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REVIEW ARTICLE

Solubility and Solubility Enhancement Techniques: A Comprehensive Review

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ABSTRACT

Solubility, defined as the phenomenon of a solute dissolving in a solvent to form a homogeneous system, is one of the key criteria for achieving the correct drug concentration in systemic circulation for the intended (expected) pharmacological response. As a result, despite their potential pharmacokinetic action, low water solubility of medicines is a key limiting factor in the successful introduction of many novel treatments on the market. The rate of dissolving of solids, the pace and amount of absorption, and the achievement of target drug concentration in systemic circulation for intended pharmacological response are all affected by the aqueous solubility of the medication. Enhancing the medication's solubility, dissolution rate, and bioavailability are a difficult challenge in drug development; roughly, 40% of novel chemical entities found today are poorly water-soluble medicines. This article examines numerous solid dispersion methods and concepts, as well as drug selection criteria, advantages and disadvantages, characterization, and application.

Keyword: Enhancing solubility, Low water solubility, Solubility

INTRODUCTION

A variety of approaches can be used to improve the solubilization and bioavailability of a medication that is poorly water soluble. Medication solubilization methods involve micronization, chemical modification, pH adjustment, solid dispersion, complexation, solvency, micellar solubilization, hydrotropic, and many others. Solubilization of poorly soluble medicines is a typical problem in screening testing for novel chemical entities (NCEs), as well as formulation design and development.[1] Any drug that is to be absorbed at the absorption site must be in the form of an aqueous solution. Because solubility and permeability are the determining elements for *in vivo* drug absorption, enhancing procedures such as can be used to change or raise them. Solubility refers to the greatest quantity of solute that may be dissolved in a given amount of solvent. It can be characterized both quantitatively and qualitatively. It is quantified as the amount of solute in a saturated solution at a specific temperature. In qualitative terms, solubility is described as the spontaneous interaction of two or more substances to produce a homogenous molecular dispersion. A saturated solution is one in which the solute and the solvent are in equilibrium. A drug's solubility can be expressed in a variety of ways, including parts, percentages, molarity, molality, volume fraction, and mole fraction.[2]

Solubility is determined by an immediate release product's greatest dosage strength. Very soluble means that a medicine's maximum dosage strength is soluble in 250 mL or less of aqueous solutions throughout a pH range of 1–7.5. The 250 mL volume estimate is based on standard bioequivalence

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testing protocols.[3] The classification of intestinal permeability is based on a comparison to an intravenous infusion. The solubility criteria are critical, as orally delivered medications account for 85% of all drugs sold in the US and Europe.[4]

When two phases are blended together to make a homogeneous solution, this is referred to as a homogeneous solution. The characteristics of newly created active compounds have evolved toward larger molecular weight and lipophilicity as a result of the introduction of combinatorial chemistry and high-throughput screening, resulting in a decrease in water solubility. In some instances, the active ingredient has a poor solubility like carbon-based active molecule with five or more carbon atoms, log *P*-value is equal to or larger than 2, compound's molecular weight is larger than 500 Daltons.[5]

Importance of solubility

Because of its convenience of administration, high patient compliance, cost-effectiveness, sterility limitations, and flexibility in dosage form design, oral ingestion is the most convenient and widely used mode of drug delivery. The poor bioavailability of oral dose forms, on the other hand, is a major difficulty in their design. Poor solubility and permeability are the two most common causes of low oral bioavailability. Solubility is also important in other dosage forms, such as parenteral formulations.[6] One of the most critical characteristics for attaining the optimum medication concentration in systemic circulation and getting the desired pharmacological reaction is solubility. Low aqueous solubility is a critical issue in both the discovery of new chemical entities and the development of generics. Any medicine that needs to be absorbed must be in the form of an aqueous solution at the absorption site. For liquid medicinal compositions, water is the preferred solvent.[7] The majority of medications are weakly acidic or basic, with low water solubility.

More than 40% of NCEs generated in the pharmaceutical sector are nearly water insoluble. These medications' weak water solubility and sluggish absorption result in insufficient and unpredictable bioavailability, as well as gastrointestinal mucosal toxicity. Solubility is the most essential rate limiting criterion for orally delivered medicines to acquire their required concentration in systemic circulation for pharmacological response. For formulation scientists, the problem of solubility is a key concern.[8] One of the most difficult aspects of the drug development process, especially for oral drug delivery systems, is improving drug solubility and thus oral bioavailability. There are a variety of methods for improving the solubility of poorly water-soluble pharmaceuticals that have been documented in the literature. The methodologies are chosen based on factors such as the qualities of the medicine in question, the nature of the excipients to be chosen, and the nature of the intended dosage form.[9]

Bioavailability can be improved by increasing the drug's solubility and dissolution rate in the gastrointestinal fluids, especially for Class II (low solubility and high permeability) compounds, according to the BCS. Because drug release from the dosage form and solubility in the stomach fluid, rather than absorption, is the rate limiting step for BCS Class II medicines, boosting solubility increases bioavailability.[10] Poor absorption and bioavailability, insufficient solubility for IV dosing, development issues resulting to increased development cost and time, and patient burden are among negative effects of low solubility chemicals (frequent high-dose administration).

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

A drug provided in the form of solubility is immediately available for absorption and is absorbed more efficiently than a same amount of drug administered in tablet or capsule form. The importance of solubility for oral bioavailability of poorly soluble drugs cannot be overstated. Solubility is one of the factors that must be met to attain the required drug concentration in the systemic circulation and demonstrate pharmacological response. Drug dissolution rate deciding stage is for oral absorption of poorly or less water-soluble drugs that affect *in vivo* drug absorption.[2,10] Only 8% of novel drug ideas have both good solubility and permeability

at the moment. Because it is poorly water soluble, a high dose of oral administration is required before reaching plasma concentration. Low water solubility is a serious issue, which is analogous to the formulation development of new chemical entities. Any drug that needs to be absorbed should be present at the absorption site in the form of an associate solution. For liquid medicinal compositions, water is the preferred solvent. The majority of medications are weakly acidic and basic, and their aqueous solubility is poor. Because many drugs' solubility affects their bioavailability, solubility improvement is required.[2,10,11] Now, several strategies listed in Figure 1 are used to improve solubility.

Physical modification methods

Reduction of particle size

The bioavailability of a medicine is inextricably linked to its particle size. Increased surface area increases dissolving capabilities by reducing particle size. Milling techniques such as jet mills, rotor stator colloid mills, and others are used to reduce particle size. Because it does not modify the drug's saturation solubility, it is not suited for medications with a high dosage number.[2,11] Nowadays, micronization and nano-suspension are two methods for reducing particle size. For particle size reduction, each process uses distinct equipment. In micronization, drug solubility is frequently inversely proportional to drug particle size.

Advantages of particle size reduction modulation

- Liquid forms can be generated quickly for pre-clinical testing and then converted to solids for subsequent clinical development
- Low excipient-to-drug ratios are usually necessary
- If no strong surfactants are necessary for stabilization, formulations are generally well tolerated
- Crystal formations are generally more chemically and physically stable than amorphous particles
- Approach to consider for stubborn chemicals that have failed to boost solubility in the past.

Disadvantages of particle size reduction modulation

- There is a considerable tendency for particle agglomeration due to the high surface charge on discrete tiny particles.

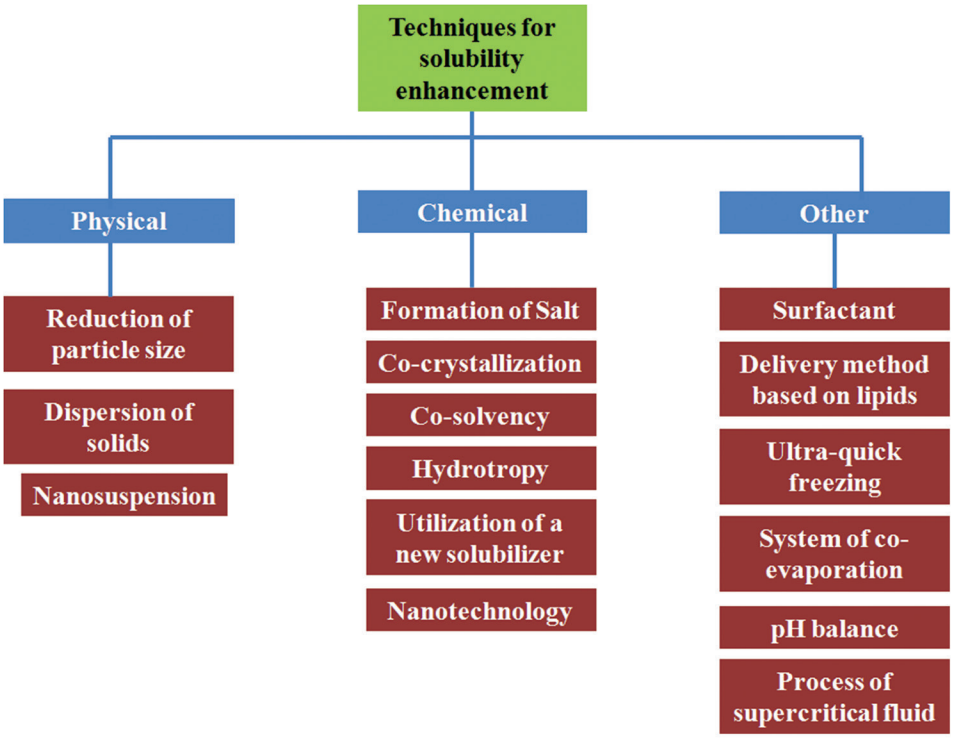

Figure 1: Solubility enhancement techniques

- Developing sterile intravenous formulations is even more difficult from a technical standpoint.

Dispersion of solid

Sekiguchi and Obi first suggested the concept of solid dispersions in the early 1960s, when they researched the formation and dissolving performance of eutectic melts of a sulfonamide medication and a water-soluble carrier. Solid dispersion is a phrase used to describe a collection of solid goods made up of at least two separate components, usually a hydrophilic matrix and a hydrophobic medication.[11] Polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGs), and Plasdone-S630 are the most often utilized hydrophilic carriers for solid dispersions. Surfactants such as Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulfate (SLS) are also used in solid dispersion formulation.[2]

Hot-melt method (fusion method)

The simplicity and cost-effectiveness of this direct melting technology are its key advantages. Sekiguchi and Obi were the first to suggest the melting for generating fast-release solid dispersion dosage forms. The melted fluid is then swiftly cooled and hardened in an ice bath while being vigorously stirred. The final solid mass is crushed, pulverized, and sieved, then tableting agents are used to compress it into tablets. The melting point of a binary system is determined by its composition, which includes the carrier used and the drug's weight fraction in the system.[9] The miscibility of the medication and the carrier in molten form is a key requirement for the creation of solid dispersion using the hot-melt technique. The thermostability of both the medication and the carrier is another significant need.

Solvent evaporation method

Tachibana and Nakamura were the first to combine the medication and the carrier in a single solvent, then evaporate the solvent under vacuum to form a solid solution. Using the solvent evaporation approach, several researchers investigated the solid dispersion of meloxicam, naproxen, and nimesulide. These findings show that the above-mentioned approach can be used to enhance and stabilize solid dispersions of pharmaceuticals that are weakly water soluble.[12]

The fundamental benefit of the solvent evaporation approach is that due to the low temperature required for the evaporation of organic solvents, thermal degradation of pharmaceuticals or carriers may be avoided. The higher cost of preparation, the difficulty in completely removing the organic solvent (from a regulatory standpoint), the possible adverse effect of the supposedly negligible amount of the solvent on the chemical stability of the drug, the use of a common volatile solvent, and the difficulty in reproducing crystal forms are all disadvantages of this method.[13]

Hot-melt extrusion

Hot-melt extrusion is similar to fusion with the exception that the extruder causes intensive mixing of the components. Miscibility of the medication with the matrix, much like in the conventional fusion procedure, might be an issue.[14] For heat-sensitive materials, large shear forces resulting in a high local temperature in the extruder are an issue. In comparison to the classic fusion approach, however, this technology allows for continuous manufacturing, making it appropriate for large-scale production. Furthermore, the product is easier to handle since the form may be modified to the next processing stage without grinding at the extruder's output.[15]

Nanosuspension

The technique of nanosuspension has been developed as a possible contender for the effective delivery of hydrophobic medicines. This method is used on pharmaceuticals that are poorly soluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system made up of nano-sized drug particles stabilized by surfactants for oral and topical administration, as well as parenteral and pulmonary delivery. Solid particles in nanosuspensions typically have a particle size distribution of <1 μ, with an

average particle size ranging between 200 and 600 nm.[6] Precipitation technique, media milling, high-pressure homogenization in water, high-pressure homogenization in non-aqueous medium, and a combination of precipitation and high-pressure homogenization are some of the methods used to prepare nanosuspensions.[8,16]

Precipitation technique

The medication is dissolved in a solvent, which is then added to an anti-solvent to precipitate the crystals in the precipitation procedure. The primary benefit of the precipitation process is the employment of simple and low-cost equipment; nevertheless, adding increasing drug crystals to minimize microparticle creation is a difficulty. The medication must be soluble in at least one solvent, and this solvent must be miscible with anti-solvent, which is a restriction of this precipitation procedure. Furthermore, the precipitation approach is ineffective for medicines that are poorly soluble in both aqueous and non-aqueous environments. Precipitation method was used to make nanosuspensions of danazol and naproxen to increase their dissolving rate and oral bioavailability. The size decrease of naproxen was also linked to a 4-fold increase in the rate of absorption.[16,17]

Media milling

High-shear media mills are used to make the nanosuspensions. The milling chamber, which contains milling medium, water, medication, and stabilizer, is spun at a very high-shear rate for many days (at least 2–7 days) under regulated temperatures. Glass, zirconium oxide, or strongly cross-linked polystyrene resin make up the milling media. The impaction of the milling media with the drug produces high-energy shear pressures, resulting in the breakdown of microparticulate drug into nanosized particles.[17]

High-pressure homogenization

Many poorly water-soluble medicines have been nanosuspended using high-pressure homogenization. A drug and surfactant suspension is driven under pressure through a nanosized aperture valve of a high-pressure homogenizer in this procedure. The basis of this approach is based on aqueous phase cavitation. The cavitation forces within the particles are significant enough to transform drug microparticles into nanoparticles. The necessity for tiny sample particles before loading, as well as the fact that several cycles of homogenization are necessary, is also concerns with this procedure. High-pressure homogenization enhanced the dissolution rate and bioavailability of poorly soluble medications such spironolactone, budesonide, and omeprazole by lowering particle size.[17]

Combined precipitation and homogenization

The precipitated drug nanoparticles have a proclivity for continuing to develop into microcrystals. High-energy forces are required to process them (homogenization). They are entirely amorphous, somewhat amorphous, or completely crystalline, which causes concerns with long-term stability and bioavailability. As a result, the precipitated particle suspension is homogenized to maintain the particle size achieved following the precipitation process.[18]

Chemical modification methods

Formation of salt

Due to different difficulties of instability, an API is frequently unable to be created in its purest form. Salts, cocrystals, solvates, hydrates, and polymorphs are formed as a result of this conversion. Each one provides a unique physiochemical feature that improves the drug's performance attributes such as stability, bioavailability, purification, and manufacturability. For decades, salt production of poorly soluble medication candidates (weak acids and bases) has been used to improve solubility.[19] When a substance is ionized in solution, salts are generated. It works effectively in both parenteral and other liquid formulations as well as solid dose forms. A salt is formed when an acidic or basic medicine is transformed into a salt with a higher solubility than the original drug. Aspirin, theophylline, and barbiturates are examples.

Progesterone, a water-insoluble steroid that is soluble in peanut oil, is a commercially accessible example of this method.[7,20]

Cocrystallization

Cocrystallization modifies molecular interactions and is seen as a promising way to improve drug properties. "Multicomponent crystal formed between two solids under ambient conditions, where at least one component is an acceptable ion or molecule" according to a more precise definition of a cocrystal. Cocrystallization helps an API overcome its physical, chemical, and physiological flaws. By reducing the interfacial tension, cosolvency encourages the dissolving of a non-polar solute. Analytical approaches and rational physicochemical studies, which include tests of solubility and stability, can be used to choose the most appropriate cocrystal.[21] The physical condition of the components is the sole distinction between solvates and cocrystals. Solvates are formed when one of the components is liquid and the other is solid; on the other hand, cocrystals are formed when both components are solid. The API and the cocrystal former are the two main components of pharmaceutical cocrystals(s). [22] The cocrystallization techniques enclosed in this review (Figure 2) range from the most common ones, eg cocrystallization by solvent evaporation. Solution stability is an important parameter for development of cocrystals and to confirm the structure of cocrystal, these are characterized by suitable techniques. We also address the different cocrystals characterization parameters in Figure 3.

Cosolvency

Cosolvents, which are water miscible solvents in which the medicine has high solubility, can be used to augment the solubility of a weakly water-soluble drug. Cosolvents are solutions made up of water and one or more water miscible solvents that improve the solubility of poorly soluble substances. Because it is simple to make and assess, this has been one of the most extensively employed strategies in the past.[23] Pharmaceuticals are always in liquid form.

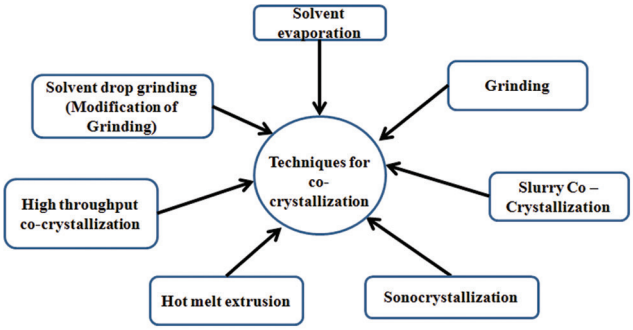

Figure 2: Different techniques for cocrystallization

Figure 3: Cocrystals characterization parameters

A cosolvent technique may be appropriate for poorly soluble chemicals that are lipophilic or highly crystalline and have a high solubility in the solvent mixture. When compared to the water solubility of the medicine alone, cosolvents can boost the solubility of weakly soluble substances by thousands of times. When compared to other solubilization methods, very high drug concentrations of weakly soluble substances can be dissolved. Because of their considerable solubilization capacity for poorly soluble medicines and low toxicity, dimethyl sulfoxide and dimethylacetamide (DMA) have been frequently employed as cosolvents.[24]

Advantages

Formulation and production are simple and quick.

Disadvantages

- The toxicity and tolerability of the solvent level supplied, as with other excipients, must be considered
- When diluted with aqueous media, uncontrolled precipitation occurs. Precipitates can be amorphous or crystalline, and their size varies. Many of the insoluble compounds phares works which are unsuited to co-solvents alone, particularly for intravenous administration. This is due to the medicines' severe insolubility in water and their inability to redispose following precipitation from the cosolvent combination
- The chemical stability of the insoluble drug, as with other solubilized forms, is poorer than in a crystalline state, posing a risk of embolism and local adverse effects at the injection site.

Hydrotrophy

Solubilization phenomenon in which the addition of a substantial amount of a second solute is causes the present solute's water solubility to rise. The method by which it enhances solubility is more directly associated with complexation, which involves a weak contact between hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, and urea and poorly soluble medicines. Ionic organic salts are hydrotropic agents.[25] Hydrotropic solutions are non-colloid and have a weak contact between the hydrotropic agent and the solute.

Utilization of a new solubilizer

Various solubilizing agents can help increase the solubility of poorly soluble drugs. Polysorbates, PEG 400 Sepitrap, are examples of conventional solubilizers. Dendrimers in Soluplus-Povacoat increase the solubility of hydrophobic API. As a new solubilizer, Sepitrap 80% of the solubilizers in Sepitrap™ (microencapsulated solubilizer for solid dose administration) are desorbed in <5 min, making them available to solubilize the medicinal component.[26] The Sepitrap-to-drug (2:1) ratio improves dissolving rate while having no effect on tablet properties and may be utilized without any formulation restrictions. Dendrimers are recognized for their three-dimensional, monodispersed, highly branching, macromolecular nanoscopic architecture with a large number of reactive end groups generated by a reiterative series of reactions, and they work as solubilizing agents for both hydrophilic and hydrophobic medicines. Dendrimers are static unimolecular micelles with a micellar structure that stays stable even at high solvent concentrations.[27]

Nanotechnology

The study and use of materials and structures at the nanoscale level of around 100 nanometers (nm) or less are referred to as nanotechnology. Oral bioavailability increase through micronization is insufficient for many NCEs with limited solubility since micronized products have a relatively small effective surface area for dissolving, hence, the next stage was nanonization.[28] Milling, high-pressure homogenization, vacuum deposition, and high-temperature evaporation are some of the preparatory procedures that can be utilized. Nanotechnology's Benefits: It leads to the development of nano- or micro-sized spherical particles with smooth surfaces, narrow particle size distributions, and large specific surface areas, which increases the dissolving rate and solubility.[29] Nanotechnology's drawbacks of agglomeration are fundamental and difficult to solve.

Other modification methods

Surfactant

Surfactants are molecules with hydrophilic (polar) and hydrophobic (nonpolar) groups in their structure. Surfactants are amphiphilic molecules with both hydrophilic and hydrophobic parts in the same structure. Surfactants can increase the solubility of difficult-to-dissolve substances by acting on surface areas or two-phase interfaces. The majority of surfactants are made up of hydrocarbon segments coupled to the polar group.[30] Polar groups include functional groups such as sulfates, amides, amines, alcohol, thiol, esters, acids, sulfonates, and phosphates, as well as heteroatoms such as N, P, S, or O.[31] Surfactants are classified into numerous categories, which will be discussed later.

Anionic

In water, this surfactant dissociates into amphiphilic anions and cations. SLS, for example, is a common surfactant of this sort.

Cationic

In water, this kind of surfactant can separate into amphiphilic cations and anions. Cationic surfactants, which contain quaternary ammonium compounds and have a bactericidal action, are commonly employed as disinfectants and preservatives. Cetrimide and benzalkonium chloride are two examples of these surfactants.

Non-ionic

Because its hydrophilic group contains a non-dissociable kind, such as amide, ester, ether, alcohol, and phenol, this type of surfactant does not dissociate in water. In the presence of PEGs chains, most non-ionic surfactants become hydrophilic. Surfactants of this kind are also less irritating than anionic or cationic surfactants. Poloxamer and polysorbate are examples of non-ionic surfactants.

Amphoteric

Depending on the pH of the water, this type of surfactant can be non-ionic, anionic, or cationic. Alkyl betaine is an example of this kind of surfactant. Surfactants can lower surface tension while also increasing medication solubility in organic solvents. When a surfactant is dissolved in a liquid, the molecules of the surfactant are drawn to the surface area, changing the surface tension.[31] Surfactants in a position near the surface area will adsorb in low quantities, changing the free energy considerably. The surfactant will aggregate to create micelles after it has occupied the full interface or surface area. Micelles are a surfactant nano system having hydrophobic sections that make up the nucleus and hydrophilic elements that make up the outer shell.[32] The diameter of this structure is generally 20–80 nm. Drugs that are difficult to dissolve in water are dissolved by this structure. Micelle formation traps pharmaceuticals in micelles, a process known as micellar solubilization.[17]

The self-assembling system has several advantages, including cellular internalization, subcellular localization, ligand-mediated targeting, high drug dissolving capacity, protecting drugs from enzymatic hydrolysis, and increasing oral bioavailability and drug loading capacity, in addition to solubilization of micelles from less soluble drugs. Micelles have a number of drawbacks, including poor tolerability of synthetic surfactants in long-term chronic administration, uncontrolled precipitation with dilution with aqueous media or physiological liquids, deposits that can be amorphous or crystalline, and dissolving other materials together, such as preservatives, can cause changes in drug effectiveness and stability. Glimepiride, gliclazide, repaglinide, pioglitazone, glipizide, and rosiglitazone are examples of antidiabetic medicines that are difficult to dissolve in water utilizing the micellar solubility method, provide some additional instances as well as the surfactants that are used to boost a drug's solubility.

pH Adjustment

Using a pH change, poorly water-soluble pharmaceuticals containing portions of the molecule that may be protonated (base) or deprotonated (acid) may be dissolved in water. In theory, pH adjustments can be employed for both oral and parenteral delivery. Because blood is a powerful buffer with a pH between 7.2 and 7.4, the poorly soluble medication may precipitate after intravenous injection. The buffer capacity and tolerability of the chosen pH are crucial factors to consider when evaluating the approach's appropriateness.[33] Because the pH in the stomach is about 1 to 2, and the pH in the duodenum is between 5 and 7.5, the degree of solubility is likely to be changed as the medication moves through the intestines after oral delivery. It's ideal to choose ionizable chemicals that are stable and soluble after adjusting the pH.[34] Acids, bases, and zwitterionic compounds are all possible.

Advantages

- Easy to formulate and analyze
- Easy to create and expedite
- Uses minimal amounts of chemical, making it suitable for high-throughput testing.

Disadvantages

- Precipitation risk when diluted in aqueous medium with a lower pH than the compound's solubility. This may produce emboli intravenously, and it may cause variability orally
- Tolerance and toxicity (local and systemic) associated with non-physiological pH and extreme pHs.

System of coevaporation

Weak basic medications, such as prochlorperazine maleate, have strong solubility in acidic pH, but not in alkaline pH, and when a standard formulation containing weak base is administered orally, precipitation of poorly soluble free base occurs within the formulation in the intestinal fluid. The medicine is no longer able to release from the formulation, resulting in a reduction in bioavailability.[35] This problem can be solved using a coevaporate system, which combines a carrier with a solubilizing effect in alkaline intestinal fluid that can operate in the microenvironment, immediately surrounding the drug particle, with polymers to control the dissolution rate to formulate dosage forms with maximum bioavailability and controlled release of weak base.[36]

Ultra-rapid freezing (URF)

URF is a cutting-edge cryogenic technique for creating nanostructured drug particles with a large surface area. Based on management of the solvent system and process parameters, the technique has the ability to generate particles with a variety of particle morphologies. This method entails freezing a dissolved drug in an aqueous or anhydrous polymer water solution onto the surface of a cryogenic substrate with a thermal conductivity (k) of 10–20 W/(m K), collecting the frozen particles, and removing the solvent, resulting in highly porous, agglomerated particles. The polymer serves as a crystal growth inhibitor while also functioning as a stabilizer.[37]

The URF method has the potential to generate powders with superior physicochemical qualities, similar to those produced by other rapid freezing technologies, due to rapid conductive heat transfer resulting in high supersaturation and nucleation rates. The quick freezing of the drug/polymer mixture, like with other freezing technologies, is critical in preventing phase separation during freezing and allowing the active to be molecularly disseminated with the polymer.[38] This approach, like controlled precipitation, employs pharmaceutically approved solvents, excipients, and standard process equipment to make it quick and scalable. The use of high glass-transition temperature (Tg) polymers like PVP or HPMC prevents the medication from recrystallizing. This approach can be used to improve *in vivo* absorption of BCS Class-II compounds.

Delivery method based on lipids

Lipid-based delivery systems, such as emulsions, microemulsions, liposomes, microspheres, solid-lipid nanoparticles, and others, have the ability to overcome chemical and physical barriers to oral absorption, and are particularly effective at increasing the bioavailability of poorly water soluble but highly permeable drug molecules (BCS Class II).[19,39] The following are some of the suggested mechanisms of action for lipid-based systems to improve drug oral bioavailability:

- Reduction of particle size to molecular size, resulting in a solid-state solution within the carrier
- Increased rate of breakdown into aqueous environment from high surface area oil droplets
- Enhanced dissolving due to increased wetting of hydrophobic substances
- Promotion of absorption through intrinsic lipid pathways
- Increased thermodynamic activity due to supersaturation of the digestive tract's aquatic media.

Microemulsion

A microemulsion is an isotropical dispersion made up of a polar solvent, oil, a surfactant, and a cosurfactant that are thermodynamically stable. Microemulsions are formed naturally without the use of additional power. Negative interfacial tension is one idea, whereas inflated micelles are another.[40] Surfactant and cosurfactant alternate, generating

a mixed film at the boundary that contributes to the microemulsions stability. Because of their propensity to solubilize pharmaceuticals in the oil phase, microemulsions might be used as a drug delivery method for medications that are weakly water soluble.[41,42] Even if the microemulsions are diluted below the critical micelles concentration after oral administration, the resulting drug precipitates have a tiny particle size, allowing for better absorption.

Self-emulsification

The mixture of oil, surfactant, cosurfactant, one or more hydrophilic solvents, and cosolvent generate a clear isotropic solution in the absence of an external phase (water), which is known as the self-emulsifying drug delivery system (SEDDS). When diluted in the aqueous phase, this produces fine O/W emulsions or microemulsions, which are utilized to improve lipophilic medication solubility and absorption. The nature of the oil/surfactant combination, surfactant concentration, oil/surfactant ratio, and temperature at which self-emulsification happens determine the self-emulsification process.[43] The ease with which water penetrates the different liquids crystalline or gel phases created on the droplet's surface might be linked to the ease with which emulsification occurs.

The rate of emulsification, the emulsion size distribution, and the charge of resultant droplets have all been presented as factors to define self-emulsifying performance. Emulsion droplet size, for example, is a critical component in self-emulsification/dispersion performance since it controls the pace and degree of drug release and absorption.[44] Incorporating a little quantity of cationic lipid (oleyl amine) into such a system might also result in positively charged emulsion droplets. In comparing to the similar negatively charged formulation, the oral bioavailability of progesterone was dramatically increased in rats by creating positively charged emulsion. One of the benefits of SEDDS in terms of scale-up and manufacturing is that they develop spontaneously when their components are mixed with gentle agitation and are thermally stable.[41,45,46] Chemical instability of pharmaceuticals and high surfactant concentrations are two disadvantages of this approach. GIT is irritated by the substantial amount of surfactant in self-emulsifying formulations (30–60%). As a result, the surfactant vehicle's safety had to be taken into account. Furthermore, it is known that volatile cosolvents in traditional self-emulsifying formulations migrate into the shells of soft or hard gelatin capsules, causing lipophilic medicines to precipitate. Neoral® is made up of ethanol, maize oil mono-, di-, and triglycerides, Cremophor RH 40, and propylene glycol as an example of self-emulsification. When compared to Sandimmune®, it has less variability and improved medication uptake. Water soluble, insoluble, and surfactant excipients can all be used as solubilizing excipients.

Process of supercritical fluid (SCF)

With the critical point of carbon dioxide, SCFs may dissolve nonvolatile solvents. It is secure, eco-friendly, and cost effective. Above its critical temperature and pressure, a SCF exists as a single phase. Because they are halfway between pure liquid and pure gas, SCFs offer features that are beneficial in product processing. Furthermore, near the critical points, slight changes in operating temperature, pressure, or both affect density, transport qualities (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity). SCFs have lately been adapted to pharmaceutical applications due to their unique processing characteristics, which have long been known and used in the food sector.[47]

Carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water are all common supercooled solvents. Precipitation with compressed anti-solvents process (PCA), rapid expansion of supercritical solutions, gas anti-solvent recrystallization, precipitation with impregnation or infusion of polymers with bioactive materials, condensed fluid anti-solvent, solution enhanced dispersion by cryogenic liquid fluid, solution enhanced diffusion by SCF (SEDS), and aerosol supercrystallization have all been developed to address individual aspects of these shortfalls.[47]

Advantages

- SCFs are attractive for pharmaceutical research due to their low operating conditions (temperature and pressure)
- Drug particles that have been solubilized in SCF can be allowed to react at much smaller particle sizes. Current SCF processes have demonstrated the ability to create nano suspensions with particles ranging in size from 5 to 2000 nanometers in diameter
- SCF processes allow drug particles to be micronized within narrow particle size ranges, often to sub-micron levels, thanks to their versatility and accuracy.

FACTORS AFFECTING SOLUBILITY[48]

Particle size

Solubility is influenced by particle size. The surface area to volume ratio rises as article size decreases. The bigger the surface area of a particle, the more it interacts with the solvent.

Temperature

Temperature has an impact on solubility. If the solution process absorbs energy, the solubility rises as the temperature rises. When the process usually releases energy, the solubility decreases as the temperature increases.

Molecular size

When atoms have a greater molecular weight and a bigger molecular size, the solubility of such substance is reduced because larger particles are more difficult to surround with solvent molecules which are made up to solvate the substance.

Nature of solute and solvent

The nature of the solvent and the solvent are determined by the solute concentration in a certain amount of solvent at a specific temperature. At room temperature, only 1 g of lead (II) chloride may be dissolved in 100 g of water, whereas 200 g of zinc chloride can be dissolved.

Pressure

A rise in pressure enhances solubility for gaseous solutes, whereas a drop in pressure decreases solubility. Changes in pressure have no influence on the solubility of solids and liquids.

Polarity

Solubility is affected by the polarity of both the solute and the solvent molecules. Non-polar solute molecules dissolve in non-polar solvents, while polar solute molecules dissolve in polar compounds.

Polymorphs

Polymorphism refers to a substance's capacity to crystallize in several crystalline forms. A polymorph is a substance that may crystallize in several crystalline forms. It is conceivable for a solid to crystallize in a variety of shapes or polymorphs. Melting points of polymorphs can differ. Because solubility is connected to the melting point of a solid, polymorphs will have varying solubilities.

CONCLUSION

The rate determining step for oral absorption of weakly water-soluble medicines is drug dissolution, and solubility is the basic need for drug absorption from the GIT. The different strategies outlined above can be employed alone or in combination to improve medication solubility. The key to achieving the goals of a good formulation, such as excellent oral bioavailability, reduced dose frequency, and improved patient compliance while maintaining a cheap cost of manufacturing, is to choose the right solubility enhancement technology. The choice of solubility enhancement method is influenced by drug properties such as solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior, and so on, as well as dosage form requirements such as tablet or capsule

formulation, strength, immediate, or modified release, and regulatory requirements such as maximum daily doses of any excipients and/or drug, approved excipients, analytical accuracy, and so on.

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