STUDY ON ENHANCING THE SOLUBILITY OF AN INADEQUATELY WATER-SOLUBLE DRUG

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ABSTRACT

One crucial factor in achieving the optimum medication concentration in the bloodstream so that a pharmacological reaction may be seen is solubility. Since poorly soluble medications have limited absorption and bioavailability, it is crucial to increase their solubility and dissolving rate. The bioavailability of around 40% of all novel chemical entities is low. One of the main difficulties for formulation scientists in the future will be to increase the bioavailability of medications that aren't easily soluble. This review tries to focus on the polymers used to achieve solubility enhancement, process of solubilization, and factors that affect it in addition to discussing the various traditional novel techniques like sono crystallization, spray freezing in to liquid, pearl milling, solid dispersion, salt formation, and pH adjustment for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation. In this article, we concentrated on how important solubility of the medication is to achieving adequate bioavailability following drug absorption, making it the most important component in formulation creation.

Keywords:- *Solubility Enhancement, Poorly Water Soluble Drug,*

INTRODUCTION

The bioavailability and solubility of a drug's molecules both have a role in its therapeutic effectiveness. Drug solubility is the maximum amount of the drug that can be dissolved in the solvent at a given temperature, pH, and pressure. As a critical factor in determining drug liberation, solubility also has a significant impact on bioavailability. Any medicine that is intended to be absorbed must be present at the absorption site in the form of an aqueous solution. The bioavailability of around 40% of all novel chemical entities is low. Changes in dissolution and disintegration may boost the bioavailability. Aqueous solubility less than 1 g/ml will undoubtedly cause a bioavailability issue and have an impact on the medication's effectiveness. The drug's water solubility may be improved using a variety of techniques. Raising the drug's solubility and rate of dissolution in the gastro-intestinal fluids might increase bioavailability, particularly for class II drugs according to the Biopharmaceutics Classification System.

To improve the solubility of a medicine that is just moderately water soluble, several strategies are available and documented in the literature. The methods are chosen based on a number of factors, including the characteristics of the medicine under consideration, the kind of excipients to be chosen, and the kind of dosage form planned.

Drugs with a log p value of 2 and those that are poorly soluble in both aqueous and organic media make the challenge much worse. Because their performance is dissolution rate restricted and influenced by the patient's fed/fasted condition, these medications often exhibit an irregular absorption profile and highly variable bioavailability.

The oral absorption of medications from solid dose forms may be divided into two distinct processes:

- The medicine is dissolved in the body to create a solution, and then it is transported through the intestinal membrane.
- Each process has a rate constant that may be used to describe it.
- Drug dissolution becomes the rate-limiting phase in the absorption process if the rate of dissolve is noticeably slower than the rate of absorption.

As a result, several efforts have been undertaken to alter the way that certain medications dissolve in order to achieve a quicker and more thorough absorption. The drug's particle size plays a significant role in the transport from the gastrointestinal tract to the site of action by speeding up GI tract dissolution.

BCS Classification: Class I-High Solubility, High Permeability

Drugs of the class I have high absorption and dissolution numbers. It is not necessary to have in vivo bioequivalence data to ensure product comparability for those Class I compounds that are formulated as immediate release products because the dissolution rate typically exceeds gastric emptying. Instead, nearly 100% absorption can be predicted if at least 85% of a product dissolves within 30 minutes of in vitro dissolution testing across a range of pH values.

Class II -Low Solubility, High Permeability

Drugs in class II have high absorption rates but low dissolution rates. The rate-limiting phase for absorption, except for at extremely large dosage numbers, is hence in vivo drug dissolution. A link between in vivo bioavailability and in vitro dissolution rate may be seen since the bioavailability of these compounds is probably dissolution-rate restricted.

Class III – High Solubility, Low Permeability

The rate-limiting stage in this kind of medication absorption is permeability. The pace and volume of drug absorption for these medications vary greatly. Dissolution will most likely happen very quickly, but absorption is permeability-rate limited, so it has been suggested that waiver criteria similar to those for Class I compounds may be appropriate as long as the test and reference formulations don't contain substances that can change drug permeability or GI transit time.

Class IV- Low Solubility, Low Permeability

These substances typically do not diffuse well through the intestinal mucosa and a considerable degree of variability is anticipated with extremely low oral bioavailability. These substances not only take a long time to dissolve, but once they do, they often only have partial permeability across the GI mucosa. These medications often demonstrate very high levels of intra- and inter-subject variability and are notoriously difficult to synthesize.

Class boundaries:

Highly Soluble:

When the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5 then drug substance is considered highly soluble

Highly Permeable:

When the extent of absorption in humans is determined to be > 90% of an administered dose then drug substance is considered highly permeable.

Rapidly Dissolving:

A drug product is considered to be rapidly dissolving when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a

volume of < 900 ml buffer solutions.

Process of solubilization

In the process of solubilization, the solute's inter-ionic or intermolecular connections are broken, the solvent's molecules are split apart to make room for the solute, and either the solvent and the solute's molecules interact.

Factor affecting solubilization:

Molecular size:

A substance's solubility will decrease as its molecular weight or particle size increases. To solvate a material, larger molecules are difficult to enclose in solvent molecules. The amount of carbon branching in organic compounds will enhance their solubility since more branching will result in smaller (or lower volume) molecules, which are simpler to dissolve in solvents.

Temperature:

The temperature will rise as the solubility increases if the solution process consumes energy. The solubility will decrease with rising temperature if the solution process releases energy. In general, a solid solute becomes more soluble as the solution's temperature rises. All gases become less soluble as the solution's temperature rises.

Pressure:

For gaseous solutes, solubility is increases with the application of presser. For solids and liquid solutes, changes in pressure have nearly no effect on solubility.

Particle size:

The temperature will rise as the solubility increases if the solution process consumes energy. The solubility will decrease with rising temperature if the solution process releases energy. In general, a solid solute becomes more soluble as the solution's temperature rises. All gases become less soluble as the solution's temperature rises.

$\log S/S0 = 2\gamma V/2.303 RTr$ Eq. 1

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.

Polymorphs:

Although a crystal of a certain material may have a different form or habit, the angles between the faces never change. Polymorphism is the capacity of a material to crystallize in more than one crystalline form. All crystals may crystallize in a variety of shapes or polymorphs. Enantiotropy is the scientific term for a process when one polymorph transforms into another in a reversible manner. If the system is monotropic, a transition point exists above both polymorphs' melting temperatures. Without a phase transition, the two polymorphs cannot be changed into one another. Melting points may vary amongst polymorphs.

Since a solid's solubility and melting point are connected, various polymorphs will have varied solubilities. Due to very minor variations in free energy, the range of solubility variances between various polymorphs is typically just 2–3 folds.

Rate of solution:

The rate of solution is determination of how fast substances dissolve in solvents. A various factors affecting rate of solution like-

Size of the particles:

When a solute is divided into smaller pieces, its surface area rises. As a result, the solute dissolves more quickly since the action only occurs at the surface of each particle, which enhances its rate of solution.

Temperature:

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

dissolve. For the gases reverse is true.

Amount of solute already dissolved:

When there was little solute in the solution before, dissolution happened quite quickly. Dissolution happens more slowly when the solution gets closer to the point where no solute can be dissolved.

Stirring:

Stirring increases the rate of solution for both liquid and solid solutes by bringing new solvent parts into contact with the solute.

Methods of solubility enhancement:

There are various techniques available to improve the solubility of poorly soluble drugs.

Surfactants:

Reducing the interfacial tension between the surfaces of the solvent and the poorly soluble substance's surface will improve wetting and salvation interaction. A wide variety of surfactants like polyglycolized glyceride, tweens, spans, polyoxyethylene stearates and synthetic block copolymers like poly (propylene oxide)-poly (ethylene oxide)- poly 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. Reduced surface tension between the drug and solvent, improved wetting properties, and micellar solubilization are the main reasons why amphiphilic surfactants promote drug solubility.

pH adjustment:

The impact of pH fluctuations in the gastrointestinal system on the bioavailability of medications has long been known. The pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization, are all factors that influence how well a drug is absorbed. These factors are all influenced by the pH of the various regions of the gastrointestinal tract. Poorly water soluble pharmaceuticals containing molecular components that may be protonated or deprotonated may be dissolved in water by changing the pH. While the importance of important pre-formulation factors like salt choice and pH adjustment has been emphasized, the usage of pH-altering excipients inside drug delivery systems is also very useful. In theory, both parenteral and oral delivery may involve pH adjustment. Because blood acts as a powerful buffer, a poorly soluble medication may precipitate with a pH between 7.2 and 7.4 after being administered intravenously. The buffer capacity and tolerability of the chosen pH are crucial factors to take into account when evaluating the approach's appropriateness. Following oral administration, the degree of solubility is likely to be affected as the medication travels through the intestines since the pH of the stomach is between 1 and 2 and that of the duodenum is between 5 and 7.5. Excipients that are soluble and raise the pH of the environment within a dosage form to a range higher than the pKa of weakly acidic medications make such pharmaceuticals more soluble. Similarly, excipients that function as alkalizing agents may make weakly basic drugs more soluble.

Salt formation:

Since many years ago, one method to improve solubility has been to salt-form medication candidates with weak acids and bases. It is an effective approach for the nearly 300 novel chemical entities that the FDA authorized for sale over the twelve

years from 1995 to 2006, 120 of which were in salt forms. It may be used for parenteral and other liquid formulations as well as solid dosage forms. The water solubility of an acidic or basic medicine as a function of pH determines whether the molecule will form acceptable salts. Of the 101 authorized salts of basic pharmaceuticals, 54 salts were made using hydrochloric acid, indicating that chloride was the main salt form.

The interrelationships between pH and solubility also determine what counter ions would be required 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 or not common ions would affect salt solubility and dissolution rate. General guidelines and factors for salt selection have been established in a number of reviews.

Particle Size Reduction:

One of the most likely methods for increasing the surface area and saturating solubility of lipophilic medicines is micronization or nanonization, which is accomplished by reducing the particle size to sub-micron levels.

By using traditional milling methods, it is impossible to decrease particle size below the submicron range. Engineering techniques that have been granted patents include spray freezing into liquid, evaporative precipitation into aqueous solution, solution enhanced dispersion by supercritical fluids, rapid expansion from supercritical to aqueous solution, and pearl milling high-pressure homogenization.

Co-grinding/Co-micronization:

It is quite successful to increase a drug's apparent solubility while preserving part of the drug's crystallinity by co-grinding it with water-soluble polymers like hydroxyl propyl methyl cellulose, poly vinyl alcohol, etc. in the presence of a tiny quantity of water. However, the enhanced Van der Waal contacts and electrostatic magnetism between particles caused by the energy provided to reduce particle size result in a reduction in the effective surface area owing to agglomeration, which lowers the dissolving rate.

To lessen or eliminate cohesive and electrostatic forces, co-micronization of pharmaceuticals utilizing excipients such microcrystalline cellulose is one alternative. By producing an ordered mixture and lowering particle-particle agglomeration or by lessening Van der Waal interactions, this method enhances the apparent surface area accessible for drug breakdown. Due to the natural surface roughness and porosity of the microcrystalline cellulose-Drug combination, an increase in the real surface area of the ordered powdered mixture is anticipated.

Following methods can be used for achieving Micronization:

- Jet milling
- Solid solution & eutectic mixtures
- Micro precipitation.
- Controlled crystallization
- Supercritical fluid technology
- Spray freezing into liquid
- Spray freeze dry

Pearl Milling:

Using pearl milling, the drug's microscopic particles are reduced to nanoparticles and trapped between the pearls as they move. The characteristics of the drug, the medium, and the stabilizer all affect how well it mills. The first FDA-approved nanoparticle medication employing Elan Drug Delivery's Nano-Crystals technology

is the immuno suppressor rapamune. Another product created using this method, Emend, has 80 or 125 mg of aprepitant. The main drawbacks of the pearl milling process are batch-to-batch variability, the risk of microbiological damage following milling in an aqueous environment, and the introduction of product contamination from the grinding material.

High- Pressure Homogenization:

In order to create Disso Cubes, a medication powder is mixed with an aqueous surfactant solution and then homogenized under high pressure to create nano suspensions. The cavitation force is sufficient to separate the drug into microparticles and nanoparticles. The stiffness of the drug material, the processing pressure, and the number of cycles used all affect particle size. The following might be intriguing characteristics of nano suspensions:

- Increase in saturation solubility and dissolution rate of drug
- Increase in adhesive nature, thus resulting in enhanced bioavailability
- Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility
- Possibility of surface modification of nano-suspensions for site-specific delivery

However, this approach can only fragment fragile drug candidates into nanoparticles. The chemical instability of delicate drugs under the harsh production conditions, Ostwald ripening in long-term storage, the toxicity of surfactants, the redispersibility of dried powder, batch-to-batch variation in crystallinity level, and finally the difficulty of quality control and the stability of partially amorphous nanosuspensions are a few things that need to be taken into consideration.

Solution Enhanced Dispersion by the Supercritical Fluids:

The University of Bradford invented and filed for a patent on the SEDS method. The usage of a coaxial nozzle offers a method by which the medicine in the organic solvent solution combines with the compressed fluid CO_2 in the nozzle's mixing chamber prior to dispersion and flows into a vessel for particle formation via a small opening. Through the impaction of the solution by a fluid moving at a greater velocity, such a nozzle breaks up the solution. The solution separates into droplets as a result of the strong frictional surface forces produced by the fluid's fast velocity. The SEDS technique has been used to generate a broad variety of materials as carriers of micro and nanoparticles. Enhancing the mass transfer rate between the droplets and the antisolvent before the droplets coalesce to create larger droplets is a crucial stage in the production of nanoparticles. In a different investigation, the ultrasonic nozzle-based supercritical antisolvent method is used to significantly reduce the particle size.

Rapid expansion from Supercritical to Aqueous Solution:

Through this process, medicines and surfactants dissolve in supercritical fluid quickly and produce particles with a desired size distribution in a very short amount of time. Spraying this mixture (drug + surfactant + C_{O2}) into an aqueous solution containing a second surface modification prevents any propensity for particle agglomeration or growth because the surfactants in the supercritical fluid stabilize the newly created tiny particles.

The pharmaceutical sector cannot use this technology due to the limited solubility of weakly water soluble medicines and surfactants in supercritical CO_2 and the high pressure needed for these procedures.

Ultra-Rapid Freezing:

A cutting-edge cryogenic technique called ultra-rapid freezing produces nano-structured drug particles with significantly increased surface areas. Based on management of the solvent system and process parameters, the technique may create particles with a variety of particle morphologies. To create highly porous, agglomerated particles, the process involves freezing a dissolved drug in an aqueous or anhydrous polymer water solution onto the surface of a cryogenic substrate with a thermal conductivity between 10 and 20 W/(m K).

The polymer works as a stabilizer and an inhibitor of crystal formation. The URF method has the ability to generate powders with better physicochemical qualities, comparable to those produced by other rapid freezing technologies, due to fast conductive heat transfer, which leads to high super-saturation and nucleation rates. Similar to previous freezing methods, the drug/polymer combination must freeze quickly in order to avoid phase separation and enable the active to remain molecularly distributed with the polymer. Similar to controlled precipitation, this method is quick and scalable since it employs solvents, excipients, and standard processing tools that are acceptable to pharmaceutical companies.

The use of high glass-transition temperature polymers, such as PVP or HPMC, prevents the medication from recrystallizing. This method may be used in many different situations to improve in vivo absorption of BCS class-II drugs.

Sono crystallization:

Sono crystallization is a cutting-edge particle engineering technology to enhance hydrophobic medication solubility and dissolution and to research its impact on the drug's crystal characteristics. It has also been successful to use recrystallization of poorly soluble compounds with liquid solvents and antisolvents to lower particle size. Sono crystallization uses ultrasonic energy with a 20–100 kHz frequency range to cause crystallization. Ultrasound is often used in applications between 20 kHz and 5 MHz.

Solvent Deposition/Evaporation:

In this procedure, the medication is dissolved in a clear solution using a solvent such methylene chloride. The solvent is then eliminated by evaporation at a controlled temperature and pressure after the carrier has been separated from the solution by stirring. The last steps include dehydrating, grinding, and sieving the produced material. Reduced drug particle size when placed on the carrier and improved particle wettability brought on by the carrier are attributed to the increase in dissolving rate.

Solid solutions/dispersions:

Solid dispersion is the term used to describe the solid state dispersion of one or more active substances in an inert matrix or carrier. By creating eutectic mixes of pharmaceuticals with water-soluble carriers, it was first developed to combat the limited bioavailability of medications having a lipophilic structure. It was described as the solid-state dispersion of one or more active compounds in a solvent- or melting-solvent-prepared inert carrier matrix. Celecoxib, halofantrine and ritonavir's solubility may be increased by solid dispersion using the appropriate hydrophilic carriers.

Method of solid dispersions:

Hot melt method (fusion method):

This procedure included immediately heating the physical combination of a medication and a water-soluble carrier until it melted. The melted slurry was vigorously stirred while being swiftly cooled and hardened in an ice bath. With the use of tabletting agents, the final solid mass may be compressed into tablets after being crushed, pulverized, and sieved. A binary system's makeup, including the choice of carrier and the weight percentage of the medicine in the system, determines its melting point.

The miscibility of the drug and the carrier in the molten state is a crucial requirement for the creation of solid dispersion using the hot melt technique. The thermostability of the medication and carrier is another crucial need.

Solvent Evaporation Method:

For the first time, a common solvent was used by Tachibana and Nakumara to dissolve both the drug and the carrier, and the solvent was subsequently evaporated under vacuum to create a solid solution. In the highly water soluble carrier polyvinyl pyrrolidone, they were able to create a solid solution of the highly lipophilic -carotene as a result.

Due to the low temperature needed for the evaporation of organic solvents, the fundamental benefit of the solvent approach is that thermal breakdown of medications or carriers may be avoided. This method has some drawbacks, including a higher preparation cost, a challenge in completely removing liquid solvent, a potential negative impact of the solvent's purportedly negligible amount on the chemical stability of the drug, the use of a common volatile solvent, and a challenge in producing crystal forms.

Hot melt extrusion:

The main difference between hot melt extrusion and the fusion process is that the extruder induces vigorous mixing of the components. Miscibility of the medication and matrix might be an issue, much as in the conventional fusion procedure. For heat-sensitive materials, strong shear pressures and high local temperatures in the extruder are a challenge. But unlike the conventional fusion approach, this technology allows for continuous manufacturing, which qualifies it for large-scale production. Additionally, the product is simpler to handle since, at the extruder's output, the form may be modified to fit the requirements of the next processing step without grinding.

Characterization of solid dispersion:

Several analytical techniques may be used to describe solid dispersion. For the evaluation of solid dispersion, it is possible to use FT-IR spectroscopy, scanning electron microscopy (SEM), X-ray diffraction, dissolution rate estimation, and thermal analysis techniques like the thermo-microscopic method, differential thermal analysis (DTA), and differential scanning colorimetry.

Co-evaporate System / Co-precipitation:

Weak basic medications, such as prochlor perazine maleate, are well soluble in acidic pH but significantly less so in alkaline pH. When a conventional formulation containing a weak base is administered orally, the formulation precipitates a poorly soluble free base within the formulation in the intestinal fluid. Drug bioavailability decreases as a result of precipitated drug's inability to release from formulation. The co-evaporate system, which combines a carrier with a solubilizing effect in alkaline intestinal fluid and may function in the

microenvironment, immediately surrounding the drug particle, and polymers for controlling the dissolution rate to formulate dosage forms to ensure maximum bioavailability with controlled release of weak base, can be used to solve this issue.

Supercritical fluid method:

Drug particles may be micronized down to sub-micron sizes using a supercritical fluid process. The term "supercritical fluid" refers to fluids with temperatures and pressures above the critical temperature and critical pressure, respectively. Since SCFs are extremely compressible at near-critical temperatures, small changes in pressure may significantly modify a fluid's density and mass transport properties, which are key factors in determining its solvent power. The drug particles may be recrystallized at much smaller particle sizes after being solubilized inside SCF. The two supercritical fluids that are most often utilized are carbon dioxide and water. Particles measuring 5-2,000 nm in diameter may be suspended in nanoparticulate form using the SCF technique. Supercritical fluid processing, for instance, may increase the water solubility of etraconazole when combined with the water soluble polymer HPMC.

Drug dispersion in carriers:

The phrase "solid dispersions" refers to the solid-state dispersion of one or more active substances in an inert carrier, which is often made using the melting technique, solvent method, or solvent-fusion method. Rapid precipitation employing freeze drying, supercritical fluids, and spray drying, often in the presence of amorphous hydrophilic polymers, as well as using techniques like melt extrusion, are examples of novel additional preparation procedures. For solid dispersions, polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630 are the most often employed hydrophilic carriers. Surfactants are often used in the creation of solid dispersion. Tween-80, sodium docusate, Myrj-52, Pluronic-F68 poloxamer, and sodium lauryl sulphate are a few examples of surfactants utilized.

Carriers for Solubility Enhancement:

Pharmaceutical formulations often include soluble, quickly-dissolving carriers to increase the solubility and dissolution of medicines. For solubility improvement, the various carriers indicated in table 1 are utilized.

Table 1: List of carriers used for solubility enhancement

Category	Examples of carrier
Polymeric materials	Povidone (PVP), polyeth cyclodextrin, hydroxypropyl cellulose, hydroxy ethyl ce cellulose.
Acid	Citric acid, succinic acid.
Miscellaneous	Microcrystalline cellulose, di gel, sodium chloride.
Hydrotrops	Urea, sodium acetate, nicotin sodium salicylate, sodium-o-hy
Sugars	Dextrose, sucrose, galactose, lactose.
Surfactants	Deoxycholic acid, tweens, stearate, renex, poloxamer 188
Insoluble or enteric polymer	Eudragit L100, Eudragit S10 RS, Hydroxy propyl methyl ce

Conclusion:

In this article, we came to the conclusion that the drug's solubility is the most important variable and the key to achieving excellent bioavailability following drug absorption, making it the most important variable in formulation creation.

There are several strategies and procedures

available to increase solubility and bioavailability, and we attempted to include them all in this script. However, solid dispersion systems have been identified as a very beneficial method for enhancing the dissolving characteristics of medications that are not very water-soluble. Solid dispersion technology has gained a lot of knowledge recently, but other techniques like micronization, complexation, and pro-drugs ideas are also helpful in pharmaceutical operations. To avoid any method's restriction, a thorough investigation is necessary. We compile the medicine list. Whose solubility was improved using one of the aforementioned techniques also sought to concentrate on the polymers and carrier utilized to achieve solubility improvement.

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