Original Article

SOLUBILITY ENHANCEMENT TECHNIQUES: UPDATES AND PROSPECTIVES

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DOI: 10.47750/pnr.2022.13.S08.353

Abstract

Solubility, the process by which a solute dissolve in a solvent to create a homogenous solution, is one of the crucial elements in attaining the ideal medicine concentration in the circulating system for the desired pharmacological effect. It's that simple action. Insufficient water solubility is the main issue with formulation development. A significant difficulty for formulation scientists is solubility. Any medicine that is to be absorbed must be present in solution at the absorption site. Particle size reduction, crystal engineering, salt creation, solid dispersion, application of surfactants, complexation, and other techniques like these are used to increase the solubility of poorly soluble pharmaceuticals. These approaches also involve physical and chemical drug modification. The choice of a solubility-improving technique is influenced by the drug's properties, the site of absorption, and the necessary dosage form and properties. The paper provides detailed information on solubility enhancement techniques, as well as the importance of solubility and the latest approaches to increasing solubility.

Keywords: Solubility Enhancement techniques, Nanosuspension, Hot Melt Method, Nanosuspension, Challenges.

Introduction

Solubility is the property of a solute that causes it to mix uniformly with a solvent. Fundamentally, the solvent being used, along with temperature and pressure, has an impact on a substance's solubility. The concentration of the solute in the solution does not increase as more of it is added [1]. The saturation concentration describes the amount of a material that is soluble in a particular solvent[2].

A liquid, which could be a single chemical or a combination of two liquids, serves as a solvent frequently. The phrase solution in a gas can also albeit rarely refer to a solid solution[3].

Solubility should not be confused with a substance's capacity to dissolve or liquefy since these processes can result from both chemical reactions and dissolution [4]. Zinc for instance dissolves in hydrochloric acid even though it is insoluble in the solution. This is because the amount of solvent needed for every part of the solute is a descriptive phrase[5].

Table 1. Solubility in terms of Parts of Solute[6]

Sl No	Solubility	% of the solvent needed for every % of the solute
1	Very soluble	under1
2	Free of charge	1to10
3	Soluble	10 to 30
4	Easily soluble	30 to 100
5	Barely soluble	100 to1000
6	Very slightly soluble	1000 to 10000
7	Literally unsolvable	>10000

Importance of solubility

Solubility also has a significant impact on other dosage forms such as parenteral formulations. Solubility is one of the most significant aspects of achieving the required drug concentration in the systemic circulation and the required pharmacological response[7].

After oral administration poorly water-soluble medications sometimes require considerable dosages to attain therapeutic plasma levels. Low water solubility is the fundamental problem with formulating novel chemical entities and developing genetic material[8].

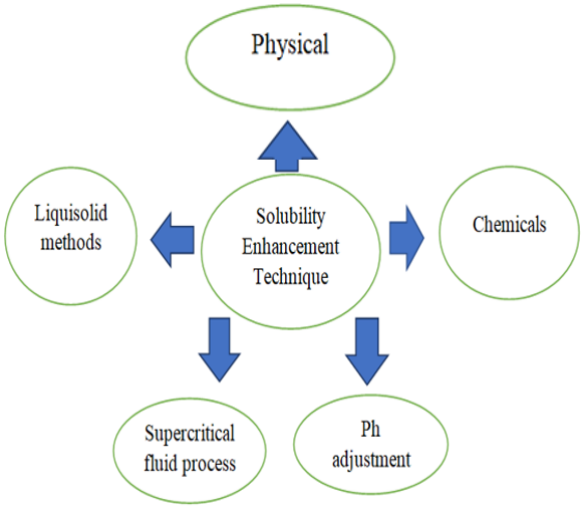
For liquid medicinal compositions water is the ideal solvent. This is because it allows for the presence of any substance that needs to be absorbed at the absorption site in the form of an aqueous solution[9]. Most medications have poor aqueous solubility and are either weakly basic or mildly acidic.

Solubility enhancing technique

1. MODIFICATION IN PHYSICAL CONDITION

Drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions, cryogenic technologies, particle size reduction techniques like micronization and nano suspension, and changes to crystal habit like polymers' co-crystallization and the amorphous state are all examples[10]**.**

Figure 1. Classification of Solubility Enhancement Techniques[11]



2 MODIFICATION IN CHEMICAL STRUCTURE

Salt production derivatization complexation, pH change, and buffer utilization [12].

3 OTHER METHODS

Utilizing a surfactant-like adsorbent in a supercritical fluid technique allows for the co-solvency of hydrotropes and various excipients to be dissolved[13].

A. PARTICAL SIZE REDUCTION

The relationship between the solubility of a drug and its particle size is inherent. A particle's surface area to volume ratio decreases as it grows smaller. Rises and a wider surface area enables better interaction with the solvent which promotes solubility[14].

Another common method for reducing particle size is micronization. Through increased surface area micronization speeds up the pace at which pharmaceuticals dissolve it does not speed up equilibrium solubility[15]. These medications rate of dissolution is increased by reducing the particle size of the pharmaceuticals which results in an increase in surface area[16]. Micronization is not suitable for drugs with large dose numbers because it does not alter the medication's saturation solubility. Instead it is done via milling procedures employing jet mills rotor stator colloid mills and other devices[17].

To increase the therapeutic efficacy of medications in dose form, solid dispersion is a fully utilised pharmaceutical approach[18]. A solid dispersion, which is a collection of dry goods having at least two distinct hydrophilic and hydrophobic components, is often made up of a hydrophilic matrix and hydrophobic drug components[19].

HOT MELT METHOD [fusion method]

A medication and a water-soluble carrier are physically combined and heated rapidly until they melt[20]. The melting liquid swiftly cools and hardens in an ice bath after being forcefully stirred. Following the breakdown, pulverisation, and sieving of the resulting solid mass, the mixture is crushed into tablets using tableting agents[21]. A binary system's melting point is determined by the composition, or the choice of carrier, and by the weight percentage of the medication[22].

SOLVENT EVAPORATION METHOD

Due to the low temperature needed for the evaporation of organic solvents, the fundamental benefit of the solvent evaporation strategy is that thermal disintegration of pharmaceuticals or carriers can be avoided[23].

B. NANO SUSPENSION

A pharmaceutical nano suspension is a biphasic system made up of drug particles that are nano in size and stabilised by a surfactant[24]. It is intended for either oral and topical application or parental and pulmonary delivery. Having particles that range in size from 200 to 600 nanometers on average, solid particles in nano suspensions typically have a particle size distribution less than 1 micron[25].

The distribution of hydrophobic medicines has been made possible by the development of nano suspension technology[26]. Medications that are insoluble in water or oils or have low solubility are handled using this technique. Nanosuspension further classified into 2 types[27].

1. Precipitaton Technique

In the precipitation method, the medication is dissolved in a solvent and introduced to an antisolvent to cause crystals to form[28]. The utilisation of basic, inexpensive equipment is one of the precipitation technique's main benefits,but developing drug crystals is a challenge since it prevents the production of microparticles[29]. The drug must be soluble in at least one solvent and that solvent must be miscible with an antisolvent in order for these precipitation techniques to work. Additionally, drugs that are simultaneously poorly soluble in aqueous and non-aqueous solutions cannot be precipitated[30].

2. Media milling

High-sheer media mills are used to create the nano suspension. For a number of days, from two to seven, the milling chamber is rotated at a very high shear rate while being kept at a regulated temperature[31].

3. High pressure homogenization

This method involves forcing a drug and surfactant suspension through a nano-sized high-pressure homogenizer's aperture valve while under pressure[32]. Cavitation in the aqueous phase is the method's basis. Drug microparticles can become nanoparticles thanks to the high cavitation forces within the particles[33].

C. SUPERCRITICAL FLUIDS [SCF]

The term supercritical fluid describes fluids that can display both liquid and gaseous qualities because there is an increase in temperature and pressure over their critical values[34]. Since the density and mass-transport characteristics of SCFs are crucial in defining their solvent power, a little change in pressure can have a substantial impact. SCFs are very compressible at temperatures near critical due to their high compressibility[35]. The drug particles may solubilize within the SCF which is commonly carbon dioxide, and then recrystallize at much smaller particle sizes.

D. CRYOGENIC TECHNIQUES

Drug dissolution can be accelerated using cryogenic techniques, which create nanostructured, amorphous drug particles with large porosities at extremely low temperatures[36].

1. Spray freezing onto cryogenic fluid

In this procedure, the drug was dispersed in liquid and then atomized across the fluorocarbon refrigerant's surface that was bubbling and agitated [37]. Maltose, lactose, inositol, mannitol, or dextran are examples of potential

carriers. A probe for sonication can be introduced into the agitated refrigerant to enhance the aqueous solution's dispersion [38].

2.Spray freezing into cryogenic liquids[SFL]

Using the SFL particle engineering technique drug powder aggregates with an amorphous nano structure and high surface area have been produced. In this technique severe atomization into tiny droplets and a significantly faster freezing rate are achieved through direct liquid-liquid impingement between the cryogenic liquid and the automized feed solution [39]. Lyophilized frozen particles are used to produce micronized dry fluid powders [40].

3.Spray freezing into vapour over liquid [SFV/L]

Tiny drug particles with high wettability were produced when the drug solution was frozen in cryogenic fluid vapours and the frozen solvent was eliminated [41]. Prior to coming into contact with the cryogenic liquid during SFV/L the automized droplet frequently starts to solidify in the vapour phase. Small drug particles may form and multiply as the solvent freezes and the drug becomes oversaturated in the automized droplets' unfrozen zone[42].

4. Ultra-Rapid Freezing [URF]

Solid cryogenic materials are used in the Nobel Prize-winning cryogenic procedure known as ultra-rapid freezing to create nanostructured drug particles with the correct surface morphology[43]. The solid surface of a cryogenic substrate rapidly freezes when a drug solution is applied to it. Lyophilization is the next step, producing a micronized medication powder with improved solubility. Phase separation and crystallisation of the medicinal components are avoided by ultra-rapid freezing. Amorphous drug-carrier solid dispersion and solute solution are intimately mixed[44].

E. INCLUSION OF COMPLEX FORMATION-BASED TECHNIQUES

The aqueous solubility, dissolution rate, and bioavailability of medications that are only mildly water-soluble have been improved more successfully than any other solubility augmentation techniques[45].

These are created when nonpolar molecules cannot dissolve into the area of another molecule, most frequently cyclodextrin[46].

Cyclodextrins are the host molecules that are used most frequently. Inclusion complexes are created when a nonpolar molecule, or a nonpolar component of a molecule, is incorporated into the cavity of a different molecule or group of molecules, known as the host[47].

F. CRYSTAL ENGINEERING

Comminution operations can result in highly homogeneous cohesive particles that could harm product performance and subsequent processing operations. The production of high purity powder with precisely defined particle size distribution has been made possible by the development of crystal engineering techniques. This can result in exceedingly heterogeneous charged and cohesive particles[48].

Another step in the crystal engineering process that accelerates dissolution is the production of hydrates and solvates. During crystallisation it is possible to confine solvent molecules inside the lattice. The resulting crystal is a hydrate if the solvent is dissolved water otherwise any other solvent acts as a solvent[49].

Challenges

Factors affecting solubility

The hydrogen concentration of a solution is measured by its pH level; the more hydrogen ions present, the lower the pH, and vice versa[50]. While weak pH levels only partially dissociate, strong pH values cause complete dissociation. One approach to determining an acid's potency is its PKa value. A stronger acid that more fully dissociates in water has a lower pKa value than a pharmacological compound. For a medicine to be soluble enough to be taken orally, solvent ionisation and drug polarity are crucial. The medicine must also successfully capture ions for it to function. Drug absorption occurs because it is non-ionized in the stomach or intestines. To stop it from becoming ionized again when it enters the bloodstream.

Drug particle size- The size of the particle has a direct impact on a drug's solubility. Larger particles are frequently less soluble, especially when the solutes have the same polarity, pressure, and temperature. When a substance is soluble, it can be easily diffused into the bloodstream without requiring energy or protein to do so.

Solution Process-The majority of chemicals are endothermic, meaning they absorb heat throughout the dissolving process. As a result, their solubility increases as the temperature rises from room temperature storage to oral ingestion to body heat. Agitation aids in speeding up the drug's dissolution in addition to temperature

Conclusion

There are various techniques and methods, including solubility and the importance of solubility, categories of solubility-enhancing technique, physical modification, chemical modification, miscellaneous methods, particle size reduction, solid dispersion, hot melt method, nano suspension, media milling, high pressure homogenization, ultrarapid freezing, inclusion complex formation-based technique, crystal engineering. However solubility is an important parameter for therapeutic effect of a drug.

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