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Review Article

Review On Methods Of Solubility Enhancement Of BCS Class II Drugs

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ABSTRACT

Due to low water-solubility, which makes their formulation challenging or even impossible, over 40% of the novel chemical entities (NCEs) identified by pharmaceutical industry screening programmes have historically failed to be commercialised. Several existing pharmaceuticals' distribution is hampered by the solubility problems that complicate the delivery of these new medications. In this article, numerous conventional and cutting-edge strategies for improving the solubility of BCS Class II medicines are briefly described. Co-solvents, Hydrotropy, Micronization, Alteration of Solvent's Dielectric Constant, Amorphous Forms, Chemical Modification of Drug, Surfactant Use, Inclusion Complex, Solvent's pH Alteration, Use of Hydrates or Solvates, Use of Soluble Prodrugs, Application of Ultrasonic Waves, Functional Polymer Technology, Controlled Precipitation Technology, Evaporative Precipitation in Aqueous Solute. Size reduction technologies, lipid-based delivery systems, micellar technologies, and porous microparticle technology are new drug delivery methods created in recent years to improve the solubility of insoluble pharmaceuticals. Also, a brief explanation of solid dispersion technique and several solid dispersion systems has been provided

INTRODUCTION

Due to simplicity and ease of consumption, the oral route of medication administration is the most popular and favoured way of delivery. Nevertheless, for many medicines, this strategy can be troublesome and ineffective for a variety of reasons. The main issue that could arise when administering an active medication orally is limited drug absorption caused by low drug solubility, which results in poor bioavailability. A drug's bioavailability and, eventually, its solubility are both necessary for therapeutic success. One crucial factor in achieving the optimum medication concentration in the bloodstream so that a pharmacological reaction may be seen is solubility. Just 8% of potential novel drugs have

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good solubility and permeability at the moment1.The greatest amount of a solute that may dissolve in a particular amount of solvent or solution at a specific temperature is known as the solute's solubility [2]. In other terms, solubility may also be defined as a material's capacity to combine with another substance to produce a solution [3]. Several medications already on the market are affected by the solubility problems that complicate the delivery of these new drugs [1,2,3]. Table 1 provides definitions for several terminology related to solubility.

Table 1: Definition of Solubility (I.P.1996)

Definition	Parts of solvents required for one part of solute (in ml)
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

Due to simplicity and ease of consumption, the oral route of medication administration is the most popular and favoured way of delivery. Nevertheless, for many medicines, this strategy can be troublesome and ineffective for a variety of reasons. The main issue that could arise when administering an active medication orally is limited drug absorption because of low drug solubility, which causes poor bioavailability [4].

FACTORS AFFECTING SOLUBILITY

The solubility is influenced by the solid's physical structure, the kind and make-up of the solvent medium, and the system's temperature and pressure [5].

- **Particle size:**

Because the surface area to volume ratio rises as a particle becomes smaller, the size of the solid particle affects how soluble it is. The higher contact with the solvent is made possible by the bigger surface area. Where V is the molar volume, G is the surface tension of the solid, R is the radius of the fine particle, and S is the solubility of infinitely big particles and fine particles, respectively.

- **Temperature:**

Solubility will be affected by temperature. If the energy is absorbed during the solution process, the solubility will rise as the temperature rises. The solubility will decrease with rising temperature if the solution process releases energy [7]. In general, a solid solute becomes more soluble as the solution's temperature rises. In heated solutions, some solid solutes become less soluble. All gases become less soluble as the solution's temperature rises8.

- **Pressure:**

A drop in pressure causes a decrease in the solubility of gaseous solutes, whereas a rise in pressure causes an increase. The solubility of solid and liquid solutes is mostly unaffected by pressure changes [8].

- **Nature of the solute and solvent:**

At room temperature, 200 grammes of zinc chloride may dissolve but only 1 gramme of lead (II) chloride can in 100 grammes of water. These two compounds' very different solubilities are a result of the natures of these two substances being quite different [8].

- **Molecular size:**

The less soluble the chemical, the bigger the molecule or the greater its molecular weight. To solvate a material, it is harder to surround larger molecules with solvent molecules. The quantity 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 [9].

- **Polarity:**

Polar solute molecules will typically dissolve in polar solvents, while non-polar solute molecules will often dissolve in non-polar solvents. The polar solute molecules have a positive and a negative end to the molecule. Positive ends of solvent

molecules will attract negative ends of solute molecules if the solvent molecule is similarly polar. Dipole-dipole interaction is a sort of intermolecular force that causes this.

- **Polymorphs**:

A solid has a distinct shape and a firm form. The angles between the faces of a crystal of a certain substance might have a variety of shapes or habits, but they are always the same. A crystal is composed of atoms, ions, or molecules that are arranged in a repeating, regular geometric pattern called a lattice in three dimensions. The unit cell is the name given to this pattern that repeats. Polymorphism [10] is the ability of a material to crystallise in more than one crystalline form.

- **Bioavailability: [FDA CDER 2004]**

The pace and extent to which the active ingredient or active moiety is absorbed from a drug product and made available at the site of action is referred to as "bioavailability" [5]. There are three main elements that limit a drug's bioavailability. [6]. Some variations include,

- Rate and extent of release of the drug from the dosage form
- Absorption from the solution state thereafter
- Biotransformation occurring during the absorption process.

BCS states that a medicine can be categorised into one of the four groups shown in Table 2 based on these solubility and permeability properties.

Table 2: Classification of drugs using Biopharmaceutical.

BCS Class	Solubility/ permeability	Problems
Class I	High solubility High permeability	Enzymatic degradation, gut wall efflux
Class II	Low solubility High permeability	Solubilization and bioavailability
Class III	High solubility Low permeability	Enzymatic degradation, gut wall efflux, Bioavailability
Class IV	Low solubility Low permeability	Solubilization, enzymatic degradation, gut wall efflux and bioavailability

A Class II medicine will often have restricted absorption due to dissolving rate, whereas a Class IV drug will usually have limited absorption due to permeation rate. As a result, two fields of pharmaceutical research concentrate on increasing an API's oral bioavailability (4). Which are:

- Improving the solubility and pace of medication dissolution for weakly water-soluble substances
- Increasing the permeability of medicines with low permeability

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 utilisation. During the past 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:

a Conventional Methods
b Newer and innovative methods
c The Solid Dispersion Method

TRADITIONAL TECHNIQUES:

Conventional methods consist of

- Co-solvent use
- Hydrotropy

- Micronization
- Variation of the solvent's dielectric constant
- Undefined forms
- drug chemical modification
- Surfactant use
- Complex inclusions or clathrates
- pH changes in the solvent
- usage of soluble prodrugs, hydrates, or solvates
- the use of ultrasonic wave
- Technology utilising useful polymers
- technique for regulating precipitation
- Precipitation caused by evaporation in aqueous solutions
- use of preventatives for precipitation
- Deposition of solvents and precipitation
- adsorption with preference on insoluble carriers.

- **Use of Co-Solvents**

It's common and efficient to make a nonpolar medication more soluble by adding a water-miscible or partly miscible organic solvent. 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 frequently used. It is possible to utilise cosolvents such ethanol, propylene glycol, glycerin, sorbitol, and polyoxyethylene glycols. When more than one solvent is utilised, ternary diagrams are used to show where maximal solubility occurs [8],[9].

- **Hydrotropy Method**

By adding significant amounts of a second solute (hydrotropic agents), one solute can 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 called "hydrotropic salts," which are salts with big anions or cations that are also extremely soluble in water. Using hydrotropes like urea and nicotinamide helped make rofecoxib more soluble [10].

- **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. Also known as "Micromilling," the procedure. Since micronization does not alter the drug's saturation solubility, it is not appropriate for medications with large dosage numbers. Because of the tendency of micronized products to agglomerate and reduce the effective surface area for dissolving, micronization of drugs is not recommended. By lowering the solvent's dielectric constant, the addition of a cosolvent can make hydrophobic molecules more soluble. 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 oppositely charged bodies [12].

- **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**

Through boosting hydrogen bonding and the contact with water, polar groups like carboxylic acids, ketones, and amines promote solubility [12].

- **Use of Surfactants**

Amphiphilic in nature, surfactants have a polar end (the round head) and a non-polar end (the tail). Micelles will develop when a surfactant, like 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 [13] have been used to show 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 can 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. The dry substance is passed through mesh number 12014 for sieving.

- **Alteration of ph of solvents**

When the pH of the solvent is lowered, solubility is improved. Also synergistic in nature is the combined impact of pH and complexation on solubilization. With the aid of a pH modification technique, gliclazide solubility was hoped to be improved [15].

- **Use of Hydrates or Solvates**

Non-stoichiometric adducts or inclusions, which are solvent molecules trapped inside the crystal lattice, may be present in crystalline materials. The term "Solvate" refers to a chemical compound called a stoichiometric adduct, which also comprises molecules of the solvent that are crystallising at certain points in the crystal lattice. When water is used as the solvent, the chemical is known as "Hydrate". A material is described as being anhydrous if it has no water atoms in its crystal structure. In comparison to hydrate forms, anhydrous forms are more soluble in water [16].

- **Use of Soluble Prodrugs**

The physicochemical properties of the drugs are improved through bio-reversible chemical modification. The most common prodrug strategy involves adding a polar or ionizable component to the parent molecule to boost water solubility. The pro-drug approach has been successfully used to improve the water solubility of corticosteroids, vitamins, and benzodiazepines. The rate of allopurinol's disintegration was accelerated by prodrug generation [17].

- **Application of Ultrasonic Waves**

Ultrasonic vibrators can be used to increase solubility. A device called the "Pohlman whistle" makes use of a high-frequency oscillator (100–500 KHz) [12].

- **Functional Polymer Technology**

Functional polymers accelerate the dissolution of medications that are poorly soluble by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid disintegration in aqueous conditions. The basic or acidic groups in these polymers interact with the ionizable molecules in the surrounding media to exchange mobile ions of equal charge in a reversible, stoichiometric way, making them ion exchange materials. Resinate, the end product, can be produced as a tablet, dry powder, or solution. As the resins are insoluble and cannot be absorbed by the body, the medication is released from the resinate when contacted to physiological fluids [12].

- **Controlled Precipitation Technology**

In this method, the drug is dissolved in a water-miscible organic solvent before being dissolved into an aqueous medium that contains stabilisers

(HPMC, cellulose ethers, gelatin). Drugs with limited solubility dissolve more quickly thanks to the stabilisers' significant hydrophilized surface area from adsorption, which also controls particle formation. Consider Solids' patented nanomorph technology for the carefully regulated crystallisation of medications.

- **Evaporative Precipitation in Aqueous Solution (EPAS)**

The EPAS approach uses rapid phase separation to assemble and create lipophilic drug nano- and microparticles. First, a low boiling point organic solvent is used to dissolve the medicine. Via the use of a thin atomizing nozzle, this solution is pushed through a tube, heated there under pressure to a temperature over the solvent's boiling point, and then sprayed into a heated aqueous solution. Surfactants are added to the organic solution and aqueous solution to improve particle formation and solubilization. The danazol18 was more soluble thanks to this technique.

- **Use of Precipitation Inhibitors**

Super saturation is caused by a rapid rise in the free drug concentration above the equilibrium solubility; this might result in drug precipitation or crystallisation. Using inert polymers that work in one or more of the methods indicated below, such as HPMC, PVP, PVA, PEG, etc., can stop this from happening.

- Reduce the pace at which pharmaceuticals crystallise by increasing the viscosity of the crystallisation media.
- For further information, see the website.
- Adsorb onto host crystal surfaces, slowing host crystal development and resulting in 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 evaporate [19]. An illustration of this technique is the use of liquisolid compacts to speed up piroxicam's dissolving rate [20]. Using liquisolid compacts, the weakly soluble medication indomethacin's solubility rate was increased [21].

- **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" [22]. Hydrosols are colloidal aqueous solutions used for intravenous delivery that include drug nanoparticles of poorly water-soluble medicines. They are made using a precipitation procedure in which a sizable amount of water (96–98% after mixing) and stabilising chemicals such poloxamer and modified gelatins, which serve as "short term stabilizers"[23], are added to the drug solution. Due to the stabilisers and high non-solvent content, the amorphous hydrosol remains stable after precipitation for around 60 minutes. The drug crystallises after this point. The correlation between clouding and particle size allows for the observation of crystallisation and particle growth by a sharp rise in absorbance at a wavelength where the medicinal component does not absorb. As a result, the hydrosol is promptly spray-dried with excipients like lactose or mannitol before crystallisation takes place in order to effectively stabilise 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 (1:20 drug to gelatin ratio).

1. NEWER AND NOVEL TECHNIQUES:

Other modern and innovative drug delivery strategies created to increase the solubility of insoluble medicines include

- Methods for size reduction
- Using Nanoparticles
- Crystalline Engineering
- Nanosuspension
- Technology Cryogenic
- High-Risk Technology
- System for delivering lipids.
- The Microemulsion Method
- Formulation of Self Dispersing Lipids (SDLF)
- Micelle mixture
- Micelle made of polymers.
- Technology Using Porous Microparticles

- **Size Reduction Technologies**

The drug particles must be thoroughly stabilised and formed in order to keep the nature and characteristics of the nanoparticles, in addition to being reduced to nanoscale [24],[25].

- **Lipid based delivery system**

It has been demonstrated that lipophilic medication oral absorption is improved by lipid-based formulations [26].

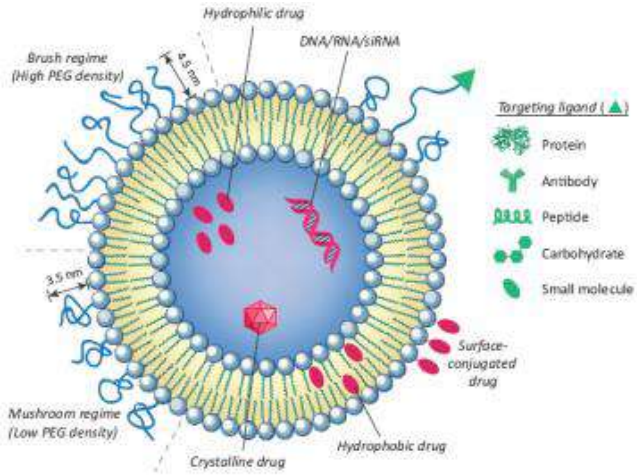

Figure 1: Lipid-based delivery system

- **Micro-emulsion Technology**

Microemulsions are dispersions of two immiscible liquids that are thermodynamically stable, isotropically transparent, and stabilised by interfacial coatings of surface-active molecules. Simple agitation of oil, water, surfactant, and co-surfactant produces the microemulsions. In conjunction with the surfactant, the co-surfactant brings the interfacial tension to extremely low and even momentary negative values [27],[28].

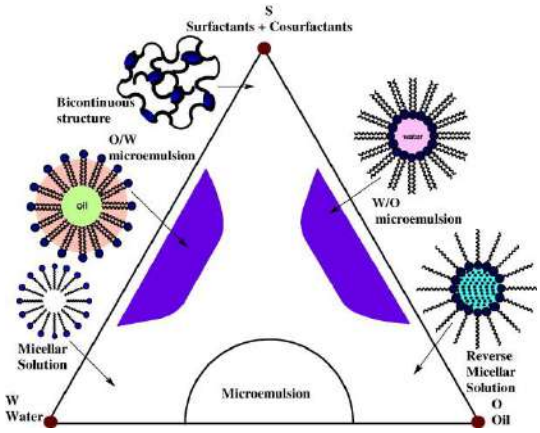

Figure 2: Microemulsion methods

- **Self-Dispersing Lipid Formulation (SDLF)**

The medication is integrated into the oil and surfactant combination found in the SDLFs. When combined with an aqueous environment, they emulsify [29].

- **Micellar Technologies**

a. Mixed Micelles –

Above a certain critical concentration, amphiphilic, ionic, anionic, or ampholytic molecules that may reduce a solvent's surface tension tend to group together to form micelles. Only at solution temperatures over the critical micellar temperature (CMT) and above a certain solute concentration, the critical micellar concentration (CMC), can micelle production take place [30]. Figure 3 depicts the process of mixed micelle production.

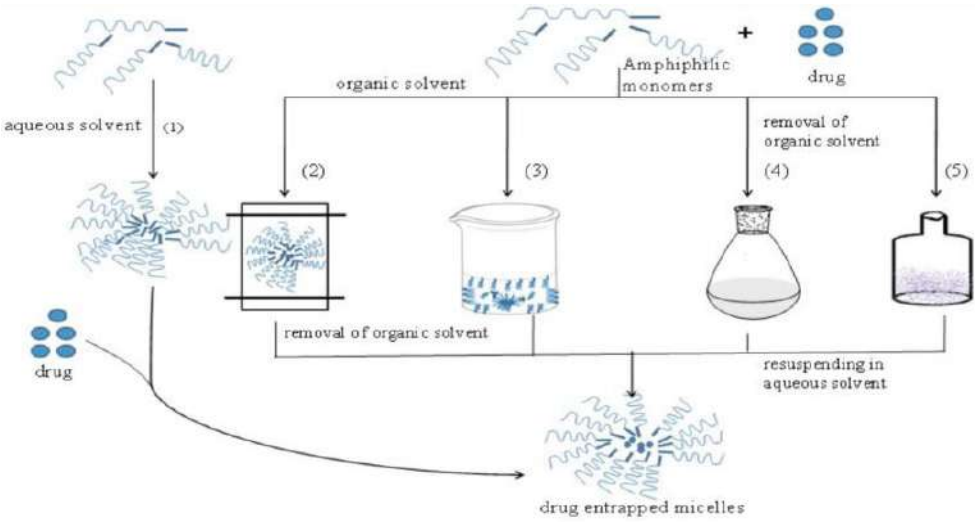

Figure 3: Process of mixed micellar production

b. Polymeric Micelles –

Polymeric micelles are nanoscopic supramolecular core-shell structures made of amphiphilic polymers. The block copolymers utilised for creation of polymeric micelles include Pluronics®, poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly (ester), and PEG-b -poly (Lamino acids) (Lamino acids) Figure 4 depicts the polymeric micelles.

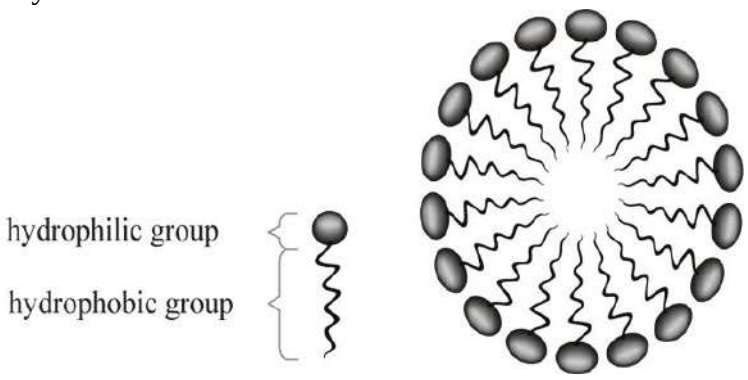

Figure 4: Schematic representation of Polymeric micelle

c. Porous Microparticle Technology –

The weakly water-soluble medication is embedded in microparticles with a porous, sponge-like matrix that is water soluble. When combined with water, the matrix dissolves, soaking the drug and leaving a suspension of fast dissolving drug particles. This is the fundamental technology used in HDDSTM (Hydrophobic Drug Delivery System).

A. SOLID DISPERSION SYSTEM

Solid dispersion is "a dispersion involving the production of eutectic mixes of pharmaceuticals with water soluble carriers by melting of their physical mixtures," according to Chiou and Riegelman [31]. A collection of solid goods with at least two separate components, often a hydrophilic matrix and a hydrophobic medication, are referred to as solid dispersion. Either the matrix is crystalline or amorphous. The medication can be spread molecularly, in crystalline or amorphous particles (clusters).

Types of Solid Dispersion System

There are six main forms of solid dispersions that may be identified based on their molecular configuration [6, 31, 32]. Table 3 provides a description of them.

Table 3: Types of Solid Dispersion4

Sr No.	Types of Solid dispersion	Matrix*	Drug**	No. of phases	Remarks	References
I	Eutectics	C	C	2	First type of solid dispersion prepared	31
II	Amorphous precipitations in crystalline carrier	C	A	2	Rarely encountered	33,34
III (a)	Solid solution Continuous solid solutions	C	M	1	Miscible at all compositions, never prepared	35
(b)	Discontinuous solid solutions	C	M	2	Partially miscible, two phases even though drug is molecularly dispersed	32
(c)	Substitutional solid solutions	C	M	1 or 2	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter	36
(d)	Interstitial solid solutions	C	M	2	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Example: Drug in helical interstitial spaces of PEG.	31
IV	Glass suspension	A	C	2	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	31
V	Glass suspension	A	A	2	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	31
VI	Glass solution	A	M	1	Require miscibility, complex formation or upon fast cooling OR evaporation during preparation e.g. PVP	37

*A: drug scattered as amorphous clusters in the matrix, **C: drug disseminated as crystalline particle in the matrix, and M: drug molecularly diffused throughout the matrix. *A: matrix in the amorphous state, C: matrix in the crystalline state.

Simple Eutectic Mixture

A and B crystallise out simultaneously when a mixture of A and B with composition E is chilled, but when other compositions are cooled, one of the components begins to crystallise 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 [32,38]. The resultant suspension's huge surface area ought to increase the dissolution rate and, consequently, the bioavailability. The phase diagram for a eutectic solution is shown in Figure 5

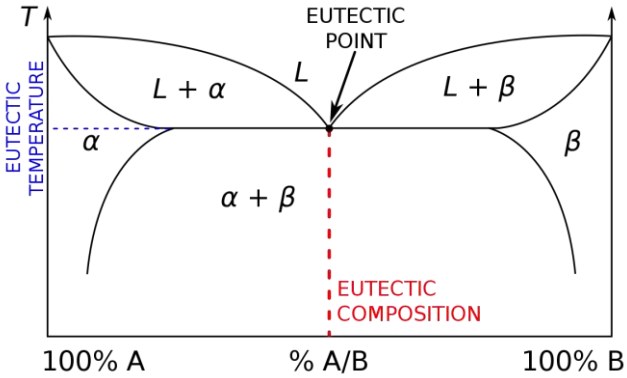

Figure 5: Phase diagram of Eutectic mixtures

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%. (35). 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.

Substitutional Crystalline Solid Solution

Traditional solid solutions have a crystalline structure, and the solute molecules can 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 differs 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 spaces 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. Moreover, the volume of the molecules making up the solute must be less than 20% that of the solvent [39].

Amorphous Solid Solution

The solute molecules are irregularly but molecularly scattered inside the amorphous solvent in an amorphous solid solution. It was the first attempt to document the development of an amorphous solid solution to enhance a drug's dissolving capabilities using griseofulvin in citric acid. Other carriers that were utilised in early investigations included urea and sugars such as

sucrose, dextrose and galactose. Organic polymers have lately been used for this purpose, including polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and different cellulose derivatives [39].

Glass Solution and Glass Suspension

When a solute dissolves in a glassy solvent, the result is a homogeneous, glassy system known as a glass solution. Typically, the melt is abruptly quenched to produce the glassy or vitreous state. Below the glass transition temperature, it is transparent and brittle in nature (Tg). On heating, it softens steadily and constantly without a definite melting point [31].

CONCLUSION:

Based on the available literature, it can be concluded that there are several methods available for enhancing the solubility of BCS class II drugs. These methods include physical methods such as micronization, amorphous solid dispersion, and inclusion complexation, as well as chemical methods such as salt formation, prodrug formation, and co-crystallization.

Each of these methods has its advantages and limitations, and the choice of method will depend on the specific drug and its physicochemical properties. Micronization is a simple and cost-effective method but may not be suitable for all drugs due to issues such as stability and agglomeration. Amorphous solid dispersion has shown promising results in enhancing solubility, but its long-term stability and scale-up feasibility need to be further investigated. Inclusion complexation can improve the solubility and stability of the drug, but it may require additional excipients and can be limited by the solubility of the complexing agent.

Salt formation is a common method used in the pharmaceutical industry, but it may not be suitable for all drugs due to issues such as taste and stability. Prodrug formation is an effective method to improve solubility and bioavailability, but it requires additional synthesis steps and can lead to toxicity issues. Co-crystallization has shown promising results in enhancing solubility, but its scale-up feasibility and long-term stability need to be further investigated.

In conclusion, the selection of an appropriate solubility enhancement method for BCS class II drugs should be based on a thorough understanding of the drug's physicochemical properties and the advantages and limitations of each method. Further research is needed to investigate the long-term stability, scale-up feasibility, and toxicity issues associated with these methods.

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