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Review Article

Contemporary Review on Solubility Enhancement Techniques

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Abstract

The limited water solubility of pharmacoactive molecules hinders their ability to be used as pharmacological agents, yet the indispensability of a certain solubility parameter precludes any compromises. To overcome this challenge, various methods are employed in order to increase their bioavailability. Pharmaceutical molecules with lower solubility present an elevated risk of failure for drug development and innovation. Their solubility affects important processes such as pharmacokinetics, pharmacodynamics, distribution, protein binding, and absorption. As a result these parameters are greatly impacted by the dissolution rate of a particular molecule. Out of all pharmaceutical dosage forms, more than half are oral. For the drug molecule to reach its target site and be effective therapeutically, solubility and bioavailability must be taken into consideration. Unfortunately, during screening programs conducted by the pharmaceutical industry it became evident that nearly 40% of new chemical entities (NCEs) face various roadblocks when transitioning from formulation to development due to their poor solubility and bioavailability. The pharmaceutical industry is constantly confronted with the difficulty of improving drug bioavailability and solubility in formulations. This article covers a range of technological advancements to boost the solubility of insoluble drugs, such as complexation, emulsions and micelles production, microemulsion generation with cosolvents, polymeric micelle preparation methods, particle size decrease techniques, pharmaceutical salts application, prodrugs usage, solid-state alteration practices, soft gel technology implementation crystal engineering approaches and nanomorphology. Through this review, we will discuss a variety of more complex methods for improving solubility and bioavailability such as crystal engineering, micronization, solid dispersions, nano sizing, and use of cyclodextrins, solid lipid nanoparticles (SLNPs), colloidal drug delivery systems and drug conjugates. We'll also provide references to studies that have been conducted in connection with these topics.

Keywords: Solubility, permeability, bioavailability, nano particles drug delivery systems, microemulsions, low water solubility

1. Introduction:

Understanding the solubility, solution properties, and gastrointestinal permeability of a drug is vital for determining just how much is absorbed into the system as well as its absorption speed - all of which contribute to its overall bioavailability. After oral administration of a drug, the rate at which molecules or dosage forms dissolve into solution is pivotal for successful absorption. This process - known as solubility - plays an essential role when dissolution time frames are limited[1–3].

Nevertheless, the drug's absorption and effectiveness relies on water solubility, dissolution velocity, permeability to drugs, susceptibility to efflux processes as well as first-pass metabolism. "Solubility" is the ability of a solute to dissolve in a given solvent, and is usually represented by its concentration in terms of parts, percentage, molality, molarity, volume fraction or mole fraction. It can also be defined as the quantity of solute which dissolves in a certain amount of solvent at an established temperature. Solubility is a phenomenon that occurs when two substances combine to form a single homogenous solution on the molecular level. The solute and solvent achieve an equilibrium in the saturated solution, forming a unified entity of equal parts. In the last couple of years, drug detection has revealed a dramatic rise in drugs that are difficult to dissolve. An astonishing 70% of newly-developed medications have been identified as having low solubility in water. Pharmaceutical experts face a major challenge in drug development: to devise an effective way of increasing the dissolution rate and bioavailability of drugs with low solubility. In vivo studies have shown that these factors are critical for determining the success of oral formulations, so understanding their intricate workings is fundamental to improving results. Through careful analysis in vitro, researchers can gain insight into how they might be able to improve those rates and thus ultimately enhance the efficacy of such treatments[4–10].

To permit a medicinal product to be absorbed effectively, it must first dissolve in water at the point of absorption. The solubility and permeability serve as reliable indicators of enhanced absorption in vivo. With the help of advanced

solubility improvement techniques, these two factors can be dramatically improved. Quercetin is a polyphenolic flavonoid compound with potent antioxidant properties, making it an ideal candidate for countering the proliferation of cancerous cells in organs such as the lungs, ovaries, and breasts. Unfortunately, its hydrophobic nature limits the effectiveness of Quercetin due to poor solubility and low bioavailability[11–14].

To increase solubility and bioavailability of quercetin nanoparticles, high-pressure homogenization as well as bead milling processes were applied in a top-down manner. On the other hand, EPN (evaporation precipitation of nanosuspension) was used to achieve the same result from a bottom-up strategy. Over the past few decades, solid dispersion technology has become a focal point for research to create an amorphous carrier and boost bioavailability, solubility and dissolution rate of drugs with low water solubility[15–17]. Nevertheless, it is imperative to carefully select carriers when preparing solid dispersions as they will play a decisive role in its biological performance. To improve the solubility, bioavailability and therapeutic efficacy of drugs, consider these various techniques to prepare amorphous solid dispersions: (a) cryogenic processing, (b) freeze drying, (c) fluid-bed coating, (d) spray drying (e) microwave irradiation ,(f)co-precipitation method ,(g)electrostatic spinning ,(h) supercritical anti-solvent technique ((SAS), (i)HME approach ,(j) MeltrexTM strategy, and finally the KinetiSolVR dispersing technique. With this variety of methods you will be able to ensure optimal performance in your drug application. The solubility of any drug is heavily determined by the chemical make-up and the components of its solution[18–23].

2 Strategies for Maximizing Solubility

2.1 Physical Modifications

2.1.1 Particle Size Reduction

The solubility of any drug is highly dependent on its particle size; larger particles have a decreased surface area, thus limiting the interaction between them and their surrounding solvent. However, to improve this dissolution property and increase the total surface area of said drug, we can reduce its particle size - leading to more efficient absorption rates.

a) Micronization:

Creating micron-sized drug particles through physical means such as freeze-drying, crystallization, spray drying and milling is often used to improve the solubility of drugs belonging to Biopharmaceutics Classification System (BCS) Class II. To reduce particle size in a conventional manner, mechanical methods such as grinding, milling, and crushing are applied. This is done by subjecting the heavier particles to friction, pressure, and attrition shearing or impact forces. For achieving micronization through mechanical means jet mills and high-pressure homogenizers are employed while ball mills remain the most preferred option for dry milling which is an efficient method of micronizing materials[24–30].

b) Nanosuspension:

Nanosuspension is a colloidal dispersion of sub-micron drug elements, stabilized with the assistance of surfactants. To create this suspension, wet milling and homogenization are used as methods. Milling breaks up the active compound in combination with a surfactant to generate nanoscale particles. There are two main ways to construct a nanosuspension—"bottom-up" and "top-down" technology—which can provide excellent results. With these two methods, you're sure to make the most of your nanosuspension preparation[31–33].

c) Milling Techniques

i. Media milling

Utilizing the media milling process, drug nanoparticles are created through the collision of drugs and grinding means.

ii. Dry grinding

This process involves taking polymers and soluble copolymer with a barely-soluble drug, dispersing it in liquid medium and then utilizing dry grinding to form nanosuspensions.

d) Lipid Emulsion/Microemulsion Template

A microemulsion is a mixture of oil, water and stabilizer (cosurfactant or surfactant) fluids that are not miscible. The drugs can be introduced into the internal phase in order to create a microemulsion, or they can form part of an informal mixture upon saturation. By using H_2O, taurodeoxycholate sodium salt, butyl lactate and lecithin as components in this process we have developed Griseofulvin nanosuspensions[34–39].

e) Microprecipitation—High-Pressure Homogenization (Nano Edge)

By combining the high-pressure homogenization and microprecipitation techniques, this procedure can effectively precipitate breakable components which then breakdown into smaller parts.

f) Nanojet Technology

The Reverse Flow Technique, developed by Nanojet, is an innovative procedure in which a suspension current is split into two or more parts. The high pressure colloids interact to create a tremendous shear force that leads to the reduction of particle size[40–43].

2.1.2 Modification of the Crystal Habit

a) Crystal engineering: Through the utilization of Crystal engineering, scientists are researching techniques to wisely design and synthesize crystalline solids which contain a specific combination of ions and molecules. This method capitalizes on non-covalent interactions among ionic or molecular components allowing for solid structures with remarkable optical, magnetic and electrical properties[44,45].

b) Hydrates/solvates: Solvates are advanced molecules that form a crystal lattice with solvent molecules at their core. These hydrated variants, in which the solvent is H_2O, have become known as hydrates and have been found to possess incredible properties[46–48].

c) Polymorph: Polymorphs are a phenomenon where different crystal structures of the same chemical composition exist, resulting in disparate physical and chemical properties due to their distinct network architecture and molecular conformation. Many drugs often crystallize into polymorphism for enhanced solubility, demonstrating just how commonplace this occurrence is.

2.1.3 Drug Dispersion in Carriers

a) Eutectic Mixtures

Blending two or more substances typically does not form a homogenous entity; however, at certain proportions, the components can inhibit each other's crystallization process. This creates an amalgamation with a melting point lower than either of the starting ingredients alone[49–51].

b) Solid Dispersion

Combining a hydrophilic matrix and a hydrophobic drug forms amorphous clusters or crystalline particles[52,53].

c) Solvent evaporation method: To form a solid, the total dissolution of both drug and carrier in an organic solvent is evaporated. Subsequently, this dense mass must be ground down to size before it can be sieved and dried - such as when preparing furosemide with eudragits[16,54–56].

d) Hot-melt extrusion method:

Through the hot-stage extrusion technique using a co-rotating twin-screw extruder, carriers and active pharmaceutical ingredients are combined with a drug concentration of 40% (w/w). This method is highly effective for creating diverse dosage forms such as sustained-release pellets[57–60].

e) Kneading technique: By using this method, the drug carriers with H_2O are turned into a paste. Then, blend in the drug compound and press it for a fixed time frame. After pressing is complete, pass through a sieve until fully dried[61–63].

f) Co-precipitation method: A specific amount of the drug must be mixed into the carrier solution under continuous magnetic stirring, and this mixture needs to remain away from sunlight for successful co-precipitation[64–66].

g) Melting method: Mix your drugs and their carriers using a mortar and pestle, then heat the mixture until all ingredients have completely melted to achieve an even dispersion. Cool it down afterward to acquire a solid mass; further reduce this by crushing and sieving out any larger particles - like albendazole or urea. Perfectly homogenous results each time[67–73].

h) Co-grinding method: The combination of the carrier and drug is carefully crafted using a blender, combining ingredients with precise timing and speed. The mixture is then transferred to the vibration ball mill where steel balls are added for pulverization. Following this process, samples are removed and stored at room temperature - such as chlordiazepoxide and mannitol.

i) Gel entrapment technique: To create a clear and understandable gel, an organic solvent is applied to dissolve hydroxyl propyl methylcellulose. Furthermore, the drug compound is liquefied into the mixture through sonication for a certain time period. After removing the organic solvent via vacuum, these solid dispersions are then taken with a mortar and pestle in order to reduce their sizes before being further filtered using sieves.

j) Spray-drying method: To create a clear solution for medical purposes, the required amount of drug must first be solubilized in water with appropriate agents and vehicles. Sonication or additional techniques can then be used to prepare this solution which is later spray-dried in a special dryer specifically designed for such use[74–78].

k) Lyophilization technique: This process was proposed as an alternate to the solvent evaporation approach. It is a kind of molecular blending procedure in which drug compounds and their carriers are integrated, solubilized with a universal solvent, frozen solid then sublimed in order to create a lyophilized molecular distribution that involves both heat transfer and mass from the product being prepared.

l) Melt agglomeration process: This process is distinctive from other strategies, as the binder itself works to fabricate a homogenous solid dispersion. Furthermore, this can be done by either raising the drug compound's temperature above its melting point alongside its excipient and binder or using a high shear mixer. Once all constituents are warmed up, droplets of the dissolution are sprayed onto them in order to achieve an unblemished dispersion. By offering convenient temperature management and a high binder content, rotary processors are an ideal supplement to any equipment setup[60,79].

m) Solid Solutions

When two elements mix, they form a distinct, homogenous phase that is known as a solid solution. Solid solutions can be divided into two distinct categories: substitutional and interstitial. Substitutional solid solutions come in both random and ordered varieties, while interstitial solid solutions are composed of atoms that are situated between the original lattice structure points[80–82].

2.1.4 Solubilization by Surfactants Microemulsion

Microemulsions are a unique combination of two liquids—such as oil and water—that form an unstable, transparent mixture. To stabilize the emulsion, surfactants act as interfacial films which help to alleviate them.

a) Components of microemulsion

Aqueous phase: Water is the most commonly used liquid phase. To ensure successful execution, its pH must be adjusted accordingly. For instance, in microemulsions that are intended for parenteral administration - it should be isotonic with blood; this is achieved by incorporating sodium chloride, glycerol, dextrose and sorbitol within the aqueous phase.

Oil phase: Careful selection of oil is essential to the drug administration process, as it should ensure optimal solubilization potential for the medication being used. Additionally, when exposed to unsaturated and saturated fatty acids, this oil will have an increased penetration rate due to its ability to alter shape and expand surfactant tail assembly. Oleic and Isopropyl Palmitate, two unsaturated fatty acids employed to increase permeability of the stratum corneum, interact with dense lipids within this layer. Each drug reacts differently when exposed to oleic acid-based penetration enhancers; thus it is essential for researchers to understand how their desired drug interacts with multiple fatty acids before implementing them into a formula or treatment plan. In particular, Isopropyl Palmitate is an exceptionally well-known ester used specifically for enhancing skin absorption rates in cosmetics and dermaceuticals alike.

Nowadays, more people are turning to semi-synthetic oils because they're far sturdier than their natural counterparts. Low water solubility medications must possess the capability of dissolving in oil so that a potent oil/water microemulsion can be formed. The size of droplets within this microemulsion will get bigger if more oil is included.

Surfactant: Surfactants are molecules consisting of a hydrophilic head and a hydrophobic tail. At interfaces between two systems, they reduce interfacial tension by lowering the concentration of surfactant at that interface. Their main

objective is to effectively minimize this tension so it's almost nonexistent, promoting microemulsion formation during dispersion. The microemulsion must possess the proper lipophilic character to achieve its optimal form, and that's where surfactants come in. Surfactant molecules unite both polar and non-polar groups within themselves through their Hydrophilic Lipophilic Balance (HLB) value. This HLB value can indicate which kind of emulsion is being formed - either an o/w or w/o emulsion – so it needs to be carefully chosen for maximum efficacy[83–89].

Co-surfactants: Co-surfactants are amphiphilic, accumulate at the interfacial layer, and increase the fluidity of interfacial film by penetrating the surfactant layer. Single-chain surfactants are unable to decrease the interfacial tension of o/w to form a microemulsion. Chain alcohols are used, utilizing co-surfactants to increase the fluidity of the interface.

Classification of microemulsion

Depending on their composition, microemulsions can be broken down into three distinct classifications: oil-in-water (o/w), water-in-oil (w/o) and bi-continuous. Each of these types offer unique properties for a range of applications across many industries.

To make sure that the ingredients in microemulsions remain stable, use a balanced combination of surfactants and/or other stabilizing agents. If you're looking for ways to create your own microemulsion, there are several methods available depending on what components you need to include:

Self-Emulsifying Drug Delivery Systems (SEDDS)

To resolve the issue of low bioavailability with poorly soluble and porous drug molecules, this scheme has been devised. Hydrophobic drug molecules can be liquefied within this system. Upon administering these constituents in the GI tract, they'll interact with intestinal fluid to form a micro/nanoemulsion- hence why it is called Self Emulsifying Drug Delivery System (SEDDS). This emulsion will then enable an increase absorption rate for drugs into systemic circulation. As a result, drug solubility is heightened, and absorption occurs through lymphatic pathways that sidestep the initial hepatic metabolism. Research has indicated various in vivo aspects of the lipid preparations are connected to increased bioavailability[90–93].

Formulating a self-emulsifying drug delivery system:

To formulate SEDDS, a variety of excipients are utilized such as oils, surfactants, co-surfactants, viscosity enhancers, polymers and antioxidant agents. With each ingredient playing their own unique role in the process to create an effective delivery system for drugs with poor solubility.

2.1.5 Complexation

Through the formation of various molecular bonds, such as hydrogen bonds and hydrophobic interactions, two or more molecules can be combined to form a unique entity. This balance is held in place by relatively weak forces known as London Forces. Stanching Complexation offers an effective way to tap into this phenomenon and utilize these compounds for our benefit.

a) Inclusion Complexation

Inclusion complexation has been developed as a technique to combine nonpolar particles or fragments of guest molecules into the cavities of distinct particles or collections of molecules (known as hosts). This process requires ideal alignment between the host and guest molecule in order for the inclusion complexing to be successful. In order for the host particle to properly house the guest molecule, it must have a cavity spacious enough without being too large, as that would minimize interaction between H_2O and nonpolar domains of both molecules. The three naturally occurring cyclodextrin variants are α-, β- and γ-cyclodextrin. Cyclodextrin is utilized to boost solubility through complexation. This molecular phenomenon creates a cavity that allows one guest particle to form and establish stable associations. Cyclodextrin molecules are comprised of an external hydrophilic activity, as well as its inner hydrophobic characteristic due to the arrangement of its hydroxy group. Analyzing the positions of either a one-step reaction or two-sequence reactions with structural transformations can prove to be a difficult task. However, cyclodextrins have made it possible for us to do so as they enhance the solubility of drug molecules via inclusion complexation. Many drugs such as clofibrate, rofecoxib, melarsoprol, celecoxib, cyclosporin A and Taxol now offer better water solubility owing to their complex formation with cyclodextrin[94–96].

b) Peptide Complexation

Using protein nanoparticles to deliver materials such as genetic matter, water-insoluble drugs, peptide hormones, growth factors and DNA/RNA has many benefits. In comparison with other suspended carriers, these particles boast stability whilst being easier manufacture. Consequently this makes them an ideal material for drug delivery systems. By utilizing a straightforward, economical, and eco-friendly synthesis process, proteins from various sources can be transformed into nanoparticles with minimal chemicals. These particles have been observed to possess great potential for in vivo applications. Chang et al. observed that the hydrophobic encapsulation of cur- cumin in egg white protein nanoparticles was enhanced, thus effectively decreasing its degradation rate and safeguarding its antioxidant activity when compared to non-encapsulated particles[97–99].

c) Cryogenic Techniques

Cryogenic techniques are employed to improve the dissolution speed of drugs by formulating an amorphous drug of the nanostructure with a high degree of porosity at minimal temperatures. Afterwards, on completion of cryogenic treatment, the powder is dried via the drying method (vacuum, spray, and lyophilization).

2.2 Chemical Modifications

2.2.1 pH Adjustment

The pH of the solution can profoundly impact drug solubility, as it changes the electric charge state of molecules. When a substance carries no net charge at a certain pH level - referred to as its isoelectric point (IEP) - it often precipitates out from water and has minimal solubility. Thus, adjusting solution acidity or alkalinity through varying pH levels plays an essential role in determining drug solubility.

2.2.2. Hydrotrophy

This is a solubility breakthrough; with it, the dissolution of the solute can be improved by loading up on extra amounts of another substance. The phrase hydrotrophy was once used to characterize non-micelle-forming materials that could help

dissolve insoluble substances - these materials may range from organic or inorganic components to either liquids or solid states.

2.2.3 Co-Crystallization

Co-crystals are an innovative solution to challenges related to physical properties, like drug solubility, bioavailability and stability - all without altering the chemical structure of APIs. This approach is especially advantageous for molecules with low pharmacological properties caused by nonionizable functional groups, offering a variety of approaches to crystallize them[100–102].

2.2.4 Co-Solvency

As the structural complexity of newly developed entities rises, its water solubility drastically decreases. To obtain high solubility with a compound that has low therapeutic dose when it is dissolved in H_2O, co-solvents are brought into play to heighten drug's solubility by providing multiple nonpolar groups and increasing its aqueous (water) solubility. Thus, making them essential for pharmaceutical formulation as they may be required at times to improve the drug's ability to dissolve in water.

2.2.5 Salt Formation

Compared to their salts, acidic and basic drugs have exceedingly low solubility in water. Therefore, for the purpose of parenteral administration, salt formation is greatly preferred as it significantly enhances solubility.

2.2.6 Nanotechnology in Pharmaceuticals

Nanotechnology can enhance the solubility of drugs which have poor aqueous solubilities. Nanoscale structures and materials that measure up to 100nm are explored in depth for this purpose, and as opposed to micronization, tend not to agglomerate and thus retain an effective surface area for dissolution.

The application of Nanotechnology for nanonization presents us with many possibilities. For example, the use of nanomorphs, or drug nanocrystal technology have demonstrated remarkable success in recent years[103–105]. Various strategies that are available for solubility enhancement are captured in Figure 1.

Figure 1: Various strategies for solubility enhancement

2.3 Miscellaneous Methods

2.3.1 Supercritical Fluid Technology

This innovative technique was and still is widely used for crystallization and precipitation of materials due to its safety, environmental friendliness, and low-cost nature. The temperatures and pressures required are comparatively lower than other methods making it a preferred choice amongst pharma research professionals. Above this critical pressure (Pc) and temperature (Tc), an SCF remains as one phase.

2.3.2 Micellar Solubilization

Micellar solubilization is a process in which insoluble components can be easily and effectively incorporated into or onto micelles. A benefit of this technique is that it significantly improves the water-solubility of otherwise difficult to mix substances. This method offers an efficient way for compounds to become more soluble, making them easier to work with moving forward. By way of definition, solubilization is the reversible interaction between a surfactant's micelles and a compound in water to form an isotropic solution with a lowered thermodynamic activity for the solubilized substance.

a) Cyclodextrins

Cyclodextrins are circular oligosaccharides with an exterior that's hydrophilic in nature and a moderately hydrophobic central cavity. When combined with certain drugs, cyclodextrin molecules form water-soluble complexes to enhance their solubility. Furthermore, they have been found to play a major part in the production of non-inclusion complexes. Over the last two to three decades, numerous studies have been conducted on cyclodextrins and their complexes. These investigations

provided a wealth of data about the physical requirements for complex formation as well as associated forces. Hydrophobic drugs which form complexes with is positioned in an aqueous medium are also identified. Additionally, surface-active preservatives and water-soluble polymers can be used to improve solubility of such drugs[106–108].

b) Solid-Lipid Nanoparticles

Solid-lipid nanoparticles are an innovative and efficient way to deliver drugs with exacting precision. Not only do they possess biocompatible and biodegradable properties, but their average size range of 50 nm - 1000 nm makes them incredibly versatile. Plus, the solid hydrophobic phospholipid coating on these particles facilitate transport both of hydrophilic or hydrophobic drugs across the matrix. By utilizing this novel drug delivery system, you can rest assured that your medicine will reach its intended target in a safe and reliable manner. For more information about solid lipid nanoparticles, please look into the Table 1.

Table 1: A detailed list of formulations developed by solid lipid nanoparticle approach

Drug	**Lipid Utilized**	**Biopharmaceutical Application**
5-Fluoro uracil	Dynasan 114 and Dynasan 118	Prolonged release in simulated colonic media
Ibuprofen	Stearic acid, triluarin and tripalmitin	Stable formulation with low toxicity
Apomorphine	Glycerylmonostearate, polyethylene glycol monostearate	Enhanced bioavailability in rats
Idarubicin	Glycerylmonostearate, polyethylene glycol monostearate	Enhanced bioavailability in rats
Idarubicin	Emulsifying wax	Delivery of oral proteins
Calcitonin	Trimyristin	Improvement of the efficacy of proteins
Lopinavir	Campritol 888 ATO	Bioavailability enhanced
Clozapine	Trimyristin, tristearin and tripalmitin	Improvement of bioavailability
Nimesulide	Glycerylbehanate, glyceryltristearate, palmitostearate	Sustained release of the drug
Cyclosporin A	Glycerylmonostearate and glycerylpalmitostearate	Controlled release
Progesterone	Monostearin, oleic acid and stearic acid	Potential for oral drug delivery
Gonadotropin release hormone	Monostearin	Prolonged release
Repaglinide	Glycerylmonostearate and tristearin	Reduced toxicity

c) Polymeric Micellar Carriers

Enhancing the solubility of poorly water-soluble compounds in surface-active agents can forestall drug precipitation when exposed to gastrointestinal conditions. Three systems where dynamic equilibrium ensues, including monomeric surfactants, micellar aggregates and surfactants adsorbed as a film at an interface are present in a surfactant solution. Exceeding the critical micellar concentration (CMC) in a surfactant solution initiates micelle formation. Once dissolved, amphiphilic chain copolymers structures made of both hydrophobic and hydrophilic segments create micelles. The inner and outer layers of the micelles are generated by hydrophobic domains and

hydrophilic tails in the copolymer, respectively. In this way, contact between aqueous mediums and hydrophobic drugs is stabilized through their encapsulation by the corona. Additionally, deposits of lipophilic medicines can be loaded into these cores to improve solubility levels within them. Recently, amphiphilic block copolymers were identified as far more reliable alternatives to deliver hydrophobic medications with amplified bioavailability. The amalgamation of hydrophilic and hydrophobic polymeric segments in an amphiphilic block copolymer results in a precise synthesis that can be achieved through ATRP, RAFT, or radical polymerization. This technique has been effectively demonstrated by multiple researchers to create the desired product. The combination and amount of co-polymeric segments within these block copolymers are paramount in order to guarantee maximum efficiency and bioavailability for the delivery[109–111].

d) Mesoporous Silica Particles

Porous silica-based drug delivery systems have demonstrated significant potential in improving the oral administration of water insoluble drugs. Particularly, micro and meso porous silica carriers present high surface areas which allow them to adsorb a large amount of drug molecules or amorphous forms; these can then be released into an aqueous gastro-intestinal environment through supersaturation, leading to increased absorption and bioavailability. Also, mesoporous silica particles are very useful in transdermal drug delivery for enhancing solubility and permeability[112–114].

3. Conclusions

From prodrug strategies to particle size reduction technologies and nanosizing, this review provides a detailed analysis of existing and developing pharmaceutical technologies. Additionally, it summarizes some current breakthroughs such as formulation design, solid dispersions, crystal engineering, micronization techniques,, cyclodextrins, nanoparticles made from lipids or drugs conjugates, exploring the depth of colloidal drug delivery systems, complexation of drugs, forming emulsions and micelles through microemulsion and cosolvents technology, synthesizing pharmaceutical salts for prodrugs application as well as solid state alteration, employing soft gel along with nanocrystals-nanomorph technology to comprehend its cutting edge advancements coupled with research reports.

Enhancing the drug's bioavailability and solubility are important hurdles in pharmaceutical formulations, particularly when it comes to NCEs. Researchers are currently developing numerous techniques to improve the solubility of poorly soluble molecules, such as using new excipients. To optimize these methods, scientists have been rigorously studying the molecular properties of poor-soluble compounds and formulating ideal solutions that can potentially overcome all cases, with an overall goal to provide 100% dissolution efficacy. Though we may be far from realizing it, in the near future scientists will likely have the ability to predict which polymer is best suited for a specific technique based on models of molecules and their corresponding properties. This could drastically accelerate processes by allowing us to find answers more quickly than ever before.

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