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Original Research Article

A Review on Solubility Enhancement Technique

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Abstract

The systemic effects of medicinal medicines are best achieved by the oral mode of administration, yet low drug solubility presents a significant issue for formulation scientists. The solubility and solubilization procedure have been explored in this research. Drugs are divided into four groups according to their solubility in water using the BCS classification system. The BCS system's Class II and Class IV compounds have poor solubility. Several categories of variables are discussed, each of which affects the drug's soluble nature. We employ a number of different approaches or procedures to enhance the solubility as well as bioavailability of drugs that are poorly soluble. Co-solvency, nanonization, Particle size reduction, hydrotrophy, pH adjustment, sonocrystallization, the supercritical fluid (SCF) process, solid dispersion, inclusion complexation, self-emulsifying or microemulsifying systems, and liquisolid techniques are all covered here. In this review, we have looked at how several techniques may be utilized to increase the drug's solubility in water.

Keywords: Solubilization, BCS Classification, Bioavailability.

Introduction

The ability of a chemical to dissolve in a given solvent is called solubility. What this number represents, quantitatively speaking, is the amount of solute dissolved in a saturated solution at a certain temperature. What this implies qualitatively is that two even more compounds are constantly interacting with one another to generate a single phase, a distinct homogenous dispersion of molecules. The maximum amount of solute that may be dissolved in a solvent at equilibrium is the unit of measurement. A saturated solution is the end outcome. You can see which ions form precipitates and which ones stay watery by consulting a solubility chart. [1]

Maximum drug solute concentration in a given solvent at a given temperature, pressure as well as pH is defined as drug solubility. In contrast to the static property of drug solubility in a saturated solution, the dynamic property of drug dissolution rate is more closely related to the bioavailability rate. [2]

Solubilization Process: In order to dissolve a solute, its intermolecular or interionic bonds must be dissolved. The

interaction of the solute's molecules and ions with the solvent, and the separation of the solvent's molecules to make room for the solute.

Biopharmaceutics classification system (BCS) drugs are categaries into four categories based on their permeability and solubility, a system devised by the US Food and Drug Administration (FDA). Low solubility is a problem for drugs in Classes II and IV, because dissolution is the rate-limiting stage in drug absorption.[3]

Table 1: Biopharmaceutics classification system

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Factors Affecting Solubility [4,5,6,7]

1. **Drug particle size:**

   Solubility is affected by particle size. The ratio of surface area to volume grows when the size of an object decreases. The interaction between particle and solvent grows as its surface area grows.

2. **Nature of solvent as well as solute:**

   The characteristics of both the solute and the solvent are temperature and concentration dependent. One gram of lead (II) chloride cannot be dissolved in one hundred grams of water at normal temperature, but two hundred grams of zinc chloride can.

3. **The size of molecules:**

   Particles' solubilities change as their molecular sizes change. When the molecular weight and size of a substance's molecules increase, it becomes less soluble because the solvent molecules have a harder time completely encasing the bigger molecules.

4. **Temperature:**

   Temperature impacts solubility. If energy is being absorbed during the process of solution, then solubility should increase as temperature rises. Solubility would be expected to decrease with rising temperature if energy were released during the solution process.

5. **Pressure:**

   The solubility of a solid or liquid solute does not vary with a change in pressure, whereas the solubility of a gaseous solute does rise with increasing pressure and decrease with decreasing pressure.

6. **Polarity:**

   Solubility is also affected by the polarity of the molecules, both of the solute and the solvent. In general, solute molecules of polarity will dissolve in solvents of the same polarity, while solute molecules of non-polarity will dissolve in solvents of the opposite polarity.

7. **Polymorphs:**

   Polymorphism describes a substance's potential to crystallize in different shapes. A polymorph can take on several crystal structures depending on the conditions. The solid may crystallize into several distinct "polymorphs," or shapes. Melting

points of polymorphs are known to differ. Different polymorphs will have distinct solubilities due to the correlation between melting point and solubility.

Techniques to Overcome Poor Solubility [8,9,10,11,12]

a) Co-solvency
b) Particle Size Reduction
c) Hydrotrophy
d) Nanonization
e) pH Adjustment
f) Inclusion Complexation
g) Sonocrystallization
h) Supercritical Fluid (SCF) Process
i) Solid Dispersion
j) Liquisolid Methods
k) Self-Emulsifying or Self-Micro Emulsifying Systems

a) Particle Size Reduction: The medicine's bioavailability is directly proportional to the particle size of the drug. Dissolution capabilities can be enhanced by decreasing particle size and increasing the surface area. Milling processes, such as those employed by jet mills, rotor-stator colloid mills, etc., are used to reduce particle size. Because it does not alter the drug's saturation solubility, it is not appropriate for high-dose medicines.

These days, particle size reduction is frequently accomplished using micronization or nanosuspension. The particle size reduction equipment used by the various methods is also distinct. In the process of micronization, drug solubility is frequently inversely proportional to drug particle size.

b) Cosolvency

"Solvent blending" is another name for this process. By decreasing the interfacial tension among the aqueous solution and the hydrophobic solute, the addition of a water-miscible solvent where the medicine has high solubility improves the drug's solubility in water. Liquid is usually used as the medicinal form. A co-solvent strategy may be useful for solubilizing chemicals that are poorly soluble on their own but are extremely crystalline or lipophilic. Because of the comparatively increased capacity of co-solvents to solubilize nonpolar pharmaceuticals and the low toxicity of many co-solvents, it has found its major usage in parenteral dosage forms. Cosolvents including propylene glycol, glycerol, PEG400, and dimethyl are frequently utilized.

c) Nanotechnology:

Many medications are only moderately soluble in water, however nanonization techniques have allowed for significant improvements in both these metrics. The term "nanonization" is used to describe the study and utilization of materials as well as structures with dimensions of 100 nm or less. Improved medication solubility and pharmacokinetics through nanonization may lead to fewer systemic adverse effects.

Wet milling, homogenization, the emulsification-solvent evaporation process, pear milling, spray drying, etc. are all methods utilized for the nanonization of pharmaceuticals. Nanotechnology has been widely used to the pharmaceutical industry.

d) pH Adjustment: Some medications that aren't very water soluble include basic or acidic portions of the molecule, therefore changing the pH of the water might help them dissolve. In theory, adjusting the pH can be employed for both oral as well as parenteral dosing. Because blood is a powerful buffer, the poorly soluble medication may precipitate after intravenous delivery due to the blood's pH range of 7.2 to 7.4. The buffer capacity & tolerance of the chosen pH are crucial factors in determining the

approach's viability. If a medicine is taken orally, its solubility may change as it travels through the intestines, where the pH ranges from around 1 to 2 in the stomach to about 5 to 7.5 in the duodenum. Compounds that can be ionized and are stable & soluble at the intended pH are ideal. Acids, bases, and zwitterionic compounds are all possible. Crystalline and lipophilic weakly soluble molecules are both suitable for this method.

e) Hydrotrophy

In the process of hydrotrophy, the aqueous solubility of one solute is increased by the addition of a substantial amount of a second solute. Alkali metal salts of different organic acids make up the solute. Ionic organic salts are hydrotropic agents.

Sodium acetate, sodium benzoate, urea, sodium alginate and other hydrotropic agents help make poorly soluble medicines more soluble by a process that is more closely linked to complexation. Ionic organic salts are hydrotropic agents. Colloidal behavior is absent in hydrotropic solutions, and the interaction among the hydrotropic agent & solute is minimal.

f) Sonocrystallization:

Particle size can also be decreased by the use of recrystallization using liquid solvents as well as antisolvents for materials that are not easily soluble. Sonocrystallisation is a revolutionary technique for crystallization-based particle size reduction utilizing ultrasound. The process of song crystallization makes use of ultrasonic energy between 20 and 100 kHz in frequency to induce crystallization. In addition to increasing the nucleation rate, this method is also useful for decreasing particle size and regulating the particle size distribution of medicinal components. Ultrasound frequencies between 20 kHz and 5 MHz are typically used.

g) Supercritical Fluids (SCF):

The use of supercritical fluids in many technologies and applications has also increased dramatically in recent years. Carbon dioxide's critical point makes it the most common supercritical fluid and has been utilized for over a century because of its ability to dissolve nonvolatile solvents. It's risk-free, sustainable, and cheap. SCFs are desirable for the pharmaceutical industry because of their low operating conditions (temperature and pressure).

Once the temperature and pressure of a SCF are raised over its critical values, the SCF remains in a single phase. Because of their unique qualities that fall somewhere in between those of a pure liquid and gas, SCFs can be used in a variety of product processing applications. Small shifts in operating temperature, pressure, or both can have large effects on the density, transport characteristics (like viscosity and diffusivity), and other physical properties (like dielectric constant and polarity) around the critical points.

h) Solid Dispersion:

To create a solid solution, two crystalline solids are mixed together to form a third crystalline solid. Because of the simultaneous crystallization of the two substances, a mixed crystal is produced. Therefore, greater dissolution rates than simple eutectic systems are anticipated.

When a medication is suspended in an inert carrier and precipitates out in an amorphous form, this is known as amorphous precipitation. Because the drug is in a higher energy state in this system, it dissolves more quickly than in its crystalline form.

Methods of preparing solid dispersions

i. **Fusion Process:** The medication is dissolved into the carrier, which is then heated to slightly over its melting point. To ensure that the medicine is evenly distributed throughout the matrix, the mixture is chilled while being continuously stirred. The solubilizing impact of the carrier, enhanced wetting or reduced complexation, surface hydrophobicity as well as crystallization of the drug in a metastable polymorphic form with changed thermodynamic characteristics may also play a role. Disadvantages Drugs that are thermosensitive may be destroyed by storage in a container that melts easily.

ii. **Solvent Method:**

An appropriate organic solvent is used to dissolve the carrier and the active component. This solvent is removed by heating it to a high temperature or vacuuming it. Supersaturation happens as the solvent is evaporated, and the contents precipitate out at the same time to leave a solid residue. The co-precipitate is then dried in a vacuum to remove any residual solvent. It is assumed that all traces of the solvent must be eliminated. Complete solvent removal can be demonstrated using very sensitive methods like differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), or by less sensitive processes like spectroscopy, gravimetry, and more.

iii. **Fusion-Solvent Method:**

The drug(s) dissolve in the molten carrier(s) and become a part of the mixture. If the liquid is non-toxic and the carrier can contain that amount of liquid while still preserving its solid qualities, then there is no reason to remove the solvent. This technique is helpful for medications that have a high melting point or are sensitive to heat.

iv. **Spray Drying:**

In a good solvent, both the carrier and the active substance are dissolved and suspended. The solvent is evaporated by subjecting it to a stream of hot air during the drying process. Since each droplet has such a huge surface area, the solvent evaporates quickly, and a solid dispersion is created in a short amount of time.

v. **Spray freeze drying (lyophilization):**

Spray freeze drying (SFD) is a technology that has been developed to successfully manufacture solid dispersions at room temperature, avoiding the heating required for the manufacturing of thermosensitive medications. Feed liquids with weakly water-soluble or insoluble APIs and excipients are atomized into a cryogenic liquid at room temperature using SFD technology, resulting in a frozen micronized powder that is then dried. This method's amorphous form and large surface area provide a number of benefits over more conventional methods of producing solid dispersions.

vi. **Dropping Method:**

Pipetted drug carrier liquid is dumped onto a plate and allowed to cool until spherical particles form. A number of variables, including melt viscosity and pipette diameter, can affect the final particle size and form. Due to the temperature's effect on viscosity, it is crucial to get the melt to solidify into a sphere when deposited upon the plate.

i) **Inclusion Complexation:**

Inclusion complex production is the most widely used method for increasing the dissolution rate, aqueous solubility in addition with bioavailability of medicines that are

otherwise weakly water-soluble. Nonpolar molecules or regions of molecules are inserted into the cavity of another molecule / group of molecules to produce inclusion complexes. Inclusion complexation relies on a close structural match between the host and the guest molecules.

j) Self-Emulsifying or Self-Micro Emulsifying Systems:

The idea of in situ forms of emulsion in the gastrointestinal tract is utilized by self-emulsifying / self-micro emulsifying devices. A self-emulsifying drug delivery system (SEDDS) is a clear isotropic solution made up of surfactant, oil, co-surfactant, one or more hydrophilic co-solvent as well as solvents.For better absorption of lipophilic drugs, they are often administered in the form of fine o/w emulsions or micro-emulsions, which develop spontaneously on dilution by the aq. phase in the GIT. One possible explanation for the simplicity of emulsification is that water readily penetrates the different liquids' crystalline or gel phases generated on the droplet's surface. SEDDS are advantageous for production on a large scale since these are thermodynamically stable and form spontaneously upon combining their components with gentle agitation. Chemical instability of pharmaceuticals and high surfactant concentrations are two problems with this approach. GIT irritation is caused by the 30–60% surfactant content in self-emulsifying formulations. Lipid-filled soft or hard-shelled gelatin capsules are the standard route of administration for most self-emulsifying systems because of the liquid consistency of the substance. To stop the hygroscopic contents from drying out or migrating into the capsule shell, the interaction between the shell and the emulsion must be taken into account.

k) Liquisolid Methods:

When a carrier material with a porous surface and fibers in its interior, such as cellulose, is introduced with the drug dissolved in the liquid vehicle, both absorption and adsorption occur; that is, the liquid is first absorbed in the interior of the particles by its internal structure, and once this process is saturated, adsorption of the liquid occurs on both the internal as well as external surfaces of the porous carrier particles. Subsequently, the coating material endowing the liquisolid system with suitable flow characteristics possesses significant adsorptive qualities along with a large specific surface area. Coating materials can include microcrystalline cellulose, amorphous cellulose, and silica powders.

Conclusion

We infer from this paper that medication solubility is a crucial consideration. Poorly water-soluble medications are absorbed more slowly when taken orally, and solubility is a prerequisite for the creation and formulation of any dosage form. The drug's solubility depends on several variables. The drug's solubility can be improved using the aforementioned methods. There are a great deal of methods for improving solubility, and this increases the solubility by a factor of fold. Increasing solubility is important because many medications have a solubility issue that reduces their bioavailability. Poorly soluble medications can currently be made more soluble by the use of the aforementioned methods.

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