric dose form, releasing .This technique uses a microwave oven to irradiate the medication and complexing agent. In a round bottom flask, a defined proportion of water and organic solvent is used to dissolve the drug and CD in a specific molar ratio.

Nanoionisation

It is a method that converts medication powder to nano crystals ranging in size from 200 to 600 nm, such as Amphotericin B. The major production procedures currently used to generate medication Nano crystals produce a dispersion of drug Nano crystals in a liquid, usually water (known as Nano suspension). Currently, nanoparticles are prepared using three fundamental technologies:

i. Pearl milling.

ii. Water homogenization (wet milling, similar to a colloid mill).

iii. Water-miscible liquids are used to homogenize non-aqueous medium or water.

Megestrol acetate (MA) nanoparticles were prepared using a liquid precipitation process. The as-prepared MA particles had a mean size of 208 nm, with 90% of the particles distributed in the range of 100-300 nm. The raw MA had a mean particle size of 3.02 μm, ranging greatly from 0.2 μm to 30 μm. The freeze-dried MA nanoparticles displayed enhanced wettability, as evidenced by the contact angle measurement result, indicating that the particles were coated with a hydrophilic coating. In dissolving rate experiments, the nanoparticles achieved 100% drug dissolution within 5 minutes, whereas raw MA did not dissolve entirely after 120 minutes, indicating that the dissolution properties of MA nano particles were greatly improved.

Supercritical Fluid Recrystallization

Supercritical fluids (e.g., carbon dioxide) are fluids with temperatures and pressures that exceed their critical temperature (Tc) and critical pressure, allowing them to behave like both liquids and gases. At near-critical temperatures, SCFs are highly compressible, allowing moderate pressure changes to dramatically modify a fluid's density and mass transport properties, which essentially define its solvent power. Once the medication is solubilized within SCF, it can be recrystallized at much smaller particle sizes. Carbon dioxide is an excellent illustration of this. Within SCF, they can be recrystallized with smaller particles. Several pharmaceutical businesses, like Nektar Therapeutics and Lavipharm, specialize in particle engineering using sSCF technology to reduce particle size. As the medication becomes solubilized within SCF, it can be recrystallized with smaller particle size. Several pharmaceutical businesses, like Nektar Therapeutics and Lavipharm, specialize in particle engineering using sSCF technology for particle size reduction.

Spray freezing into liquid and lyophilization

This technology was developed and patented by the University of Texas in 2013 by Dow Chemical. This technique entails atomizing and compressing aqueous, organic, aqueous-organic co-solvent solution, aqueous organic emulsion, and suspension containing a drug and pharmaceutical excipients directly into gas, such as helium, propane, ethane, or cryogenic liquid, using acetonitrile as the solvent. As a result, the drug loading capacity is increased, the drying time is reduced, and the dissolution rate is significantly improved from SFL powder.

Use of surfactants

Surfactants are excellent absorption enhancers, improving both medication dissolution rate and permeability. They improve dissolving rate primarily by increasing the wetting and penetration of dissolution fluid into solid medication particles. Seedhar N. et al.[15] investigated the solubility increase of the antibacterial medication enrofloxacin using a variety of co-solvents and surfactants. The aqueous solubility of enrofloxacin could be improved up to 26 times. Co-solvents alone resulted in only a slight improvement in solubility. However, the combination of co-solvents and buffer had a synergistic impact, resulting in a significant increase in solubility. Ionic surfactants were discovered to be significantly more effective solubilizing agents than non-ionic surfactants. Sodium dodecyl sulphate, an anionic surfactant, has significantly higher solubility than acetyl trim ethyl ammonium bromide, a cationic surfactant. Up to 3.8 mg/mL. Using salt forms: Salts outperform the original medication in terms of solubility and dissolving. It is widely known that stable salts require a minimum pKa difference of three units between the group and its counter ion. Alkali metal salts of acidic medications, such as penicillin, and strong acid salts of basic pharmaceuticals, such as atropine, are more water soluble than their parent drugs.

Use of precipitation inhibitors

A large rise in free drug concentration above equilibrium solubility causes supersaturation, which can lead to drug precipitation or crystallization. This can be avoided by using inert polymers such as HPMC, PVP, PVA, and PEG.

Co precipitation method

The active medication is dissolved in ethanol at room temperature, and the appropriate polymer is dissolved in distilled water. Different molar ratios of active medication and appropriate polymers are combined together. The mixture is agitated at room temperature for an hour before the solvent is evaporated. The resulting mass is crushed, passed through sieve #80, and stored in desiccators. In the precipitation procedure, the medication is dissolved in a solvent and then added to an antisolvent to form crystals. The primary advantage of the precipitation technique is the employment of simple and inexpensive equipment; however, the problem is the addition of increasing drug crystals to avoid the production of microparticles. The restriction of this precipitation process is that the medication must be soluble in at least one solvent, which must also be miscible with the antisolvent. Furthermore, the precipitation technique does not apply to medicines that are weakly soluble in both aqueous and non-aqueous media6. To increase dissolution rate and oral bioavailability, a nano suspension of Danazol and Naproxen was created using a precipitation approach. Naproxen's size decrease was also connected with an apparent fourfold increase in absorption rate

Spray drying

The medication is dissolved in a suitable solvent, and the needed stoichiometric amount of carrier material, such as B-cyclodextrin, is dissolved in water solution and combined by sonication or another method to produce a clear solution. Spray dryers are used to evaporate medication and polymer solutions in varied ratios. The solutions are made by dissolving the medication in methanol and the polymer in distilled water, then mixing

them together to generate a transparent solution. The solvent was evaporated using an evaporator. In 20-30 minutes, a spray dried drug and polymer mixture is obtained.

Alteration of pH of the drug microenvironment

This can be accomplished in two ways: in situ salt production and the insertion of buffers into the formulation, such as buffered aspirin tablets.

The simplest and most widely used strategy for increasing the water solubility of ionizable substances is to change the pH of the microenvironment. According to the pH-partition hypothesis and the Henderson-Hesselbatch equation, the ionization of a molecule is dependent on the pH of the media and the pKa of the medication. Unionized compounds cannot form salts. In addition, salt creation may correspond to the formation of related acid or base forms in the gastrointestinal system.

Use of a morphs, anhydrates, solvates and metastable polymorphs

Depending on the internal structure of the solid substance, proper drug selection with increased solubility is critical. Depending on the internal structure of the solid drug, selecting the appropriate excipient with the drug that exhibits greater solubility is critical. Amorphous forms are more stable than metastable polymorphs, anhydrates are more soluble than hydrates, and solvates are more soluble than non-solvents.

Eutectic Mixtures

This system allows for fusion. Eutectic melting processes use different solutes and solvents that are completely miscible. Eutectic melts differ from solid solutions in that the fused melt of solute and solvent has complete miscibility but little solid-solid solubility, implying that such systems are essentially an intricately mixed physical mixture of two crystalline components.

Use Of Co solvent:

A co-solvents system can considerably boost a drug's water solubility. It is a mixture of miscible solvents that is commonly used to solubilize lipophilic drugs, although the options for biocompatible solvents are restricted, such as glycerin, propylene glycol, dimethylsulfoxide, ethanol, and N, N dimethylformamide. Etman et al.[26] investigated the solubility of etodolac in four distinct co-solvents (ethanol, propylene glycol, polyethylene 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 findings, a trial was conducted to propose a formulation (100 mg/3ml) for parenteral use in an aqueous solvent blend. The formulation was physically tested for color, turbidity, and precipitation.

Self Emulsification

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

The self-emulsification process is dependent on the oil/surfactant pair, surfactant concentration, oil/surfactant ratio, and temperature at which it happens. Self-emulsification may be connected with the ease with which water penetrates the various liquids crystalline or gel phases that develop on the surface of the droplet.

To define the self-emulsifying performance, several characteristics were considered, including the rate of emulsification, emulsion size distribution, and charge of the resultant droplets. Emulsion droplet size is thought to be a critical component in self-emulsification dispersion performance because it influences the rate and degree of medication release and absorption. Furthermore, the addition of a little amount of cationic lipid to such a system could result in positively charged emulsion droplets. The oral bioavailability of progesterone was dramatically increased in rats by producing a positively charged emulsion as opposed to the corresponding negatively charged formulation.

SEDDS have the benefit of forming spontaneously under gentle agitation and being thermodynamically stable, which makes them ideal for scaling up and manufacturing.The disadvantages of this approach include chemical instability of pharmaceuticals and excessive surfactant concentrations. The high concentration of surfactant in self-emulsifying formulations (30-60%) irritates the gastrointestinal tract. As a result, the safety of the surfactant vehicle has to be examined. Water-insoluble solid medicines are conveyed in suitable nonvolatile solvent systems known as liquid carriers.

The therapeutic effectiveness of a medicine is determined by its bioavailability, which in turn depends on the solubility and dissolution rate of drug molecules. Solubility and dissolution rate are critical criteria for achieving the required medication concentration in systemic circulation.

Melt-granulation technique

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

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