STUDY ON METHODS TO IMPROVE THE BIOAVAILABILITY OF BCS-CLASS II MEDICATIONS

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ABSTRACT

Because of their low solubility in water, roughly forty percent of the novel chemical entities discovered by screening programs in the pharmaceutical industry have historically been unable to be produced. This is because the formulation of these substances is difficult or even impossible. The solubility concerns that are making the delivery of these new pharmaceuticals more difficult also influence the delivery of a great deal of other drugs already on the market. This page provides a short discussion of the many different methods, both standard and unique, that may be used for the purpose of increasing the solubility of BCS Class II medications.

The use of co-solvents, Hydrotropy, micronization, changing the dielectric constant of the solvent, amorphous forms, chemically modifying the drug, using surfactants, inclusion complex or clathrates, changing the pH of the solvent, using hydrates or solvates, using soluble prodrugs, applying ultrasonic waves, functional polymer technology, controlled precipitation technology, and evaporative precipitation are some of the traditional techniques that have been covered in this article. Size reduction technologies, lipid-based delivery systems, micellar technologies, and porous microparticle technology are some examples of the novel drug delivery technologies that have been created in recent years with the purpose of increasing the solubility of insoluble pharmaceuticals. Brief explanations have also been given on the Solid Dispersion Technique as well as the many different kinds of solid dispersion systems.

***Keywords**: NCE, Amorphous state, characterization, dissolution enhancement.*

INTRODUCTION

The oral route of medication administration is the most frequent and favored way of delivery owing to its comfort and ease of consumption; nevertheless, for many pharmaceuticals, this mode of delivery may be troublesome and ineffective for a variety of reasons. When administering an active agent by the oral route, the most significant possible issue that may arise is restricted drug absorption brought on by low drug solubility, which then leads to reduced bioavailability. This is only one of the potential difficulties that may arise. The therapeutic efficacy of a medicine is contingent on the bioavailability of the drug, which in turn is determined by the solubility of the drug molecules.

In order to acquire the correct concentration of the medication in the systemic circulation and produce the intended pharmacological reaction, one of the most critical parameters is the drug's solubility. Only 8% of novel medication candidates have good solubility and permeability at the moment. The greatest amount of a solute that may dissolve in a given amount of solvent or quantity of solution at a given temperature is referred to as the solute's solubility. To put it another way, solubility may also be defined as the capacity of one material to combine with that of another substance to produce a solution. The solubility concerns that make the administration of these new pharmaceuticals more difficult also

complicate the delivery of a great deal of already existing medication.

The oral route of medication administration is the most frequent and favored way of delivery owing to its comfort and ease of consumption; nevertheless, for many pharmaceuticals, this mode of delivery may be troublesome and ineffective for a variety of reasons. while it comes to the possible difficulties that might arise while administering an active agent via the oral route, the most significant of these issues is limited drug absorption, which is caused by low solubility of medications and ultimately results in poor bioavailability. Bioavailability "The rate and extent to which an active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action" is what "This term means.". The amount of a medicine that is available in the body is determined by three primary criteria. These many forms include, in particular:

- Rate and extent of release of the drug from the dosage form
- Subsequent absorption from the solution state
- Biotransformation during the process of absorption

Hence, two areas of pharmaceutical research focus on improving the oral bioavailability of an API.

These are:

Enhancing solubility and dissolution rate of poorly water-soluble drugs

Enhancing permeability of poorly permeable drugs

The several methods that may be used to increase the solubility of BCS Class II medications are covered in this article, with a focus on the solid dispersion method and its utilization. Over the last 40 years, a lot of study has been done on how to formulate solid dispersion in water-soluble carriers to increase solubility and associated bioavailability. Despite 40 years of ongoing study, there aren't many goods using this approach on the market. The primary cause of this, according to various writers, is the method's stability and scaling issues.

SOLUBILITY ENHANCEMENT OF BCS CLASS II DRUGS

The greatest amount of a solute that may dissolve in a given amount of solvent or solution at a given temperature is known as the solute's solubility. There are several methods for making poorly soluble medicines more soluble. These methods may be divided into three categories:

- Traditional Techniques
- Newer and Novel Techniques
- Solid Dispersion Technique

Use of co-solvents

Increasing the solubility of a non-polar medication by adding a water-miscible or partly miscible organic solvent is a popular and efficient method. The mixture of solvents used to make pharmaceuticals more soluble is referred to as cosolvency, and the solvents themselves are referred to as cosolvents. The cosolvent system operates by lowering the interfacial tension between the hydrophobic solute and the mostly aqueous solution. Blending solvent is another name for it that is often used. It is possible to utilize cosolvents such ethanol, propylene glycol, glycerin, sorbitol, and polyoxyethylene glycols. When more than one solvent is utilized, ternary diagrams are used to show where maximum solubility occurs.

Hydrotropy Method

By adding significant quantities of a second solute (hydrotropic agents), one solute may be made more soluble in water. This process is known as hydrotropy. Alkali metal salts of different organic acids make up the solute. Ionic organic salts are hydrotropic agents. The solute is said to be "salted in" by additives or salts that improve solubility in a particular solvent, and "salted out" by additives or salts that reduce solubility. The phenomenon known as "Hydrotropism" is caused by the "salting in" of non-electrolytes termed "hydrotropic salts," which are salts with big anions or cations that are also extremely soluble in water. The use of hydrotropes like urea and nicotinamide improved the solubility of rofecoxib.

Micronization

Due to the huge surface that is produced, the particle size reduction approach improves the solubility and rate of dissolution of medications that are weakly water soluble. By using air attrition techniques such fluid energy mills, jet mills, rotor stator colloid mills, etc., the process requires shrinking the size of the solid drug particle to 1 to 10 microns, which is often accomplished by spray drying or other means. It is also known as "Micro-milling" throughout the procedure. Because micronization does not alter the drug's saturation solubility, it is not appropriate for medications with large dosage numbers.

Drugs should not be micronized since they have a propensity to clump together, which reduces their effectiveness. Change in Solvent Dielectric Constant By lowering the solvent's dielectric constant, a cosolvent may improve the solubility of hydrophobic compounds. Water has a high dielectric constant and is an excellent solvent for polar compounds because of hydrogen bonding. The energy required to separate two charged objects that are at odds with one another is measured by a substance's dielectric constant. The dielectric constant of the medium has an inverse relationship with the energy needed to separate two charged substances that are at odds with one another.

Amorphous forms

Amorphous structures have greater thermodynamic energies than equivalent crystalline forms due to the random placement of atoms or molecules. In general, solubility and dissolution rates are higher.

CHEMICAL MODIFICATION OF DRUG

By boosting hydrogen bonding and the interaction with water, polar groups like carboxylic acids, ketones, and amines promote solubility.

Use of Surfactants

Surfactants are amphiphilic substances with a circular head that is polar and a tail that is non-polar in nature. Micelles will develop when a surfactant, such tween-80 sodium lauryl sulphate, is added to water. A non-polar medication will partition into the micelle's hydrophobic core, and the polar tail will cause the complex to dissolve. The solubilization and wetting effects of bile salts on the solubility of steroids have served as examples of this.

Inclusion complex/clathrates

The usage of cyclodextrins has significantly improved the drug's solubility and dissolution. ß-cyclodextrin (ß-CD) and HP-ß-CD may be used to make these complexes; the necessary amount of ß-CD is weighed, and water is then added to

create a tough consistency. A measured amount of the medicine is introduced to the bulk. The mixture is thoroughly dried in a hot air oven at 60 0C for two hours after being kneaded in a glass mortar for an hour.

Alteration of ph of solvents

When the pH of the solvent is lowered, solubility is improved. Additionally synergistic in nature is the combined impact of pH and complexation on solubilization. By changing the pH, it was hoped to improve gliclazide solubility.

Use of Hydrates or Solvates

A crystalline substance may include inclusions, which are solvent molecules trapped within the crystal lattice, or non-stoichiometric adducts. A stoichiometric adduct, also known as "Solvate," is a chemical complex that contains molecules of the solvent that is crystallizing at certain locations within the crystal lattice. The compound is referred to as "Hydrate" when water serves as the included solvent. "Anhydrous" refers to a substance whose crystal structure doesn't include any water. Anhydrous forms have greater aqueous solubilities than hydrate forms.

Use of Soluble Prodrugs

Bio-reversible chemical modification enhances the medications' physicochemical characteristics. Incorporating a polar or ionizable component into the parent chemical to increase water solubility is the most used prodrug approach. The pro-drug strategy has been utilized effectively to increase the water solubility of benzodiazepines, vitamins, and corticosteroids. By creating a prodrug, the rate of allopurinol dissolution was effectively increased.

FUNCTIONAL POLYMER TECHNOLOGY

By avoiding the lattice energy of the drug crystal, which is the principal obstacle to fast dissolution in aqueous environments, functional polymers increase the rate of dissolution of poorly soluble medicines. These polymers are ion exchange materials because they include basic or acidic groups that interact with the surrounding medium's ionizable molecules and exchange mobile ions of equal charge in a reversible, stoichiometric manner. The finished product, known as "Resinate," may be made as a tablet, dry powder, or solution. The medicine is released from the resinate when exposed to the bodily fluids since the resins are insoluble and cannot be absorbed by the body.

Controlled Precipitation Technology

This method involves dissolving the medicine in an organic water-miscible solvent before dissolving it in a water-based media that contains stabilizers. The medication crystallizes into microparticles as a result of the solvent dissolving in water. Due to the stabilizers' extensive hydrophilized surface area from adsorption, they regulate particle development and speed up the dissolving of drugs with low solubility. For instance, Soliqs' proprietary nanomorph technology for the controlled crystallization of pharmaceuticals.

Evaporative Precipitation in Aqueous Solution

Rapid phase separation is used in the EPAS method to nucleate and produce lipophilic drug nano- and microparticles. The medication is first dissolved in an organic solvent with a low boiling point. This solution is pumped through a tube, heated there under pressure to a temperature over the boiling point of the solvent, and then sprayed into a heated

aqueous solution via a fine atomizing nozzle. To enhance particle formation and solubilization, surfactants are added to the organic solution and aqueous solution. By using this method, the solubility of danazol was increased.

USE OF PRECIPITATION INHIBITORS

Super-saturation, which may result in drug precipitation or crystallization, is caused by a substantial rise in free drug concentration above equilibrium solubility. Utilizing inert polymers like HPMC, PVP, PVA, PEG, etc. that work via one or more of the following mechanisms will help avoid this.s

- Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs.
- Provide a stearic barrier to drug molecules and inhibit crystallization through specific intermolecular interaction on growing crystal surfaces.
- Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals

Solvent Deposition

This process involves dissolving the weakly water soluble medicines in an organic solvent like alcohol, depositing the solution over an inert, hydrophilic solid matrix like starch or microcrystalline cellulose, and then letting the solvent evaporate19. An example of this technique is the use of liquisolid compacts to speed up piroxicam's dissolving rate. Using liquisolid compact, the weakly soluble medication indomethacin's dissolving rate was accelerated.

PRECIPITATION

In this process, the medication that is not very soluble in water is first dissolved in an appropriate organic solvent, then it is quickly mixed with a non-solvent to precipitate the drug in nanosize particles. The finished product is also known as "Hydrosol". Hydrosols are colloidal aqueous solutions used for intravenous delivery that include drug nanoparticles of poorly water-soluble medicines. They are made by a precipitation method in which a significant amount of water is added to the drug solution along with "short term stabilizers" including poloxamer and modified gelatins.

Due to the stabilizers and high non-solvent content, the amorphous hydrosol remains stable after precipitation for around 60 minutes. The drug crystallizes after this point. A sharp rise in absorbance at a wavelength where the medicinal ingredient does not absorb may be used to detect crystallization and particle growth since clouding corresponds with particle size. Therefore, the hydrosol is promptly spray-dried with excipients like lactose or mannitol before crystallization takes place in order to effectively stabilize the amorphous nanosized medication. The preparations are reconstituted with water before use. Hydrosols are appropriate for parenteral administration since they contain the medication in particles that are around 200 nm in size. One such is the medicine cyclosporin, which may be made into a hydrosol.

Simple Eutectic Mixture

A and B crystallize out simultaneously when a combination of A and B with composition E is chilled, but when other compositions are cooled, one of the components begins to crystallize out before the other. In order to create a physical mixture of extremely tiny crystals of the two components, solid eutectic

mixes are often created by rapidly chilling a co-melt of the two compounds. When an aqueous medium is added to a combination of composition E, which contains a medication that is very minimally soluble in water and an inert, highly water soluble carrier, the carrier dissolves quickly, releasing extremely little crystals of the drug. The resultant suspension's huge surface area ought to increase the dissolution rate and, therefore, the bioavailability.

Solid Solution Continuous Solid Solution

The components are miscible in all ratios in a continuous solid solution. This implies, theoretically, that the molecules of the two components' individual molecules have stronger bonds than the molecules of the other two components together.

Discontinuous Solid Solution

The solubility of one component in the other component is limited in discontinuous solid solutions. The reciprocal solubilities of the two components begin to decline below a particular temperature. Goldberg has recommended that the phrase "solid solution" only be used when the mutual solubility of the two components is more than 5%. It will rely not only on the mutual solubilities of the two components but also on the dose of the medication component if a specific solid solution may be used as a dosage form approach. The maximum mass for a pill or capsule is about 1 g.

Crystalline Solid Solution in Substitution Traditional solid solutions have a crystalline structure, and the solute molecules may either fit into the spaces between the solvent molecules in the crystal lattice or replace them there. Only when the size of the solute molecules varies from the size of the solvent molecules by around 15% or less is substitution feasible.

Interstitial Crystalline Solid Solution

In interstitial solid solutions, the dissolved molecules fill the voids in the crystal lattice between the solvent molecules. The solute molecules must have a molecular diameter that is no larger than 0.59 of the solvent molecules' molecular diameter in order to occupy interstitial space. Additionally, less than 20% of the solvent's volume should be made up of molecules of the solute.

Amorphous Solid Solution

The solute molecules are irregularly but molecularly scattered inside the amorphous solvent in an amorphous solid solution. It was the first effort to document the development of an amorphous solid solution to enhance a drug's dissolving capabilities using griseofulvin in citric acid. Early experiments also employed urea and sugars like sucrose, dextrose, and galactose as carriers. In more recent times, this function has been served by organic polymers such polyvinylpyrrolidone, polyethylene glycol, and other cellulose derivatives.

Glass Solution and Glass Suspension

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature. On heating, it softens progressively and continuously without a sharp melting point.

CONCLUSION

BCS Class II medications are characterized by high permeability but low

solubility. This classification includes drugs that have good absorption in the gastrointestinal tract, but their dissolution and solubility can be limiting factors for effective absorption. As a result, these medications may exhibit variable and often low bioavailability. The low solubility of BCS Class II drugs can lead to incomplete dissolution in the gastrointestinal fluids, which hinders their absorption into the systemic circulation. Consequently, the drug's therapeutic efficacy may be compromised, and higher doses might be required to achieve the desired therapeutic effect. Various strategies have been employed to improve the bioavailability of BCS Class II medications, such as formulating them into more soluble salts, using lipid-based formulations, employing particle size reduction techniques, or incorporating them into self-emulsifying drug delivery systems or solid dispersions

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