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Review Article

An Overview On Various Techniques To Enhance Solubility Of Poorly Soluble Drugs

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ABSTRACT

Solubility is the process of dissolution of a solute in solvent, which is essential to formulate number of dosage forms. Bioavailability of drugs can be improved by increasing the solubility of drugs. To design oral formulations using drug candidates with poor solubility is a big challenge in pharmaceuticals. Solubility of drugs can be enhanced by different techniques by modifying their chemical properties, physical characteristics and by converting the drugs into their salt forms. Few methods to increase solubility of poorly soluble drugs is reviewed in this study.

INTRODUCTION

One of the most common, straightforward, and easiest ways to administer medications is through oral delivery. For a medication taken orally to penetrate through the GI tract membranes and enter the systemic circulation, it must dissolve in the stomach and intestinal fluids.[1]Therefore, a medicine with low membrane permeability will usually show permeation rate limited absorption, and a drug with poor aqueous solubility would usually show dissolution rate limited absorption. Most medications have low solubility.[2]Thus, studies in pharmaceuticals that aim to increase the solubility and rate of dissolution of medications with low water solubility, in order to increase the oral bioavailability of active ingredients.[3] A collection of solid substance made up of a hydrophilic matrix and a hydrophobic substance are referred to as solid dispersions. There are two types of matrixes, amorphous and crystalline. It is not necessary for solid dispersion to be in the micronized form. It is possible for a portion of the medication to molecularly disperse in the matrix and create a solid dispersion.[4]The carrier dissolves and the medicine releases as a fine colloidal particle when the solid dispersion comes into contact with watery fluids, increasing the surface area. Consequently, medications that are poorly soluble in water dissolve more quickly and have a higher bioavailability.[5]Furthermore, in a

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solid dispersion, some of the drug dissolves right away to saturate the fluid in the gastrointestinal tract, while the remaining drug either precipitates as fine colloidal particles or just as submicron-sized globules. For enhancing BCS Class II medication bioavailability and oral absorption, solid dispersion methods have great promise.[6]Three primary factors are considered by BCS: dissolving rate, intestinal permeability, and solubility. These factors determine the rate and amount of oral drug absorption from solid oral-dosage forms.[7]

Solubility:

The greatest quantity of solute that dissolves in a given amount of solvent or the concentration of solute in a saturated solution at a specific temperature, pressure, or chemical presence is known as solubility. Numerous approaches, such as chemical modification, changing the solvent's composition, using a carrier system, and physical modification using the solid dispersion method, have been explored to address the problem of poor aqueous solubility. But among the rest, solid dispersion technology is the most promising method for making poorly soluble medications more soluble. When creating oral drug delivery systems, the ability to formulate poorly soluble medicines into solid dispersions increases operational flexibility by providing a range of processing and excipient alternatives. Developing extended-release dosage forms has been the focus of recent research on solid dispersion systems, in addition to improving solubility and bioavailability. The usage of medications that are highly permeable through biological membranes but poorly soluble in water has been the subject of extensive research on solid dispersion strategies since the rate-limiting step in absorption for these medications is dissolution. Thus, it has been projected that a rise in the rate of dissolution will coincide with an increase in the rate of absorption. Sub-class II medications are often defined as those with strong membrane permeability and low aqueous solubility according to the Biopharmaceutical Classification System (BCS). As a result, the solid dispersion approach is especially employed to increase Class II medicines oral absorption and consequently bioavailability. [9,10,11].

Factors Affecting the Solubility of drugs:

A. Temperature:

Temperature has an impact on solubility, as the temperature rises, solubility increases correspondingly, and as the temperature falls, solubility decreases.

B. Crystal characteristics:

Many medications are polymorphic, meaning they have various crystalline forms of the same chemical. These polymorphic forms have variable lattice energies, which are reflected in changes to their solubility and melting points. The medication is present in both amorphous and crystal forms, with the amorphous form being more soluble than the crystal form.

C. Molecular structure of solute:

The nature of the solute molecule determines its solubility, even little structural changes in the solute can alter its solubility.

D. Polarity and Nature of solvent:

The solubility of the chemical is influenced by the polarity of the solvent and solute molecules, polar solvents dissolve in polar solvents, while non-polar solutes dissolve in non-polar solvents.

E. Particle size:

The solubility of a substance is influenced by its particle size, smaller particles have a larger surface area and are therefore more soluble than larger particles, which have a lower surface area and are therefore less soluble.

F. pH:

The solubility of the chemical is affected by pH, unionized species are less soluble than ionized solutes.

G. Dielectric constants:

Dielectric constants of polar and non-polar molecules have an impact on solubility, which is a function of dielectric constant.[12]

Solubility enhancement techniques:

Few techniques to enhance solubility of drugs is listed below:

- Surfactants
- PH adjustment
- Co-solvency
- Co-crystallization
- Solubilizing agents
- Salt Formation
- Micro emulsion
- Solid Dispersion [13,14]

Surfactants:

The technique known as surfactant is used to lower the vacancy fraction in liquid-solid, liquid-liquid, or liquid-gas mixtures. Surfactants are frequently utilized to increase a drug's solubility. The best agents for increasing solubility and aiding in dissolving are surfactants. It encourages improved wetting and penetration when dissolving solid medications in fluid. Examples include sodium lauryl sulfate (SLS), propylene glycol, and soap (fatty acid). The benefit is increased medication stability. [15]

pH- Adjustment:

A higher pH is needed for a medicine to be soluble, ionic drugs dissolve more readily. The primary pharmacological response and solubility maintenance parameter for a medication is its pH. The pH is necessary in order to provide medication. Because blood has an acidic composition, a medicine with low solubility may precipitate in the blood rather than being soluble in it. The right pH level is necessary for the medicine to be absorbed. Stomach pH is 1-2 and duodenum pH is 5-6, the solubility level determines how well the substance enters the body. This technique is frequently applied for pH correction in pre-clinical settings. This is a novel approach to gauging low-soluble medication effectiveness. [16]

Co-solvency:

Co-solvency is the concoction of one or more miscible liquids, which is necessary to increase the solubility of the medication. The solubility and miscibility of the solution can be improved and better dissolution can be demonstrated by adding a co-solvent solution. This is a straightforward procedure that may be carried out by mixing a solvent or having a solvent mixture that increases solubility of a medication with low solubility. Co-solvents include things like PEG 300, ethanol, and propylene glycol. When the simple medicines were compared, the co-solvent boosted the low solubility medication by more than a thousand times. This has been shown to be heavily utilized in the scheme of many formulation types. Its primary objective when administered parenterally is to treat any annoying or unique adverse effects of [17, 18].

Co-crystallization:

Increasing the solubility is most commonly achieved by co-crystallization. As a result, co-crystals usually increase the drug's solubility, which isn't achievable when using a different molecule. The effectiveness of medication therapy is directly influenced by the drug's solubility, which is strongly dependent on the drug's concentration in blood. The most crucial elements in a drug's pharmacological impact that demonstrate the pharmacological response are its solubility and dissolution. [19]. A medication with improved solubility characteristics will also have better absorption, which will increase its bioavailability. Nevertheless, the drug's water solubility is poor in about 40% of cases. Due to its limited solubility, the medication is absorbed slowly by the body and has lower blood levels than necessary. Within the pharmaceutical industry, one percent of the most prominent instances on the market are related to the lack of certain biologic therapeutic qualities, such as ineffective medicine. These problems stem from the drug's solubility

characteristic. Developing drug processes and dosages is a huge risk in the pharmaceutical industry because about 70% of drug candidates have solubility issues. [20, 21].

Solubilizing agent:

In order to improve the drug solubility, and improve its therapeutic effects, solvents are utilized in this procedure. Super-disintegrates, such as sodium starch glycolate and cross-carmellose sodium, are solubilizing agents that are employed in various preparations to enhance the solubility and dissolution of pharmaceuticals. Improved gum Arabic, also known as gum karaya, is a well-known substance that was thought to be a better dissolving carrier for low-soluble drugs like nimtop. The addition of caffeine and nicotinamide increases the solubility of an antimalarial agent halofantrine hydrochloride's solubility in water. [22, 23]

Salt Formation:

Drug solubility and dissolution can be improved by using salt formation procedures. This approach is intended to observe any medication or chemical response reaction. When the medication is ionized, salt is produced. It works in a variety of ways, including as physiochemical properties, and influences the drug's stability, bioavailability, purification, and manufacturability. For many years, improving solubility has been achieved by salt production of therapeutic candidates that are poorly soluble. For example, barbiturates, theophylline, and aspirin [24, 25].

Micro-emulsion:

One method that can dissolve low-soluble drugs is micro-emulsion. It can help increase the solubility of a variety of medications that are nearly insoluble in water. Micro-emulsion is a pure pre-concentrate method that dissolves easily in soluble drug and contains a hydrophilic surfactant and a mixture of oil and hydrophilic solvent. [26]. The preparations readily dissolve when they come in contact with water, producing a transparent emulsion of tiny, homogeneous oil droplets that contain the medicine that has been solubilized. This technique produces isotropic, thermodynamically stable pure systems of water, oil, and surfactant, it is frequently used in conjunction with a co-surfactant whose droplet size falls between 20 and 200 nm. The uniform systems, which may be made with a wide variety of surfactant concentrations, can be used with water, oil, and other low viscosity fluids. The disadvantage with the micro-emulsion technique is that their higher co-surfactant/surfactant concentration renders them inappropriate for intravenous administration. The medication precipitates when its concentration falls below the critical micelle concentration [27, 28].

Solid Dispersion:

Numerous techniques were employed to increase the drug's solubility, which in turn improved the drug's bioavailability and rate of dissolution. Among these, solid dispersion is a frequently employed method for improving medication solubility.[31]Solid dispersion can be achieved by different methods as mentioned below,

1. **Eutectic mixtures:**

Two compounds that are totally miscible in the liquid state but only very slightly so in the solid state make up a eutectic combination. Melt fusion is typically used to prepare these systems. The medication is in a microcrystalline form quickly becomes soluble when the eutectic combination is exposed to water, causing the soluble carrier to dissolve. The primary cause of the higher rate of dissolution is the greater surface area[32]. Phenacetin-phenobarbital, griseofulvin-succinic acid, chloramphenicol-urea, and paracetamol-urea are a few examples.

2. **Solid solution:**

These are made up of a solid solvent dissolving a solid solute. The drug’s particle size in the solid solution is lowered to that of its molecule. Similar to liquid solutions, solid solutions only have one

phase, regardless of the quantity of constituents. Solvent evaporation or co-precipitation methods, which involve dissolving the solute and carrier in a shared volatile solvent like alcohol, are typically used to create these systems.[33]

3. Glass solution:

It is a homogenous system in which a glassy or a vitreous carrier solubilized drug molecules in its matrix. By an abrupt quenching of the melt, the glassy or vitreous state is usually obtained. It is characterized by transparency and brittleness below the glass transition temperature. On heating, it softens progressively without a sharp melting point[34].

4. Compound or complex formation:

The complexation of two components in a binary system during the formation of solid dispersion is what distinguishes this system. The development of a soluble complex with a low association constant can accelerate the rate of dissolution and gastrointestinal absorption.[35] Solid dispersions are carried by a variety of water-soluble excipientsand they are Sugars like Dextrose, Sorbitol, Sucrose, Maltose, Galactose, and Xylitol; • Acids: Citric, Tartaric, and Succinic Acid; • Polymeric materials: PEG 4000, PEG 6000, HPMC, CMC, PVP, Guar gum, Xanthum Gum, MC, Cyclodextrins, Galactomannon, Sodium Alginate etc, Surfactants like Poloxamer, Tweens, Spans, Gelucire 44/14, Deoxycholic Acid, Polyoxyethylene Stearate etc,Miscellaneous agents like Urethane, Pentaerythritol, Urea 36 etc

CONCLUSION:

Rate determining step in the absorption of drugs is dissolution. Bioavailability of drugs is based on their solubility in gastric and intestinal fluids. Hence it is important to enhance the solubility of poorly soluble drugs. In this study we tried to explain few methods which are used to improve the solubility of drug candidates.

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