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SOLUBILITY ENHANCEMENT BY SIZE REDUCTION

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ABSTRACT

Solubility, which refers to the process by which a solute integrates into a solvent under defined conditions to create a uniform mixture, is a vital factor in attaining the appropriate concentration of a drug within systemic circulation, a prerequisite for producing the desired pharmacological response. This review primarily addresses the enhancement of solubility for BCS Class II drugs, known for their low solubility and dissolution rates. As a result, improving the solubility of nearly insoluble drugs poses a considerable challenge in the development of pharmaceutical active ingredients, as insufficient solubility heightens the likelihood of setbacks in drug innovation and development.

The solubility of a drug plays a crucial role in various pharmacokinetic and pharmacodynamic aspects, including absorption, distribution, and protein binding. Oral formulations represent more than 50% of pharmaceutical dosage forms, highlighting the necessity for drug molecules to exhibit water solubility. To achieve effective therapeutic outcomes at the intended site, both solubility and bioavailability are critical. Consequently, advancements in chemical sciences have emphasized the importance of developing pharmaceutical technologies that enhance patient adherence to medication regimens. This article seeks to delineate a range of techniques for improving solubility, utilizing both conventional and innovative methods such as pH modification, micronization, homogenization, salt formation, lyophilization, hot melt extrusion, solvent evaporation, melt sonocrystallization, and the prodrug strategy, all aimed at facilitating effective absorption and enhancing bioavailability.

Keywords: Particle Size Reduction, Solubility, Bioavailability, Micronization, Nanosizing.

I. INTRODUCTION

Poor aqueous solubility is a major challenge in the development of pharmaceutical compounds, particularly for Biopharmaceutical Classification System (BCS) Class II drugs. These drugs often exhibit poor bioavailability due to their limited dissolution rates in aqueous environments. Particle size reduction, through techniques such as micronization and nanosizing, has emerged as an effective strategy to improve drug solubility and bioavailability. This study aims to explore the impact of these techniques on drug dissolution and absorption, focusing on two molecules.

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

The topic of solubility enhancement continues to be a prominent area of inquiry, yet it remains partially unresolved. The improvement of solubility or dissolution poses significant challenges for researchers engaged in the design and development of formulations. These principles are essential to both physical and chemical sciences, incorporating biopharmaceutical and pharmacokinetic factors relevant to medicinal therapies. As a result, more than 40% of newly developed chemical compounds do not advance in the drug development pipeline due to insufficient biopharmaceutical characteristics, including absorption and distribution rates.The International Union of Pure and Applied Chemistry (IUPAC) characterizes solubility as the quantitative composition of a saturated solution, expressed as the ratio of solute to solvent at a designated temperature. . Given its crucial role, enhancing solubility is an important consideration in the optimization of orally administered medications that exhibit poor aqueous solubility. Solubility refers to the intrinsic capacity of a

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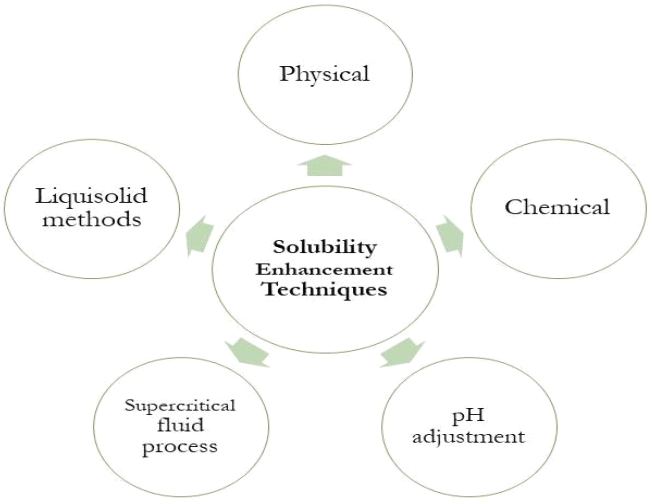
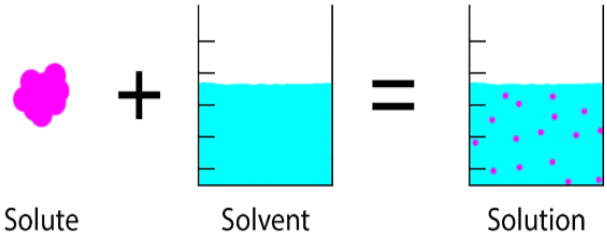
substance, known as the solute, to dissolve in a solvent, and is quantitatively described as the quantity of solute that dissolves in a solvent at a designated temperature.



Concept of solubility

To comprehend solubility, it is essential to first grasp the components of a solution. A solution consists of two primary elements: a solute and a solvent. For clarification, consider the example of saltwater. In this case, water serves as the solvent, as it is the medium utilized to dissolve the solute. The salt acts as the solute, being the substance that dissolves in the water. Typically, solvents are present in greater quantities within the solution. It is important to note that solutions can exist in any of the three states of matter; therefore, not all solutions are limited to liquids, as evidenced by steel, which is also classified as a solution.



In order for a mixture to qualify as a solution, the ratios of its various components, namely the solute and solvent, must be taken into account. The image below depicts three cups: one containing sugar, another containing salt, and the last containing mud. The cup with mud is clearly different from those containing salt and sugar. This distinction arises because the mud represents a heterogeneous mixture, whereas the other two are classified as solutions. Solutions are characterized by their homogeneous nature, indicating that their compositions are consistent throughout.

Solubility is defined as the ability of a solute to dissolve within a solvent, leading to the creation of a solution. This property allows substances like sugar to dissolve in coffee. Water is frequently referred to as a "universal solvent" because of its capability to dissolve a diverse array of substances, although there are significant exceptions to this rule.

The solubility process entails the establishment of new interactions between the molecules of the solute and those of the solvent. It is characterized as the highest quantity of solute that can be dissolved in a designated volume of solvent at a specific temperature. Solutes are categorized into three groups: highly soluble, sparingly soluble, and insoluble. A solute is considered soluble if a concentration of 0.1 grams or more can be dissolved in 100 milliliters of solvent. . Solubility can be expressed as the number of grams of solute in one liter of aA concentration of less than 0.1 grams is categorized as sparingly soluble. saturated solution; for example, a solubility of 12 g/L at 25 °C. Molar solubility, however, refers to the number of moles of solute in one liter of a saturated solution, such as 0.115 mol/L at 25 °C.

A saturated solution is characterized as one that has attained the highest possible concentration of solute that

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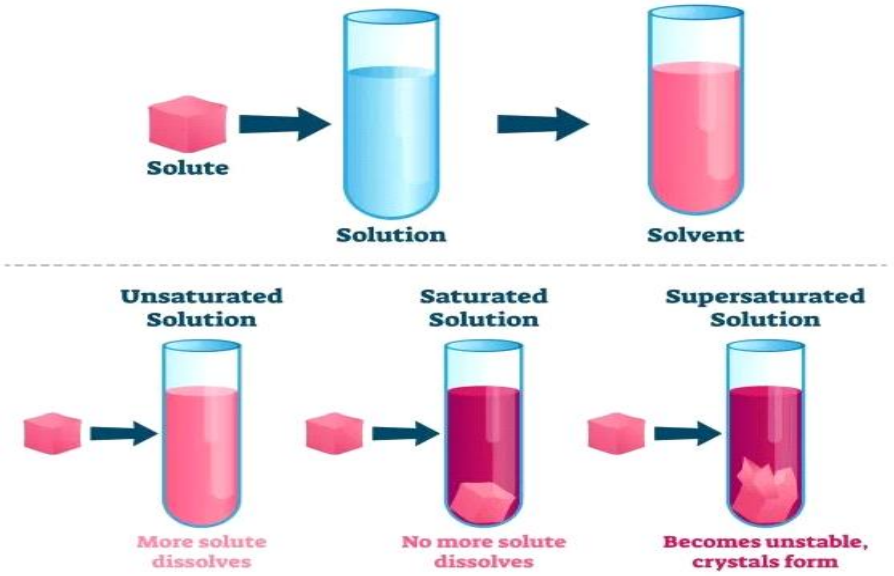
can be dissolved. At a temperature of 20°C, the maximum amount of sodium chloride (NaCl) that can dissolve in 100 grams of water is 36.0 grams. If more NaCl is added beyond this threshold, it will not dissolve, indicating that the solution has reached its saturation point. However, by adding more water to the solution, it becomes possible to dissolve additional NaCl due to the increased volume of solvent. In contrast, an unsaturated solution contains a lesser amount of solute than what can be dissolved. The accompanying figure demonstrates this process and delineates the distinctions between unsaturated and saturated solutions.



An unsaturated solution refers to a solution where the solvent is capable of dissolving additional amounts of the solute. In essence, this indicates that the solution has not yet attained its full capacity for solute dissolution.

Unsaturated solutions contrast with saturated solutions, where the solvent has reached its maximum capacity for solute dissolution. In an unsaturated solution, the concentration of solute is less than that found in a saturated solution. Such solutions can be created by either increasing the amount of solvent in a saturated solution or by decreasing the quantity of solute present in it. Unsaturated solutions are frequently encountered in daily life; for instance, a glass of water containing several ice cubes represents an unsaturated solution, as the water is capable of dissolving additional ice.

A supersaturated solution is characterized by containing a greater amount of dissolved solute than what is necessary to form a saturated solution. This type of solution can be created by first heating a saturated solution, subsequently adding additional solute, and then allowing it to cool gradually. To induce crystallization of the excess dissolved solute, a few crystals of the solute can be introduced into the supersaturated solution.

Factors Affecting Solubility

1. Solvent solvent affect solubility: The relationship between solute and solvent plays a crucial role in determining solubility. Strong attractions between solute and solvent lead to increased solubility, whereas weak attractions result in decreased solubility. Consequently, polar solutes are most effectively dissolved in polar solvents, while non-polar solutes are best dissolved in non-polar solvents. When a polar solute is combined with a non-polar solvent, or the other way around, the solubility is typically very low or negligible. A fundamental principle to keep in mind is that substances with similar properties tend to dissolve in one another.
2. Common Ion Effect : The common-ion effect refers to the reduction in the solubility of an ionic compound when a salt containing an ion that is already present in the chemical equilibrium is introduced into the solution. This phenomenon can be effectively illustrated by Le Chatelier's principle. For instance, consider the addition of the slightly soluble ionic compound calcium sulfate, CaSO4, to water. The net ionic equation representing the resulting chemical equilibrium is as follows:

$CaSO4(s) \rightleftharpoons Ca2+(aq) + SO4^2-(aq)$.

Calcium sulfate exhibits limited solubility; at equilibrium, the majority of calcium and sulfate ions are found in the solid form of calcium sulfate.

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If copper sulfate (CuSO4), a soluble ionic compound, is introduced into the solution, it will contribute additional sulfate (SO4^2-) ions due to its solubility.

CuSO4(s) ⇌ Cu2+(aq) + SO4^2-(aq) (2)

The sulfate ions released from copper sulfate are already present in the solution as a result of the minimal dissociation of calcium sulfate. Consequently, the introduction of these sulfate ions exerts pressure on the established equilibrium. According to Le Chatelier's principle, this added stress on the product side of the equilibrium will cause a shift towards the reactants side to mitigate the new stress. As a result of this shift towards the reactants, the solubility of the slightly soluble calcium sulfate is further diminished.

3. Temperature Affects solubility: Temperature changes affect the solubility of solids, liquids and gases differently. However, those effects are finitely determined only for solids and gases.

Solids:The influence of temperature on the solubility of solids varies based on whether the reaction is classified as endothermic or exothermic. Le Chatelier's principle can be employed to analyze the temperature effects in both cases.

To begin with, in the case of an endothermic reaction (ΔHsolvation > 0), an increase in temperature introduces stress on the reactants' side due to the added heat. According to Le Chatelier's principle, the system will respond by shifting towards the product side to mitigate this stress. This shift leads to a greater dissociation of the solid when equilibrium is reestablished, thereby enhancing its solubility.

Conversely, for an exothermic reaction (ΔHsolvation < 0), raising the temperature creates stress on the products' side from the additional heat. Le Chatelier's principle indicates that the system will shift towards the reactants' side to relieve this stress. As a result, less of the solid will dissociate when equilibrium is restored, leading to a reduction in solubility.

Liquids

In the case of liquids, there are no defined trends for the effects of temperature on the solubility of liquids.

Gases: To comprehend the impact of temperature on the solubility of gases, it is essential to recognize that temperature reflects the average kinetic energy of particles. An increase in temperature leads to a rise in kinetic energy, which in turn enhances the molecular motion of gas particles. This heightened motion increases the likelihood of gas particles escaping from the liquid phase into the gas phase, while simultaneously reducing the probability of gas particles being dissolved in the liquid. Conversely, a decrease in temperature results in the opposite effect. Therefore, the relationship can be summarized as follows: higher temperatures correspond to lower solubility, whereas lower temperatures correspond to higher solubility.

Le Chatelier's principle provides a useful framework for understanding these phenomena. It is important to note that the dissolution of gas in a liquid is typically an exothermic process. Consequently, when the temperature rises, it creates stress on the product side of the equilibrium (since heat is considered a product). According to Le Chatelier's principle, the system will respond by shifting towards the reactant side to mitigate this stress. As a result, the concentration of gas particles in the gaseous phase increases, leading to a decrease in solubility.

On the other hand, a reduction in temperature induces stress on the reactant side (again, because heat is a product). In this case, Le Chatelier's principle suggests that the system will shift towards the product side to counteract this stress. Consequently, the concentration of gas particles in the gaseous phase diminishes, resulting in an increase in solubility.

4. Pressure Affects Solubility of Gases The influence of pressure is primarily notable in its impact on the solubility of gases within liquids.

Solids and Liquids: The influence of pressure variations on the solubility of solids and liquids is minimal. Gases: The relationship between pressure and the solubility of gases in liquids is most effectively explained by a combination of Henry's law and the Le Chatelier principle. According to Henry's law, when the temperature remains constant, the solubility of a gas is directly proportional to its partial pressure. The following formula represents Henry's law:p = khc.

where:

p - is the partial pressure of the gas above the liquid,

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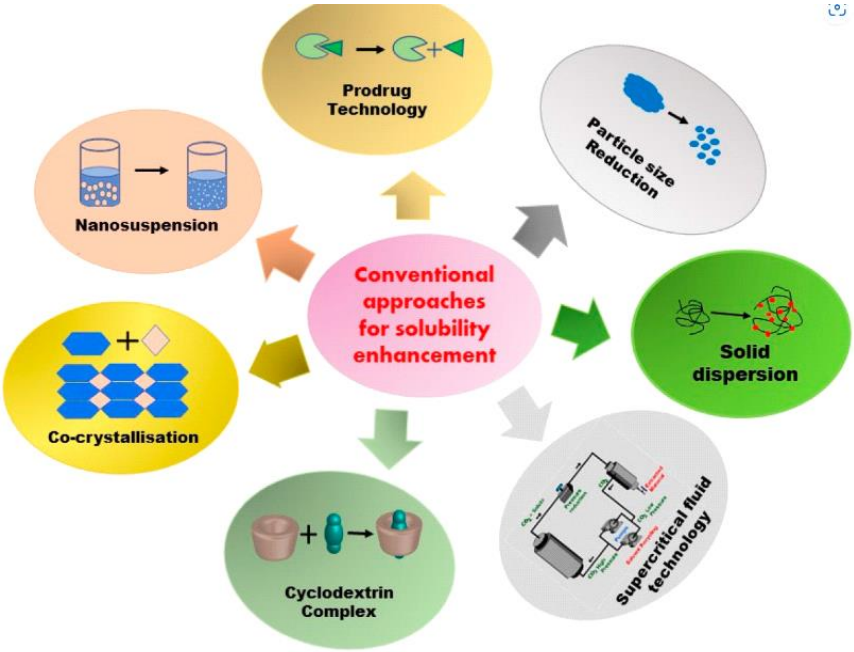
kh-- is Henry's law constant, and

c--is the concentrate of the gas in the liquid

The equation demonstrate that, at a constant temperature, a decrease in partial pressure leads to a reduction in the concentration of gas within the liquid, which in turn results in diminished solubility. Conversely, an increase in partial pressure will elevate the concentration of gas in the liquid, thereby enhancing solubility. By extending the principles outlined in Henry's law, the applicability of Le Chatelier's principle is further reinforced in forecasting the impact of pressure on gas solubility.

In a system where a gas is partially dissolved in a liquid, an increase in pressure will lead to a rise in partial pressure due to the compression of the gas. This heightened partial pressure facilitates the entry of additional gas particles into the liquid, as the reduction of gas above the liquid decreases the partial pressure. Consequently, this process alleviates the stress induced by the increased pressure, resulting in enhanced solubility.



II. METHODS AND MATERIAL

2.1. Materials

Niflumic acid (NIF) was purchased from Sigma-Aldrich Co. Llc. (St. Louis, MO, USA), papaverine hydrochloride (PAP) from Molar Chemicals Ltd. (Halásztelek, Hungary), and furosemide (FUR) from TCI Europe N.V. (Haven, Belgium). From the commercially available substances micro- and nano-sized products were prepared by milling (Retsch Ball Mill (Retsch Hungary, Budapest, Hungary), 400 rpm, 2 h) at the University of Szeged. The milling time and rpm were identical for micronization and nanonization, but for nano-sized products the polymer excipients were added in 1 to 1 mass ratio. Two different polymers were used: polyvinyl alcohol (PVA) and polyvinylpyrrolidone-25 (PVPK-25) purchased from Sigma-Aldrich Co. Llc. (St. Louis, MO, USA). The distilled water of Ph. Eur. Grade was used. All other reagents (sodium chloride, sodium hydroxide pellets, acetic acid, sodium dihydrogen phosphate) were of analytical grade. SIF powder was purchased from Biorelevant (London, UK).

2.2. Solubility Measurements

The equilibrium solubility of the samples was determined by the SSF method. The concentrations for the blank buffers were available at the manufacturer. Full and full buffers were prepared from instant SIF powder added to the blank buffers and could be used for 48 h. For FaSSIF, a full 0.224 g of SIF powder was dissolved in 100 mL of blank phosphate buffer (pH = 6.5). After 2 h, a slightly opalesque solution was formed and it meant that it was ready for the measurement. For FeSSIF, a full 1.12 g of SIF powder was dissolved in 100 mL of blank

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acetate buffer (pH = 5.0) and was ready to use. Thesamples were added in excess to the aqueous buffer solutions to produce a suspension. To measure the original samples and the micronized forms in the presence of the excipients, the same 1 to 1 mass ratio was used as in the case of nanonized samples: a physical mixture was prepared from the API and the PVA or PVPK-25. The composition of the investigated formulations and their nomination in the following can be found in Table 1.

Table 1: Composition of the investigated formulation

Composition of the Formulation	Nomination
commercially available substance without excipient	original
physical mixture of the commercially available substance and PVA in 1:1 mass ratio	original + PVA
physical mixture of the commercially available substance and PVPK-25 in 1:1 mass ratio	original + PVPK
micronized sample without excipient	micro
physical mixture of the micronized substance and PVA in 1:1 mass ratio	micro + PVA
physical mixture of the micronized substance and PVPK-25 in 1:1 mass ratio	micro + PVPK
nanonized sample with PVA excipient	nanoPVA
nanonized sample with PVPK-25 excipient	nanoPVPK

The concentration of the saturated solutions was determined by UV spectroscopy using a Jasco V-550 UV/VIS spectrophotometer. The aliquots taken out from solubility experiments were diluted if necessary with the buffer used for the given solubility measurement, and the absorbance was measured at the *l*max. The same buffer was used as a blank solution during the spectrophotometric measurements. To calculate the concentration from the measured absorption values, the specific absorbance (A1% 1cm, the absorbance of 1 g/100 mL solution over a 1 coptical pathlength at a given wavelength) of the sample in each media was determined separately at the selected wavelength using a dilution series, from the linear regression equation (Lambert–Beer law). Representatively, as an example, the calibration curve of furosemide in FaSSIF blank buffer is shown on Figure S1 (Supplementary Materials). Three parallel measurements were performed for each API with or without excipients in all media.

2.3. In situ Dissolution Measurements

The dissolution measurements were performed using the same buffer solutions as in the case of solubility measurements. The concentration versus time relationship was investigated with an in situ procedure. The operation of the used device (_DISS ProfilerTM, Pion Inc., Billerica, MA, USA) is also based on UV spectrophotometry, but through the connected fiber optic probes measuring the concentration in real-time is possible [21–23]. These fiber optic probes are inserted in 6 temperature-controlled (37.0 _ 0.1 _C) vessels,

which were stirred with a magnetic stirrer. The tips of the probes influence the pathlength (2–5–10–20 mm), therefore they should be chosen according to the expected concentration. In cases where the concentration of the solution was out of the range of the device, the real-time monitoring of the dissolution was not possible. After adjusting the right tip to the probes, the UV spectra were registered according to the following protocol: 1 spectrum per 30 s in 0–4 h, 1 spectrum per 1 min in 4–12 h, and 1 spectrum per 2 min in 12–24 h. In cases where 24 h were not enough to reach the equilibrium, further data points were also registered. For the evaluation of the concentration, the calibration data and second derivative spectra were used. The calibration was performed in each media and for each UV probe separately.

2.4. Particle Size Analysis

The mean particle size and size distribution of the original compound and the reduced size substances were determined by Laser Diffractometry and Scanning Electron microscopy (SEM). For Laser Diffractometry, 0.1 mL of milled suspensions were dispersed in 100 mL of demineralized water at a mixing speed of 1500 rpm with Mastersizer Hydro 2000 SM small volume dispersion unit. The particle size of the samples was measured at 25 _ 1 _C using a Mastersizer 2000 (Malvern Instruments Ltd., Malvern, UK). Laser diffraction measures the

angular distribution of light scattered by the diluted sample and detects particles from 0.1 to 3000 _m. General purpose measurement with enhanced sensitivity mode was utilized, which was also useful for sample characterizations containing irregularly shaped particles. Every sample was measured three times individually, and the mean values were reported to track the changing of the particle size and span values (width of particle size distributions). Each measurement took 20 s to perform suggested by the Malvern diffraction application to allow slow-moving larger aggregates to pass through the detector array. The particle size of the drug-nanoparticles—the particles were on the surface of the polymer microparticles—were investigated by SEM pictures (Hitachi S4700; Hitachi Ltd., Tokyo, Japan) at 10 kV. The distribution of the drug particle diameter was obtained by analyzing SEM images with the ImageJ software (1.50i; Java 1.6.0_20 [32-bit]; Windows NT) environment using approximately 500 particles.

2.5. Materials:

Drugs: Griseofulvin and fenofibrate were chosen as the representative drugs for this investigation.

Solvents: Ethanol, water, and surfactants were utilized to formulate the drug solutions.

2.6. Methods:

2.6.1. Particle Size Reduction:

Micronization: The micronization of both drugs was conducted using a jet mill.

Nanosizing: Techniques such as wet milling and high-pressure homogenization were applied to achieve nanoscale particle size reduction.

2.6.2. Particle Size Analysis:

The particle size distribution of the formulations, both micronized and nanosized, was assessed through laser diffraction and dynamic light scattering (DLS).

2.6.3. Dissolution Studies:

Dissolution rates were assessed using a USP II paddle apparatus, with samples taken at various time points and analyzed using UV spectrophotometry.

2.6.4. Bioavailability Studies:

An in vivo study was conducted in rats to evaluate the bioavailability of the particle size-reduced drugs. Blood samples were collected at predetermined intervals, and drug concentrations were measured using HPLC.

Reducing the size of drug particles is a widely used technique to enhance solubility, especially for poorly water-soluble drugs. This process, often referred to as particle size reduction or micronization, can increase solubility by several mechanisms:

- Increased Surface Area: Reducing particle size increases the surface area available for dissolution. The more surface area that is exposed to the solvent (e.g., water), the faster the drug can dissolve. This follows the Noyes-Whitney equation, where dissolution rate is directly proportional to surface area.
- Increased Dissolution Rate: Smaller particles dissolve faster due to the increased surface area, leading to a higher dissolution rate. This is important for drugs that need to dissolve quickly to be absorbed into the body.
- Altered Thermodynamics: According to the Ostwald-Freundlich equation, smaller particles tend to have higher solubility due to their increased surface free energy. This is because smaller particles have more surface molecules exposed, which can more readily interact with the solvent.
- Amorphization: In some cases, reducing particle size can lead to a change from a crystalline to an amorphous state. Amorphous particles have higher solubility than their crystalline counterparts because they are less structured and can dissolve more easily.

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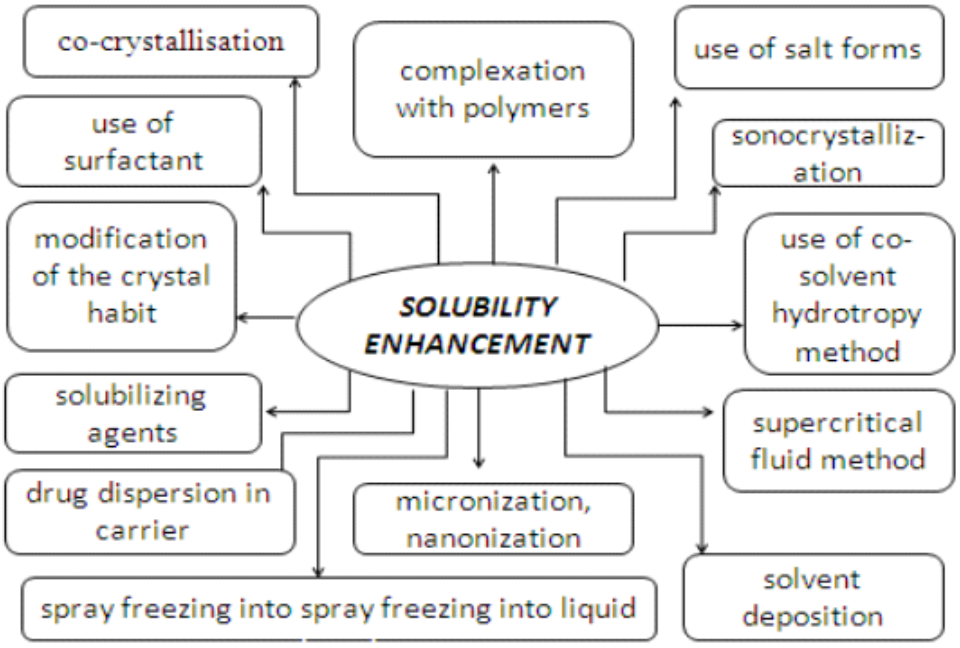
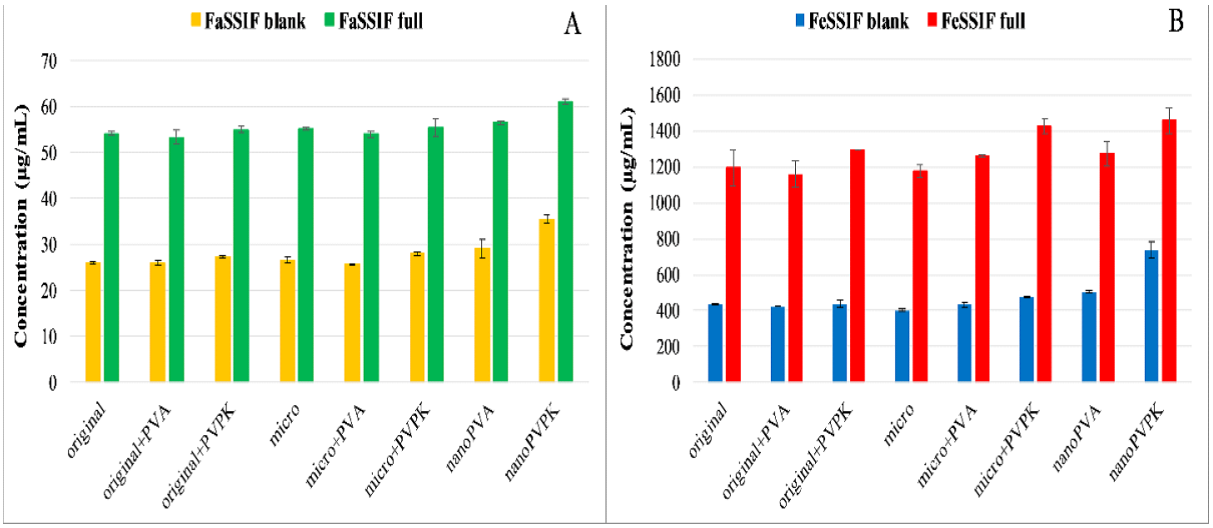


Techniques for Particle Size Reduction

- Micronization: Uses mechanical means such as jet milling to reduce particle size.
- Nanosizing: Involves reducing particles to the nanoscale, often using techniques like wet milling or high pressure homogenization. Nanoparticles have a significantly higher surface area and can show dramatic improvements in solubility.



Application

This method is commonly used in pharmaceutical formulations to improve the bioavailability of drugs with poor water solubility, such as many anti-cancer agents, antifungals, and antibiotics.

However, it's essential to carefully control particle size reduction since extremely small particles can lead to stability issues like aggregation.

Particle size reduction is a vital technique in drug formulation, particularly for drugs that have poor aqueous solubility. By reducing the particle size, pharmaceutical scientists aim to improve the solubility, dissolution rate, and bioavailability of drugs. Here's a more in-depth

1. Mechanisms of Solubility Enhancement via Size Reduction

- Surface Area to Volume Ratio:
- As particle size decreases, the surface area to volume ratio increases significantly. According to the Noyes-

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Whitney equation, the dissolution rate (dC/dt) is influenced by the available surface area (A), the concentration gradient (Cs - C), the diffusion coefficient (D), and the thickness of the boundary layer (h).

- The equation is expressed as:
- dCdt=D·A·(Cs−C)h\frac{dC}{dt} = \frac{D \cdot A \cdot (Cs - C)}{h}dtdC=hD·A·(Cs−C)
- By decreasing particle size, A (surface area) increases, leading to an enhanced dissolution rate.
- Ostwald-Freundlich Equation:
- The solubility of small particles is influenced by their curvature. Smaller particles exhibit higher solubility because molecules at the surface of a small particle experience greater energy compared to those on a larger particle. This relationship is expressed by the Ostwald-Freundlich equation:
- ln⁡(SS0)=2γVmrRT\ln\left(\frac{S}{S_0}\right) = \frac{2 \gamma V_m}{rRT}ln(S0S)=rRT2γVm
- Where:
- S = solubility of the particle,
- S_0 = solubility of a flat surface,
- γ\gamma = surface tension,
- (V-M) = molar volume,
- R = radius of the particle,
- R = gas constant,
- T = temperature.

This shows that as particle size (r) decreases, solubility (S) increases due to the rise in surface tension (γ\gamma).

2. Techniques for Particle Size Reduction

Various methods are used to achieve particle size reduction. These techniques can reduce particles from micron size to nanoscale dimensions, each with specific advantages and considerations.

- Micronization:
- Process: Micronization is a mechanical process that reduces particle size using jet mills, ball mills, or hammer mills. It typically brings particles down to the micron level (1-10 microns).
- Advantages: This method enhances the dissolution rate significantly, especially for drugs with low solubility. It is also relatively simple and scalable.
- Limitations: Micronization may induce particle agglomeration, where small particles stick together, reducing the benefits of size reduction. Furthermore, it doesn't always achieve nanoscale sizes.
- Nanosizing (Nanomilling):
- Process: This process reduces particles to nanometer size, typically <1000 nm. Common methods include wet milling, high-pressure homogenization, and solvent evaporation techniques. Nanoparticles exhibit greater solubility due to a much larger surface area and altered thermodynamic properties.
- Advantages: Nanosizing offers a higher surface area-to-volume ratio, leading to rapid dissolution, increased absorption, and better bioavailability.
- Limitations: Nanoparticles may suffer from physical instability, leading to aggregation or recrystallization over time. Stabilizers or surfactants are often needed to maintain particles.
- Spray Drying:
- Process: This involves dissolving the drug in a suitable solvent and then spraying it into a heated chamber where the solvent evaporates, leaving behind fine particles. Spray drying can produce both micro- and nanoparticles.
- Advantages: It is suitable for both crystalline and amorphous forms of the drug. Spray drying can also be used to produce amorphous solid dispersions, which have higher solubility than their crystalline counterparts.

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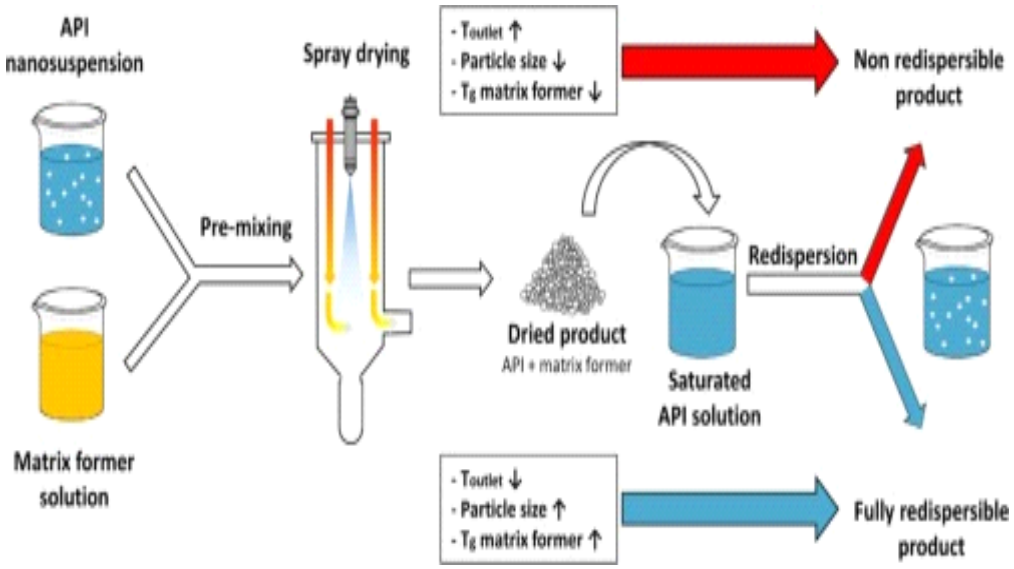
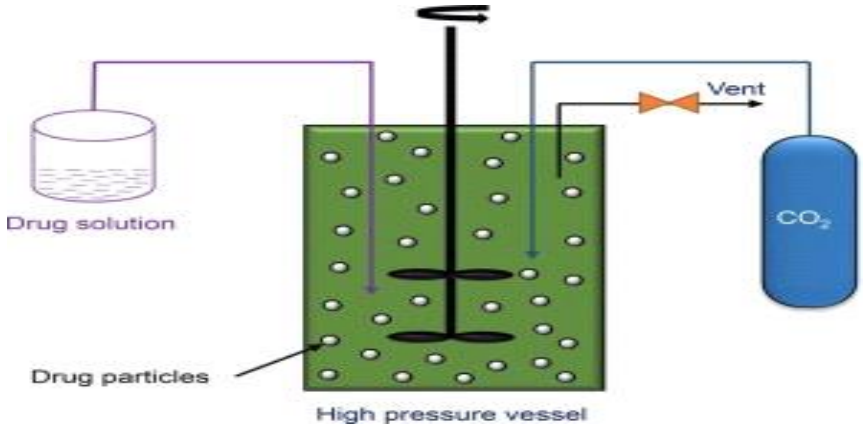
- Limitations: The process can be complex, and handling the fine particles may present manufacturing challengescle dispersion.



- Supercritical Fluid Techniques:
- Process: This method employs supercritical fluids, such as carbon dioxide, to dissolve the pharmaceutical compound, subsequently leading to the formation of fine particles through an expansion process.
- Advantages: The technique yields particles that are uniform in size with a narrow distribution, while eliminating the need for organic solvents.
- Limitations: The application of supercritical fluid methods is intricate and necessitates specialized apparatus.



3. Benefits of Size Reduction

- Enhanced Dissolution Rate: The primary benefit of size reduction is the enhanced dissolution rate, which is especially crucial for Biopharmaceutical Classification System (BCS) Class II drugs (poorly soluble, highly permeable).
- Improved Bioavailability: Drugs with better dissolution profiles tend to have improved bioavailability, meaning more drug is absorbed into the bloodstream. This leads to more consistent therapeutic effects and potentially lower required doses.
- Faster Onset of Action: Drugs that dissolve faster will reach therapeutic concentrations in the bloodstream more quickly, leading to a faster onset of action.
- Enhanced Stability: In some cases, reducing particle size (especially in conjunction with stabilizers or excipients) can enhance the stability of the drug, preventing degradation or recrystallization.

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III. RESULTS AND DISCUSSION

Three compounds with different acid-base properties were chosen to study the particlesize reduction effect on BRM solubility and dissolution. The equilibrium solubility of the original substances, the micronized forms, their physical mixtures with excipients used for nanonization and two nanonized forms (altogether 24 samples) were measured by the standardized SSF method at 37 _C in four solvents (FaSSIF blank and full, FeSSIF blank and full). Their dissolution in the same media was measured by in situ real-time monitoring using the _DISS device. The particle size was analyzed by Laser Diffractometry and Scanning Electron microscopy. The particle size distribution of the original and the micronized compounds are shown in Table 2 using the d = 0.1, 0.5 and 0.9 values. These values show the upper limit of the size range in _m, under which 10%, 50% and 90% of the particles belong. We have to note that the original, commercially available substances were not macrocrystalline materials, their particles' size were in the _m range, but size reduction by milling caused a significant decrease. These samples are referred to here as micronized.

3.1.1. Solubility Measurements

As a base with p*K*a = 6.36, it is more soluble in pH = 5.0 media than in buffers of pH = 6.5, because in the first case 95.8% of the molecules are protonated, which results in an increased polarity and therefore an increased aqueous solubility [20,24]. The solubilizing effect of the SIF powder is prevailing in both the FaSSIF and FeSSIF full buffers, resulting in a higher solubility of the compound than in the blank buffers. Micronization, as expected, did not cause a significant difference in equilibrium solubility compared to the original substance. The nanonization has led to different results: nano-sized compounds with PVPK excipient (nanoPVPK) resulted in a higher solubility, but nanonization with PVA (nanoPVA product) did not have an effect on it. PVP polymers are known for enhancing the aqueous solubility of active pharmaceutical ingredients [25]. Our experiments show that, in the case of papaverine hydrochloride, the addition of PVPK to the original and the micronized substance slightly but significantly increased the equilibrium solubility. Therefore, the solubility enhancement can be attributed to the particle size reduction and the use of PVPK excipient simultaneously.

3.1.2. Dissolution Measurements

The dissolution of the samples in different media is shown in Figure 2. For the better visualization of the supersaturation and the precipitation, the dissolution of papaverine hydrochloride in Asif blank, full and blank media is enlarged and depicted in Figure S3.

In all tested media, the samples exhibited significant supersaturation followed by precipitation until they achieved equilibrium concentration. Due to the partial amorphization observed in the nanonized samples (refer to Figure 3A), the dissolution rate and supersaturation levels in these instances are not pertinent; however, the results from real-time monitoring allow for the determination of the time required to reach equilibrium. It is important to note that the equilibration time varies depending on the medium used. In the FaSSIF blank buffer, all samples precipitate almost instantaneously. Conversely, in the FaSSIF full medium, which includes SIF powder (sodium taurocholate and lecithin as solubilizing agents), this process is prolonged, with equilibrium being reached within a timeframe of 1 to 4 hours. The presence of SIF powder may contribute to the extended period of supersaturation. Additionally, due to the ionization state, the solubility of the compound in the FeSSIF blank medium is approximately ten times greater than that in the FaSSIF blank buffer. This discrepancy may account for the lower degree of supersaturation observed in the FaSSIF buffers and could also explain the longer equilibration time. Furthermore, the concentrations of the samples in the FeSSIF full medium, as well as the nanoPVPK sample in the FeSSIF blank buffer, surpassed the instrument's measurement limits, resulting in an inability to conduct measurements in these instances.

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