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REVIEW ON DIFFERENT METHODS OF SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUGS

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ABSTRACT

Solubility enhancement technologies are critical in improving the bioavailability of poorly soluble drugs, which is major challenege in pharmaceutical development. Theses technologies encomposses a range of methods designed to increases the solubility and dissolution rates of active pharmaceutical ingrediants (API), Thereby enhancing their therapeutic approaches include the use of solubilizer, nanoparticles, solid dispersion, nanosuspnesion, pH adjustment, Cosolvency Additionally advanced, methods included liquisolid method, Nanotechnologyand micellar system has emerged to address specific solubility challanges. This review provides an overview of current solubility enhancement technologies, their mechanism and apllications in drug formulation. The ongoing development and optimization of these tecnologies are essential for advancing drug delivery system and improving patients outcome.

KEYWORDS: Solubility, BCS Class II, Sonocrystallization, Solid dissipation, Hydrotropy, Addition Complexation.

INTRODUCTION

Solubility is defined in quantitative terms as the attention of the solute in a impregnated result at a certain temperature and in qualitative terms, it may be defined as the robotic commerce of two or further substances to form a homogeneous molecular dispersionn. A logged result is one in which the solute is in equilibrium with the detergent. The solubility of a medicine may be expressed as corridor, chance, molarity, molality, volume bit, and operative bit.[1] The solubility of a medicine is described in colorful descriptive terms which is grounded on the

quantum of medicine dissolved in detergent and bandied in Table- 1.[2]

Table 1: Defination of solubility.[2]

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
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 10000
Insoluble	More than 10,000

The oral route of medicine administration is the most common and favored system of delivery due to convenience and ease of ingestion. About 10 of new chemical realities warrant there launching in request due to their poor water solubility and in malignancy of their implicit pharmacokinetic exertion and 40 of new chemical realities presently discovered are inadequately water answerable, and presently 8 of new medicine campaigners have both high solubility and permeability.[2] Limited medicine immersion performing in poor bioavailability is consummate amongst the implicit problems that can be encountered when delivering an active agent via the oral route. Hence, two areas of pharmaceutical exploration that concentrate on perfecting the oral bioavailability of active agents include enhancing solubility and dissolution rate of inadequately water-answerable medicines and enhancing permeability of inadequately passable medicines.[3] The Biopharmaceutics Bracket System is used to classify medicines grounded on solubility and permeability for expression development. BCS consists of four classes grounded on solubility and permeability. Both BCS II and IV composites are of low solubility(Table 1), and class IV composites suffer from fresh poor permeability issue[4] Solubility problem which can be answered during product development by choosing some technological approaches and Solid dissipation, Micronization, swab conformation are some approaches generally used to enhance solubility but each approach has limitations and advantages. Now new technologies like Nano suspense, Supercritical processing, Crogenic technology has openings in the delivery of inadequately answerable medicines.[5]

NEED OF SOLUBILITY IMPROVEMENT

1. Drug immersion from the GI tract can be limited by a variety of factors most significant contributor being poor waterless solubility and poor membrane permeability of the medicine molecule.[6]
2. Solubility is an important parameter in case of oral administered medicines in order to achieve asked attention of medicines in the systemic rotation to show the pharmacologic response.[7]
3. Oral ingestion is the most accessible and generally employed route of medicine delivery due to its ease of administration, high case compliance, costeffectiveness, least sterility constraints, and inflexibility in the design of lozenge form.[8]
4. Low waterless solubility is the major problem encountered with expression development of new chemical realities as well as general development.[9]

FACTORS AFFECTING SOLUBILITY IMPROVEMENT

The solubility is told by the solid's physical structure, the kind and make- up of the solvent medium, and the system's temperature and pressure flyspeck size.

Particle Size

The solubility of medicine significantly affected by its flyspeck size due to changes in face area to volume equation, the disolution rate of solid is direclty commensurable to its face area. as a particle size decreases, the face area increases, which enhances the medicine’s commerce with the detergent and accelerates the dissolution.[10]

Temperature

Temperature can significantly impact the solubility of a medicine in a detergent. Generally, as temperature increases, the solubility of utmost solid medicines in liquids also increases. This happens because advanced temperatures give further energy to overcome the chassis energy of the solid medicine, allowing it to dissolve further readily. However, the effect of temperature on the solubility of feasts is different. For feasts, adding the temperature generally decreases solubility in liquids. This is because advanced temperatures give gas motes more kinetic energy, leading them to escape from the liquid phase more fluently.[11]

Pressure

Pressure greatly affects the solubility of feasts, adding it as pressure rises, according to Henry's Law. For solids and liquids, pressure generally has a minimum effect on solubility

compared to temperature and detergent parcels.[12]

Molecular Size

Molecular size influences medicine solubility by affecting face area, opposition, and demitasse conformation. Larger motes may interact further with detergents due to their lesser face area but might have reduced solubility if exorbitantly large or hydrophobic. Increased molecular weight can drop solubility if it leads to poorer relations with detergents. Also, larger motes may form complex crystal clear structures that further lower solubility.[13]

Polarity

Opposition affects medicine solubility through the principle" like dissolves like." Polar medicines dissolve well in polar detergents like water due to relations similar as hydrogen cling, while nonpolar medicines are more answerable in nonpolar detergents like canvases. Hydrophilic medicines attract water, whereas hydrophobic medicines do not. Ionization also impacts solubility acidic medicines are more answerable in introductory surroundings, and introductory medicines are more answerable in acidic surroundings. This knowledge is pivotal for formulating medicines, as it helps enhance their dissolution and effectiveness.[14]

Polymorphs

Polymorphs are different liquid forms of the same substance, affecting a medicine's solubility and bioavailability due to variations in crystal clear structure and chassis energy. further answerable polymorphs dissolve more readily, and their stability and implicit metamorphosis under different conditions can impact medicine effectiveness. opting the right polymorph is essential for optimal medicine expression and remedial issues. Solubility enhnacement of BCS class II medicine.[15]

METHOD OF SOLUBILITY ENHANCEMENT

The solubility improvement of Biopharmaceutical Bracket System(BCS) Class II medicines, which are characterized by low solubility and high permeability, is pivotal for perfecting their bioavailability.

Then are some common strategies

a) flyspeck Size Reduction

b) Nanonization

c) Cosolvency

d) Hydrotropy

e) pH Adjustment

f) Sonocrystallization

g) Supercritical Fluid(SCF) Process

h) Solid dissipation

i) Addition Complexation

j) Self-Emulsifying Or Self-Micro Emulsifying Systems

k) Liquisolid Methods

l) Modification Of The Crystal Habit

m) Nanotechnology

A. Particle Size Reduction

The solubility of pharmaceutical compounds is intrinsically linked to their particle size. As particle size decreases, the surface area to volume ratio increases, allowing for greater interaction between the drug and solvent, which enhances solubility. Conventional particle size reduction techniques, such as comminution and spray drying, utilize mechanical forces to disaggregate the active pharmaceutical ingredient. While these methods can efficiently and economically increase solubility, they also introduce physical and thermal stresses that may lead to drug degradation, especially for thermo-sensitive or unstable compounds.[16]

i. Micronization

Micronization is a widely used technique for particle size reduction, aiming to increase the dissolution rate of drugs by enlarging their surface area. However, micronization does not alter the equilibrium solubility of the drug. The primary advantage of micronization is the enhancement of dissolution rate, which can significantly improve the bioavailability of drugs. Micronization processes, such as jet milling and rotor-stator colloid mills, have been successfully applied to drugs like griseofulvin, progesterone, spironolactone, diosmin, and fenofibrate. For instance, micronized fenofibrate demonstrated a greater than 10-fold increase in dissolution within 30 minutes in biorelevant media.[17] Despite these benefits, micronization has limitations, such as high energy consumption and the potential for generating amorphous or disordered regions in the drug product, which are thermodynamically unstable and prone to recrystallization under adverse storage conditions.[17]

ii. Nanosuspension

Nanosuspensions are particularly effective for poorly soluble drugs that are insoluble in both water and oils. This biphasic system consists of nanoparticles dispersed in an aqueous medium, stabilized by surfactants. Nanosuspensions typically feature particle sizes ranging from 200 to 600 nanometers. This technology is applicable for various drug delivery routes, including oral, parenteral, pulmonary, and topical administration. Methods for nanosuspension preparation include Nanocrystals, DissoCubes, Nanopore, and Nanoedge. This approach significantly enhances drug solubility and bioavailability by leveraging the large surface area of nanoparticles, thus facilitating better therapeutic efficacy for drugs like tarazepide, atovaquone, amphotericin, paclitaxel, and buparvaquone.

B. Nanonization

Nanonization refers to the reduction of drug particle size to the nanoscale (approximately 100 nm or less) to improve the dissolution rates and bioavailability of poorly water-soluble drugs. This technique enhances drug solubility and pharmacokinetics while potentially minimizing systemic side effects. When micronization fails due to particle agglomeration, nanonization is employed.[18]

KEY TECHNIQUES FOR NANONIZATION INCLUDE

1. Wet Milling

This method utilizes high-shear media mills where a milling chamber, filled with milling media, water, drug, and stabilizer, is rotated at high shear rates. The process lasts several days (2-7 days), generating high-energy shear forces from the impaction of the milling media with the drug, resulting in nanosized particles.[19]

2. High-Pressure Homogenization

In this technique, a drug suspension mixed with surfactants is forced through a nanosized aperture under high pressure using a high-pressure homogenizer. The cavitation forces within the aqueous phase facilitate the reduction of microparticles to nanoparticles. This method requires pre-sized samples and multiple cycles of homogenization. It has been effectively used to improve the dissolution rates and bioavailability of drugs such as spironolactone, budesonide, and omeprazole.[20]

3. Emulsification-Solvent Evaporation

This approach involves dissolving the drug in a solvent, then emulsifying it with a non-

solvent, followed by solvent evaporation. This results in the formation of drug nanoparticles.[21]

4. Pear Milling

Similar to wet milling, pear milling involves the use of spherical media to achieve nanosized particles through high-shear forces.[22]

5. Spray Drying

This technique transforms drug solutions into powders by spraying them into a hot gas stream. The rapid evaporation of the solvent leads to the formation of nanoparticles.[23]

6. Nanosuspension Technology

Nanosuspensions are biphasic systems where drug particles are stabilized by surfactants. These systems are designed for drugs that are insoluble in both water and oils. Typically, nanosuspensions have particle sizes less than one micron, with an average size ranging from 200 to 600 nm. Preparation methods for nanosuspensions include:[24]

7. Precipitation Technique

In this method, the drug is dissolved in a solvent and then introduced to an antisolvent, leading to precipitation. While it is a simple and cost-effective approach, it is limited by the solubility of the drug in at least one solvent and its miscibility with the antisolvent. This method has been used to prepare nanosuspensions of drugs like Danazol and Naproxen, improving their dissolution rate and oral bioavailability.

8. Media Milling

This technique employs high-shear media mills with various milling media (glass, zirconium oxide, or polystyrene resin) to reduce drug particle size through high-energy shear forces.

9. High-Pressure Homogenization

This method involves forcing drug suspensions through nanosized apertures under high pressure, utilizing cavitation forces to reduce particle size to the nanoscale. It is effective for enhancing the dissolution rates and bioavailability of poorly soluble drugs.

10. Combined Precipitation and Homogenization

This approach involves initially precipitating the drug nanoparticles and then processing the suspension with high-energy forces to prevent the growth of microcrystals. This combination

helps in maintaining particle size and stability, addressing issues of long-term stability and bioavailability.

C. Cosolvency

He solubility of poorly soluble pharmaceuticals in aqueous media can be substantially increased through the technique of cosolvency. This process involves the use of a cosolvent—an additional liquid that is miscible with water and in which the drug is more soluble. Cosolvency, also referred to as solvent blending, operates by reducing the interfacial tension between the hydrophobic solute and the aqueous solution. Cosolvents typicallypossess hydrogen bonding donor or acceptor groups and a small hydrocarbon segment. The hydrocarbon portion disrupts the hydrogen bonding network of water, thereby lowering the water's intermolecular attraction while the hydrophilic groups contribute to maintainingmiscible liquids to enhance the solubility and dissolution of drugs. This method can lead to an increase in drug solubility by several orders of magnitude, significantly improving the availability of poorly soluble compounds.[25] It is particularly effective for lipophilic or highly crystalline drugs that exhibit limited solubility in water but high solubility in water but high solubility in the cosolvent admixture. Common low- toxin cosolvents used in parenteral phrasings include propylene glycol, ethanol, glycerin, and polyethylene glycol. Dimethyl sulfoxide (DMSO) and dimethylacetamide(DMA) are also constantly employed due to their high solubilization capacity and fairly low toxin biographies. In parenteral phrasings, it may be necessary to adulterate the cosolvent- containing result with water or another waterless medium to achieve the asked detergent content before administration. also, cosolvency can be combined with other solubilization ways and pH adaptations to further optimize the solubility of inadequately answerable medicines.[26]

D. Hydrotropy

Hydrotropy is a solubilization miracle wherein the addition of a significant quantum of a alternate solute, appertained to as a hydrotropic agent, enhances the waterless solubility of a inadequately answerable solute. This improvement is attributed to complexation, involving weak relations between the hydrotropic agents and the solute. Hydrotropic agents are generally ionic organic mariners, similar as sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate, and sodium acetate. These agents increase the solubility of inadequately water-answerable medicines by" wreathing in" the solute, a process eased by mariners with large anions or cations that parade high solubility in water.[27] This effect is

known as" hydrotropism." Hydrotropic results are characterized by theirnon-colloidal nature and involve weak relations between hydrotropic agents and solutes. Hydrotropes, which include substances similar as sweet alcohols(e.g., resorcinol, pyrogallol), alkaloids(e.g., caffeine, nicotine), and ionic surfactants(e.g., sodium dodecyl sulfate), frequently tone-assemble in result. The bracket of hydrotropes grounded on molecular structure is complex due to the wide variety of composites flaunting hydrotropic geste. Sweet hydrotropes with anionic head groups are particularly studied due to their effective hydrotropic action, which is attributed to the presence of interactive π orbitals.

E. PH Adjustment

PH Adjustment inadequately water-answerable medicines can potentially be dissolved in waterless results by modulating the pH. This strategy relies on conforming the pH to enhance the solubility of the medicine, with considerations for buffer capacity and the tolerability of the named pH being critical. Excipients that elevate the pH of the lozenge form to situations above the pKa of weakly acidic medicines can enhance their solubility. Again, alkalizing agents that raise the pH can increase the solubility of weakly introductory medicines. This pH adaptation approach is effective for both crystalline and lipophilic inadequately answerable substances. For oral and parenteral administration, pH adaptation can ameliorate solubility, though intravenous operations must be precisely managed. Blood's pH, which ranges from 7.2 to 7.4, may precipitate the medicine if solubility is n't adequately achieved.[28] also, the pH variation from the acidic terrain of the stomach(pH 1- 2) to the further neutral duodenum (pH 5- 7.5) affects solubility and immersion upon oral administration. Compounds that are ionizable and remain stable and answerable after pH revision are optimal campaigners. This system is suitable for acids, bases, and zwitterionic composites. Increased solubility can enhance oral bioavailability through bettered dissolution rates and attention slants. still, if rush occurs into inadequately answerable patches that do n't fleetly redissolve, the increase in bioavailability may be compromised. In summary, pH adaptation is a currentpre-clinical fashion for assessing the solubility and efficacity of inadequately answerable medicines.[29]

F. SMEDDS

While effective, the eventuality for unbridled rush must be managed, andco-solvents may be used to further enhance solubility where necessary Self- Emulsifying Or Self- Micro Emulsifying Systems tone- emulsifying medicine delivery systems(SEDDS) and tone-microemulsifying medicine delivery systems(SMEDDS) are advanced pharmaceutical

phrasings designed to enhance the bioavailability of inadequately water-answerable medicines. These systems are characterized by their capability to spontaneously form mixes or microemulsions upon contact with waterless media in the gastrointestinal tract. SEDDS correspond of a admixture of lipids, surfactants, hydrophilicco-solvents, and occasionally fresh detergents. In the absence of an waterless phase, SEDDS form a clear, isotropic result. Upon contact with gastrointestinal fluids, this result spontaneously transforms into fine oil painting- in- water mixes or microemulsions.[30] This process improves the solubility and immersion of lipophilic medicines by adding their face area and easing their objectification into the lymphatic system. SMEDDS are analogous but generally contain advanced attention of surfactants andco-solvents, enhancing their emulsifying parcels. An illustration is Neoral, used for cyclosporine, which demonstrates increased bioavailability compared to conventional phrasings like Sandimmune due to bettered medicine solubilization and immersion. Despite their advantages, similar as thermodynamic stability and ease of manufacture, SEDDS and SMEDDS face challenges including implicit chemical insecurity of medicines, high surfactant attention that can irritate the gastrointestinal tract, and limitations to oral administration, frequently taking encapsulation in gelatin capsules. also, the size of the conflation driblets plays a critical part in medicine bioavailability; lower driblets generally affect in advanced tube medicine situations and better lymphatic uptake. Due to their high surfactant content, SMEDDS are generally recommended for short- term use to minimize adverse gastrointestinal goods similar as diarrhea.

G. Liqui solid method

In the liquisolid system, a liquid medicine dissolved in a suitable vehicle is introduced into a carrier material characterized by a pervious face and internal stringy structure, similar as cellulose. This process involves both immersion and adsorption marvels. originally, the liquid is absorbed into the innards of the carrier patches, where it's retained by the internal structure. Upon achromatism of this immersion process, the remaining liquid adsorbs onto both the internal and external shells of the pervious carrier patches. This system effectively converts the liquid drug into a dry, free- flowing, and compressible greasepaint with enhanced inflow properties. The liquisolid system utilizes liquid medicines with low waterless solubility, dissolved innon-volatile detergents, and latterly mixed with pulverized excipients. These excipients, comprising carrier and coating accoutrements, grease the metamorphosis of the liquid drug into a free- flowing and compressible greasepaint. Carrier accoutrements similar as microcrystalline cellulose and coating accoutrements like unformed cellulose and silica

maquillages are generally employed in this process. Solubility is a vital physical characteristic affecting a medicine's oral bioavailability, expression, remedial efficacity, and quantitative analysis. The selection of an applicable solubility improvement system is pivotal for achieving optimal expression issues, including bettered oral bioavailability, formulation, therapeutic efficacy, and quantitative analysis. The selection of an appropriate solubility enhancement method is crucial for achieving optimal formulation outcomes, including improved oral bioavailability, reduced dosing frequency, enhanced patient compliance, and cost-effective production. Employing various techniques to enhance drug solubility can significantly improve the bioavailability of poorly soluble drugs, thereby making it feasible to effectively increase their solubility.[31]

CONCLUSION

To enhance drug solubility and dissolution, various techniques are employed to maximize bioavailability and therapeutic efficacy. The proper selection of solubility enhancement methods is critical to achieving optimal oral bioavailability, patient compliance, and cost-effectiveness in drug production. Traditional methods often resulted in irregular particle sizes and inconsistent dissolution rates. In contrast, novel approaches offer more uniform particle sizes and improved performance. Recent advancements in lipid technology have significantly impacted the pharmaceutical field. This technology includes numerous patented methods that enhance the dissolution of poorly water-soluble drugs. These innovative techniques address solubility issues by overcoming dissolution rate-limiting steps, thereby improving drug bioavailability and therapeutic action. Solubility is a fundamental physical property that influences oral bioavailability, formulation development, and therapeutic efficacy. The rate of oral absorption for weakly water-soluble drugs is directly related to drug dissolution, making solubility a critical factor in the development of various dosage forms. Proper solubility enhancement techniques can reduce dosing frequency and enhance patient compliance while maintaining low production costs. In conclusion, solubility is a pivotal factor in pharmaceutical formulation and development. Techniques for solubility enhancement, whether applied individually or in combination, are essential for improving the bioavailability of poorly soluble drugs. The choice of method depends on the drug's chemical and physical properties, pharmacokinetic behavior, and specific formulation requirements. Advances in solubility enhancement techniques continue to facilitate the development of effective dosage forms for poorly soluble drugs.

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