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Exploration of Solubilization Strategies: Enhancing Bioavailability for Low Solubility Drugs

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ABSTRACT

This review explores various strategies aimed at improving the solubilization of low-solubility drugs, including formulation design, nanoparticle technologies, prodrug strategies, and particle size reduction methods. Water solubility plays a crucial role in shaping bioavailability, formulation strategies, and therapeutic efficacy. Nanotechnology, particularly in nanomedicines, is a promising avenue to tackle solubility challenges, but faces barriers like production costs, formulation reproducibility, and varying pharmacokinetics. Despite these challenges, the burgeoning landscape of innovative drug delivery technologies offers advantages, particularly for formulation scientists. Understanding molecular properties is crucial for resolving these challenges, with solid dispersions and lipid-based delivery techniques emerging as sought-after solutions. Commercializing these advancements requires a leap in technology and infrastructure, making it essential to streamline the process and identify optimal approaches. Pioneering methodologies, such as Fagerholm's predictive model for human oral bioavailability based on chemical structure, demonstrate promising predictive accuracy. The integration of artificial intelligence and innovative solubility enhancement technologies is pivotal in transforming drug delivery, tackling solubility concerns, and streamlining research and development expenses.

Keywords: Drug Solubility, Bioavailability Enhancement, Molecular Properties, Solid Dispersions, Lipid-based Drug Delivery, Nanotechnology.

INTRODUCTION

Solubility implies the dissolution of a solute (substance) in a solvent (liquid), creating a uniform mixture. It denotes the maximum solute concentration achievable in a solution under defined pH, temperature, and pressure conditions^[1]. Solubility can be described using various terms, including parts of solvent, percentage, molality, molarity, mole fraction, volume fraction and more^[2]. Solubility is typically assessed using two primary approaches: thermodynamic solubility and kinetic solubility. The key difference lies in the way the solid compound is introduced into the solution. For thermodynamic solubility, directly adding the solid compound to the aqueous solution

allows for evaluating its dissolution extent. On the other hand, for kinetic solubility, the compound that's already dissolved is used as the starting point to determine how much of the molecule precipitates. Thermodynamic solubility concerns itself with determining the quantity of a substance capable of dissolving within a solution. In contrast, kinetic solubility focuses on determining the amount of the molecule capable of precipitating from the solution^[3].

The pivotal role of thermodynamic solubility in determining the solubility of poorly soluble drugs is evident. Additionally, dissolution has a strong correlation with thermodynamic solubility. It's crucial to distinguish between 'dissolution' and 'solubility'. Dissolution represents the phenomenon

in which a solute, regardless of its phase—whether gaseous, liquid, or solid—dissolves in a solvent to yield a solution. On the other hand, 'solubility' is the maximum concentration of a solute that can dissolve in a given solvent at a given temperature ^[4].

Solid dosage forms of drugs administered orally undergo disintegration, breaking down into smaller particles or primary elements. The drug molecules' capacity to dissolve more efficiently in gastrointestinal tract (GIT) fluids is improved through this fragmentation as opposed to intact tablets. Following molecular dissolution, the drug penetrates the intestinal barrier ^[5].

Having sufficient water solubility is crucial for drug molecules to attain the necessary concentrations in the bloodstream for effective therapeutic results, as all bodily fluids primarily consist of water-based solutions. A drug molecule with extremely limited solubility will not dissolve in gastrointestinal tract (GIT) fluids. This lack of solubility impedes permeability its and subsequently affects its bioavailability, which is directly linked to the drug's solubility. Poorly soluble drugs tend to exhibit low bioavailability, resulting in the need for higher doses in the final formulation to attain the desired therapeutic effects. This can elevate the overall cost of the formulation and may even lead to potential toxicity issues^[6-7].

Drugs are classified into four BCS classes (Biopharmaceutical Classification System) based on their solubility and permeability within the gastrointestinal tract (GIT) ^[7-8].

BCS (Biopharmaceutics Classification System) class II drugs, despite high permeability, have low solubility. This leads to restricted bioavailability due to a decreased dissolution rate in the gastrointestinal tract. The restricted transport across biological membranes due to the small concentration gradient between the intestine and the bloodstream, attributed to low aqueous solubility, further exacerbates poor absorption. On the other hand, BCS class IV drugs not only

exhibit low aqueous solubility but also have low permeability, impeding their absorption. This reduced permeability poses challenges in drug development, as simply enhancing solubility and dissolution may not significantly improve their bioavailability. However, overlooking these compounds solely based on permeability challenges is not advisable. Strategies akin to those for BCS class II drugs, such as the use of absorption enhancers, can be employed in developing BCS class IV compounds. During the lead optimization stage, selecting a drug candidate with more appropriate physicochemical properties becomes a crucial formulation development approach for class IV drugs ^[9].

The necessity for efficient formulations for BCS-IV drugs classes Π and has propelled enhancing insufficient advancements in biopharmaceutical properties and comprehending oral drug delivery systems. It's essential to highlight that a significant number, nearly 90%, of new molecular entities belong to BCS classes II and IV. Additionally, reports indicate that only eight percent of newly discovered drug candidates exhibit ideal permeability and solubility. Notably, over one-third of pharmaceuticals listed in the US Pharmacopeia are either water-insoluble or poorly water-soluble [10].

Recent claims suggest that approximately 50% of drug molecules encounter development failure owing to inadequate aqueous solubility. The Lead exhibiting suboptimal compounds solubility characteristics frequently result in ineffective absorption at the site of administration, ultimately leading to increased rates of therapeutic loss because of unfavorable pharmacokinetics. The primary objective of a pharmaceutical company's R&D divisions is to optimize medication delivery to the intended site within the body for its intended therapeutic effect, achieving the highest efficacy in dosage^[11].

Our review centers on improving the solubility and bioavailability of drugs that dissolve poorly in

water. We examine traditional methods such as creating inclusion complexes, using supercritical fluid technology (SCF), employing cryogenic techniques, reducing particle size, and forming solid dispersions. These methods involve micronization, utilizing penetration enhancers or co-solvents, dispersing surfactants, forming salts, inducing precipitation, and other strategies. Yet, their ability to enhance drug solubility is somewhat constrained. Additionally, we explore alternative methods like vesicular systems like cyclodextrin inclusion complexes and solid dispersion which exhibit potential as drug delivery systems but have important limitations, like applicability to only certain drugs [13-14].

Various nanotechnological methods are utilized to improve solubility, such as dendrimers,^[15-16] micelles,^[17] solid lipid nanoparticles,^[18] liposomes,^[19] and polymeric nanoparticles.^[20]

The ability of a drug to dissolve in water significantly affects its effectiveness in the body, impacting absorption and overall bioavailability.

For years, traditional approaches such as particle size reduction, solid dispersion, co-crystallization, prodrug development, supercritical fluid technology, and inclusion complexes have been utilized to improve the solubility of poorly soluble drugs.

Nanotechnology holds promise in revitalizing drugs that have limited solubility, including previously promising candidates that were set aside due to this limitation.

Research is underway enhance the to bioavailability of poorly soluble drugs by exploring advanced nanocarrier technologies, including dendrimers, micelles, solid lipid nanoparticles (SLNs), metal-organic frameworks (MOFs), carbon nanotubes (CNTs), nanogels, and mesoporous silica nanoparticles. These advancements are crucial for future research and formulation development.

Traditional Methods

Traditional methods have been employed for many years to improve the ability of poorly soluble drugs to dissolve in water. Within the sphere of traditional approaches, these techniques encompass micronization, prodrug approach, solid dispersion, cyclodextrin inclusion complexes, supercritical fluid technology, and cryogenic technology.

Decreasing Particle Size

The bioavailability of drugs with low solubility is significantly impacted by the initial molecular dimensions of drug powder. Decreasing particle size augments the surface area, thereby enhancing dissolution properties through increased interaction with the solvent. Moreover, reducing particle size facilitates swift solvent diffusion. Various milling techniques, including rotor-stator colloid mills, jet mills, and other types, effectively reduce the particle size of raw drug materials ^[21].

Micronization methods can reduce particle sizes to less than 5 μ m in diameter, ensuring uniformity in particle size. Micronization may be achieved by various methods like milling, microprecipitation, microcrystallization, supercritical fluid technology, and spray freezing into liquids. These methods impact the properties of the micronized drug substance ^[22].

Cyclodextrin Inclusion Complexes

Inclusion complexes form when a guest molecule, which is non-polar, is introduced inside the cavity of another molecule or a cluster of molecules referred to as the "host molecules". This approach of creating inclusion complexes is highly effective in enhancing solubility, dissolution rate, and bioavailability of drugs. In this context. cyclodextrins (CDs) are the host molecules most frequently utilized. By encapsulating drug molecules within their disc-shaped hollow, they have the potential to notably modify the physicochemical and biological characteristics of therapeutics with low solubility. The hollow, lipophilic core cavity of CDs allows for attachment

of lipophilic compounds through various intermolecular interactions ^[23]. The preparation of inclusion complexes often involves methods like kneading, physical mixing, co-precipitation, and solvent evaporation ^[24].

Sherje et al. reported that Rivaroxaban (RIV), an anticoagulant, exhibits poor solubility. oral Specifically, it demonstrates a solubility of 0.005 mg/mL in water and 0.006 mg/mL in an acetate Rivaroxaban-loaded buffer at pН 4.5. β-Cyclodextrin-based inclusion complexes were effectively created through kneading, spray drying, and physical mixing techniques. The solubility of these complexes increased significantly in water by factors of 3.36, 2.34, and 4.02 for each respective method. Additionally, enhancements of 1.88-, 3.68-, and 1.78-fold were achieved in the acetate buffer^[23].

Solid Dispersions

Solid dispersions (SD) are a valuable technique for enhancing drug solubility, absorption, and thereby its therapeutic efficacy in oral dosage forms ^[25]. Solid dispersions (SD) entail the amalgamation of a hydrophilic matrix with a hydrophobic drug, constituting at least two separate components. The molecular dispersion of hydrophobic drugs within a hydrophilic carrier matrix is known as a solid dispersion ^[26-27]. In the pharmaceutical industry, this approach is extensively used to improve the solubility of drugs in various forms of medication. Solid dispersions are often formed using hydrophilic carriers such as polyvinylpyrrolidone (PVP), polyethylene glycols (PEGs), hydroxypropyl methylcellulose (HPMC), and Plasdone-S630. Furthermore, solid dispersion formulations incorporate surfactants like sodium lauryl sulfate (SLS), docusate sodium, Pluronic-F68, Myrj-52, and Tween-80. In the mid-1960s, Sekiguchi and Obi explored the qualities of eutectic melts containing a water-soluble carrier sulphonamide alongside a drug. Utilizing appropriate hydrophilic carriers, solid dispersion has demonstrated improved solubility for drugs

such as celecoxib, halofantrine, and ritonavir. Various methods are employed to formulate hydrophobic drugs into solid dispersions and enhance their water solubility ^[28].

Hyper-branched poly(glycerol ester amide) (HPGEA), having an average molecular weight between 5000 and 12,000 Daltons, serves as a drug carrier and a degree of branching at approximately 60%, was utilized in a fusion-solvent process to create solid dispersions of lovastatin (LOV SD). In this formulation, LOV was present at 5% by weight, while HPGEA made up the remaining 95%. This approach resulted in a substantial enhancement of the in vitro dissolution of lovastatin. Furthermore, this particular formulation achieved over a two-fold increase in cumulative drug release and a more than three-fold increase in solubility compared to pure lovastatin^[29].

Below are specific methods elucidating the creation of solid dispersion

Fusion Method (Hot Melt Method):

This method involves heating a drug and a watersoluble carrier until they liquefy. After rapid cooling and solidification in an ice bath while stirring continuously, the resulting solid mass is fragmented into smaller particles by crushing, pulverizing, and sieving. Later, tabletting agents are used to compress these particles into tablet form ^[30].

Hot-melt extrusion, akin to fusion, involves the extruder robustly mixing the components. demonstrating a similar process. In the traditional fusion technique, the challenge lies in ensuring the compatibility of medications with the matrix, leading to an inconsistent distribution of the drug. The high shear forces within the extruder can lead to localized temperature increases, which may pose issues for materials sensitive to heat. However, in contrast to the traditional fusion approach, this method allows for continuous production, making it well-suited for large-scale manufacturing.^[12]

To improve oleanolic acid's solubility and absorption when taken orally, a solid dispersion was formulated by blending oleanolic acid with a carrier consisting of PVP VA 64 polymer. It was observed that the drug dissolution from the prepared solid dispersion was significantly improved (approximately 90% released within 10 minutes) compared to the free drug (37% released in 2 hours) and the physical mixture (45% released in 2 hours) [³¹].

Method of Evaporating Solvents

The technique of evaporating the solvent is highly efficient in improving the solubility of drugs that have low water solubility, particularly those that are sensitive to high temperatures. Unlike the melting method, which involves heating to mix the drug and carrier, this approach employs a solvent to facilitate the blending of the drug and carrier. This method offers the advantage of accommodating carriers with exceptionally high melting points.

To attain a consistent blend, the drug and carrier are both dissolved in a volatile solvent, and subsequent removal of the solvent through continuous stirring yields solid dispersions. This technique has effectively elevated the solubility of several anti-cancer drugs with low solubility, such paclitaxel. docetaxel. everolimus. as and exemestane. In a research conducted by Chen et al., a marked improvement was observed in both the solubility and dissolution rate of docetaxel using a solid dispersion formulation. Comparing the results to the free drug, they noted a remarkable 12.7-fold improvement in dissolution and an impressive 34.2-fold increase in solubility at the 2hour mark ^[32].

Spray drying method:

Spray drying is a method for creating solid dispersions. It begins with creating a solution in water, the carrier dissolves, and the drug molecule dissolves in a particular solvent, after which the mixture is sonicated. Next, The drug molecules are transformed into tiny droplets by forcing the solution through a nozzle under high pressure in a drying chamber. Herbrink and colleagues utilized this technique to enhance the solubility of nilotinib, and their results demonstrated a significant improvement in solubility. In fact, the solubility of spray-dried nilotinib solid dispersion was enhanced by a remarkable 630-fold when compared to free nilotinib. This improvement was achieved at a drug-to-Soluplus® (a product by BASF SE in Ludwigshafen, Germany) ratio of 1:7 [33]

Prodrug:

Initially inactive, a prodrug represents a modified form of a drug. It is designed to improve its ability to dissolve in water and can be transformed into the active form of the drug quickly through biological processes. Prodrugs serve various purposes in the pharmaceutical industry. They can enhance the drug's qualities, like its smell, taste, and chemical stability. Additionally, they have the ability to decrease irritation and discomfort linked to medication intake, as well as tackle obstacles in the preparation and production of the active pharmaceutical ingredient (API). Prodrugs can also optimize the drug's behavior in the body, known as its pharmacokinetic profile, and reduce or eliminate the first-pass effect ^[34].

There are two main categories of prodrug formulations to consider:

In Carrier-Linked Prodrugs, the original drug is connected chemically to a prodrug molecule. This linkage can occur directly, making it a bipartite prodrug, or through a spacer, which makes it a tripartite prodrug.

Bio Precursor Prodrugs: These prodrugs are designed to be transformed into the active drug through biological processes ^[35-36].

Classic prodrugs, also called carrier-linked prodrugs, involve a carrier that's connected to a drug. This carrier has bioprecursor properties, and the drug is released when an enzymatic reaction breaks the bond. Another term for this type of prodrug is a Chemical Delivery System (CDS).

Similar to conventional prodrugs, mixed prodrugs represent latent structures wherein the carrier, possessing bioprecursor characteristics, binds with the drug. The enzymatic reaction facilitates the release of the drug. This particular form of prodrug is alternatively known as a Chemical Delivery System (CDS).

Similar to classic prodrugs, mutual prodrugs possess a pharmacologically active carrier. This allows the development of a prodrug with either similar or different therapeutic activities, working through distinct or similar mechanisms of action [36].

To address the challenge of limited absorption in the body for a hepatitis C virus (HCV) NS5B polymerase inhibitor with poor solubility but high permeability, a prodrug approach was employed. In a series of laboratory experiments, we utilized microsomes from liver and intestinal tissues, as well as plasma, simulated gastric fluids, and simulated intestinal fluids, to evaluate the transformation rates of different structurally distinct prodrug derivatives, the capability of potential candidates to undergo conversion within the body was determined by administering them orally to rats. The carboxylic acid part of the initial medication might have been converted to glycolic amide esters, thereby improving its solubility in a lipid-based self-emulsifying drug delivery system (SEDDS). Compared to the unmodified drug and conversions in different species, the crystalline prodrug variant exhibited superior solubility in specific SEDDS components, consistent with its in vitro stability in liver microsomes ^[37].

Co-crystallization:

Co-crystallization refers to the creation of a crystalline structure in which precise proportions of noncovalent forces bind two or more electrically neutral substances together ^[38].

There has been a documented instance of cocrystallization involving two active pharmaceutical ingredients: aspirin and acetaminophen^[39].

This process bears similarities to salt production, especially when dealing with neutral substances. Co-crystals can be produced through methods such as evaporation, sublimation, melt growth, and slurry preparation ^[21]].

In a specific study, three different types of ezetimibe co-crystals were formed and characterized using methylparaben as а conforming agent. Three different methodssolution crystallization, liquid-assisted crushing, and reaction crystallization-were employed to produce these co-crystals. Utilizing analytical methods such as Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR), Raman spectroscopy, and Powder X-ray Diffraction (PXRD), researchers observed distinct melting temperature differences among the three cocrystals. This observation indicates the emergence of a novel solid phase. The alteration in the electrostatic interaction between the medication and the co-former is responsible for the observed differences. Additionally, the crystal structure of both the drug and the co-former underwent changes.

Equilibrium solubility and dissolution studies conducted on the co-crystals showed promising results, indicating that co-crystals of ezetimibe and methylparaben have the potential to significantly enhance solubility. This strategy offers a valuable and effective approach for improving solubility ^[40].

Supercritical Fluid Technology (SCF)

SCF technology, noted for its safety and ecofriendliness, has captured the interest of numerous researchers. This sustainable approach holds immense promise for revolutionizing the pharmaceutical industry by addressing the shortcomings of traditional processes like spray drying and others ^[41-42]. The US Food and Drug Administration (US-FDA) has recognized carbon dioxide (CO2) as a secure supercritical solvent, which is the most widely employed supercritical solvent in pharmaceutical manufacturing. ^[43-44]. Many solvents commonly used in drug formulation are harmful, but SCF technology provides a means to circumvent this drawback ^[45].

Two key techniques for enhancing solubility through SCF are the supercritical solution process and compression antisolvent precipitation (PCA). Various methods exist within supercritical fluid (SCF) technology to enhance solubility, contingent upon the conditions dictating particle formation, such as the nature of the solute and solvent. Among these approaches for solvents are the rapid expansion of a supercritical solution (RESS), the rapid expansion of a supercritical solution into a liquid solvent (RESOLV), the rapid expansion of a supercritical solution into an aqueous solution (RESS-AS), and the rapid expansion of a supercritical solution using a non-solvent (RESS-N). For solute molecules, processes such as gassaturated solutions (PGSS) and depressurization of an expanded liquid organic solution (DELOS) are used to enhance solubility under SCF conditions [46]

In a similar vein, resveratrol's solubility was increased approximately 2.8 times, and its dissolution rate was boosted by about 1.8 times using a method known as solution-enhanced dispersion via supercritical fluids micronization ^[47].

Nanotechnology Solutions to Improve Drug Solubility

To improve the solubility of substances that don't dissolve well in water, Surface-active agents are employed in a technique known as solubilization. This method entails introducing a distinct element into a substance that typically doesn't dissolve in a particular liquid, thereby enabling it to create a steadfast solution. Micellar solubilization is a method for dissolving poorly soluble drugs. It works by using tiny structures called micelles,

which have changing properties, to help drug molecules dissolve better in water, making them seem more soluble ^[48-49].

Liposomes

The initial liposomal (IV) formulation debuted in 1995 and has since undergone extensive research and integration with diverse active compounds, encompassing peptides and proteins^[50]. Liposomes, formed primarily from amphipathic compounds like lipids, can be precisely tailored in size and structure^[51].

These vesicles, enveloped by phospholipid bilayers, have the unique ability to dissolve water-insoluble drugs within their lipid domains^[52]. Their similarity in structure and composition to biological membranes has led to their widespread use in non-invasive oral drug delivery. They effectively dissolve and facilitate the delivery of drugs that have limited permeability, showcasing biocompatibility^[53-54].

Due to their capacity to dissolve poorly watersoluble medications, shield drugs from degradation in the gastrointestinal tract, and enhance permeability across cell membranes, liposomal administration holds promise for orally delivering hydrophobic drugs ^[54].

In oral applications, the formulation of liposomal membranes can regulate the release of drugs, influencing absorption rates. Moreover, by circumventing the hepatic first-pass effect, liposomes enable direct drug delivery via the lymphatic system. Encapsulation within liposomes also minimizes drug interaction with the intestinal environment, potentially reducing gastrointestinal irritation ^[54-55].

Efavirenz Enhancement: Rao et al. devised a liposomal drug delivery system to enhance Efavirenz's solubility and bioavailabilityEfavirenz, classified as BCS class II because of its limited solubility in water (0.0085 mg/mL) and significant lipophilicity (log P: 5.4), demonstrated a boost in solubility (27.82 \pm 2.55 µg/mL) with the

incorporation of 900 mg of soya lecithin in a liposomal formulation. In vivo studies demonstrated a 2-fold rise in oral bioavailability with the liposomal formulation compared to the free drug ^[56].

Apigenin Solubility Improvement: Telang et al. addressed Apigenin's poor solubility by developing the apigenin phospholipid complex (APLC). To obtain this outcome, phospholipon 90H was combined with apigenin in a solution comprising 1,4-dioxane and methanol, and incubated at 50°C for 2 hours. Following precipitation in hexane and subsequent vacuum drying, the resultant complex showcased a 37-fold rise in water solubility, escalating from $0.62 \pm 0.88\mu$ g/mL to 22.80 ± 1.40 μ g/mL. This enhancement in solubility is attributed to the amorphous state of apigenin within the APLC complex ^[57].

Dendrimers

Dendrimers represent a novel category of polymers, holding significant promise for boosting drug solubility ^[58-59]. Structurally, dendrimers comprise four key components: a central core, internal layers consisting of repetitive units linked to unoccupied spaces, external surface groups, and a core denoted by generation (G) ^[60].

PAMAM-containing dendrimers have undergone extensive investigation as drug delivery systems among the various types of dendrimers. These dendrimers feature an ethylenediamine core and branch units formed from methyl acrylate and ethylenediamine [61]. The distinctive feature of these highly branched, uniformly sized molecules is their capability to covalently bind drug molecules to their outer branches and enclose them within the dendritic structure. Several research studies have successfully employed dendrimers to improve the solubility of drugs that have low solubility. Dendrimers achieve this through physical encapsulation or covalent bonding, thereby increasing the solubility of hydrophobic compounds as well^[16-58].

In specific reference to the literature, G0 PAMAM dendrimers have demonstrated substantial enhancement in the solubility of aceclofenac, an anti-inflammatory drug with limited water solubility ^[62]. Patel et al.'s research underscores that the extent of solubility enhancement was contingent upon concentration and influenced by various factors such as pH, concentration, temperature, and dendrimer generation. The sequence of solubility improvement through dendrimer synthesis. under consistent pН conditions, followed this order: G0 < G1 < G2 <G3. The increase in aceclofenac solubility, linked dendrimer pH, probably arises due to to electrostatic interactions occurring between the NH2 groups within the dendrimer and the COOH group present in the medication. Furthermore, the temperature of the dendrimer solution exhibited an inversely proportional relationship with aceclofenac solubility [62].

Gautam and Verma conducted a study on the impact of a particular dendrimer variety, known as a full-generation PAMAM (G4) dendrimer, on the solubility of candesartan cilexetil, a calcium channel blocker with lipophilic properties. They used purified water at room temperature for their tests and found that the drug's concentration was 2.63 grams per milliliter. They discovered that when the concentration of PAMAM dendrimers was 10 milligrams per milliliter, the maximum solubility of candesartan cilexetil increased by about 373 times. This increase in solubility was directly linked to the concentration of the dendrimers.

In another study, Kulhari et al. investigated the effect of three different G4 PAMAM dendrimers on simvastatin. They aimed to determine how effective these dendrimers were in improving the drug's solubility. They found that PEGylated dendrimers showed the highest improvement, increasing solubility by 33 times. Following PEGylated dendrimers were NH2-ended dendrimers (with a 23-fold increase) and OH-ended dendrimers (with a 17.5-fold increase). By

introducing 0.4% (w/v) PEGylated dendrimer complexes at a concentration of 109.04 M, the solvency of simvastatin increased from 33.4 to 1093.25 mole per liter, indicating a significant enhancement in solubility.

Micelles

Micelles, formed by combining a hydrophilic spherical shell with polar heads and a hydrophobic core consisting of polar tails, create an ideal environment for solubilizing poorly water-soluble drugs^[49-61]. Among these, polymeric micelles, typically made from amphiphilic block copolymers, have gained substantial interest in delivering hydrophobic substances over the last few decades. They self-assemble in aqueous media, boasting a low critical micellar concentration (CMC), with central hydrophobic sections (e.g., PPO, PCL, PEI, PLA, PJL, DSPE) and an outer hydrophilic shell (usually PEO) ^[63-65]. Due to their nanoscale size, stable structure, and compatibility, polymeric micelles find applicability in various fields ^[66].

Bansal et al. assessed PJL-based polymeric micelles' solubilization ability compared to Soluplus® and poly (lactide) copolymer micelles. Their findings revealed a 334-fold enhancement in clotrimazole's aqueous solubility when -COOH groups were introduced to the PJL polymer chain, outperforming Soluplus®. This suggests that incorporating free functional groups on the polymer chain significantly enhances polymeric micelles' solubilization capabilities ^[67-68].

Zhou et al. developed griseofulvin-loaded core crosslinked micelles using linear dendritic polymers to prevent early dissociation and drug leakage. Their study demonstrated a tenfold improvement in solubilization and sustainedrelease behavior of griseofulvin in these polymeric micelles ^[69].

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have garnered

attention as lipid-based nanosystems for orally delivering poorly bioavailable hydrophobic drugs ^[70]. These lipid nanocarriers offer benefits such as biocompatibility, scalability, enhanced lymphatic transport, and reduced first-pass metabolism. SLNs, the first-generation lipidic nanoparticles, comprise a solid lipid matrix dispersion stabilized by surfactants, solid at both room and body temperatures ^[70]. However, they suffer from drawbacks like inefficient drug loading and potential drug leakage ^[71]. NLCs, an advanced form of SLNs, combine solid and liquid lipids, allowing for higher drug payloads, reduced drug leaching during storage, and improved formulation versatility ^[70].

Hu et al. devised SLNs to enhance the oral bioavailability of all-trans retinoic acid (ATRA), demonstrating significant absorption improvement ^[72]. Khan et al. explored NLCs to enhance solubility and bioavailability of tacrolimus (TL), reporting a 7.2-fold increase in relative bioavailability compared to TL suspension ^[73].

Supercritical Antisolvent (SAS)

The Supercritical Antisolvent (SAS) technique offers an innovative and environmentally friendly approach to producing nanomaterials, proving more effective than liquid solvent precipitation. By utilizing supercritical CO2, a versatile substance widely employed in creating various materials from polymers to pharmaceutical ingredients, this method achieves controlled precipitation of solids that don't dissolve in the supercritical medium.

Conventional micronization techniques like milling, grinding, and spray drying often lead to drawbacks such as solvent overuse, chemical degradation of compounds, and difficulty in particle controlling size and distribution. Supercritical fluid-based processes, especially using supercritical carbon dioxide (scCO2), overcome these limitations.

SAS relies on the complete miscibility of scCO2 with the liquid solvent used. This technique

primarily produces microparticles, enhancing the solubility of pharmaceutical ingredients. Its advantage lies in rapid nucleation and growth, resulting in fine particle formation, surpassing conventional methods ^[74-75].

Newer micronization techniques, like SCF-assisted particle formation, offer solvent-free product production under standard conditions. The solubility and bioavailability of poorly watersoluble medications are notably improved by SAS methods.

The efficiency of the SAS method relies on crucial factors like temperature, pressure, solvent characteristics, flow rate, and nozzle structure. A standard SAS trial includes the injection of CO2 into a heated precipitator, followed by delivery of the solvent and injection of a solution containing the solute. Precipitation occurs due to supersaturation, and downstream. the solvent/antisolvent mixture is recovered and separated. Subsequently, scCO2 eliminates solvent residues, and the resulting precipitated powder is collected after depressurization^[76].

The fundamental mechanism of the Supercritical Fluids (SCFs) application in the SAS process hinges on the dense nature of SCFs, often compatible with organic solvents. Telmisartan, a BCS class II drug owing to its poor water solubility, exhibits high solubility in strongly alkaline solutions without any alterations in its meaning, but has limited solubility in most organic solvents. The primary challenge in achieving the desired bioavailability lies in its solubility issue. To address this, the SAS technique has been pivotal in micronizing, amorphizing, or solidly dispersing BCS class II drugs due to its distinct attributes

Utilizing the SAS method, various weight ratios of drug to polymer (1:0.5, 1:1, and 1:2) were used to create solid dispersions of hydroxypropyl methylcellulose/polyvinylpyrrolidone

(HPMC/PVP), while pure telmisartan was processed simultaneously. According to

researchers, this SAS technique holds promise in enhancing the dissolution rate and improving the solubility of telmisartan by adjusting the formulation of solid dispersions ^[77].

in investigating fluconazole Similarly, monohydrate via the SAS method, Park et al. experimented with temperature variations (40, 60, and 80 °C), Fluctuations in pressure (8, 12, and 16 MPa) and various types of solvents (acetone, ethanol, and dichloromethane (DCM)) were investigated. At elevated pressure (16 MPa), neither particle precipitation nor nucleation took place, whereas both phenomena were observed upon reducing the pressure to 12 MPa. This occurrence was attributed to the enhanced solubility of fluconazole in supercritical carbon dioxide (SC-CO2) at high pressures. Moreover, the product yield exhibited a gradual increase with rising temperatures from 40 to 80 °C while maintaining constant pressure. Elevated а temperatures augmented the organic solvent's in expediting solubility SC-CO₂, solvent extraction and aiding in the drug's precipitation ^[78].

Nanoemulsions

Nanoemulsions, complex yet stable systems comprising oil and water phases, intricately intertwined by surfactants, sustain stability ^[79]. With droplet sizes between 1 and 100 nm, nanoemulsions boast increased surface areas, enhancing solubility compared to standard emulsions ^[80]. Reddy et al. successfully crafted febuxostat nanoemulsions, elevating drug solubility, evident from the 42.37% drug release within 6 hours ^[81].

Ostwald ripening, a principal destabilization process, prompts larger droplets at the expense of smaller ones. Yet, strategic use of hydrophobic elements in the oil phase and controlled coalescence rate can impede this process. Wik et al. engineered a nanoemulsion featuring a renewable poly (δ -decalactone) and Pluronic F-68, boosting aqueous drug solubility by 3 to 10 times compared to established Pluronic micelles ^[82-83].

Nanogels

Nanogels, intricate hydrogel structures with exceptional water-retaining abilities, stem from crosslinked polymer networks in the nanoscale, distinct from dispersing in aqueous environments ^[84]. These networks, formed by physically or chemically interlinking neutral or cationic polymers like PEG and PEI, maintain sizes between 100 and 200 nm ^[85-86]. Manipulating solvent quality ensures the stability of the nanogel's three-dimensional structure ^[87].

Nanoemulsion based gels

Nanoemulsion gels are highly regarded as versatile polymer-based nanodrug delivery systems. They efficiently encapsulate both hydrophilic and hydrophobic molecules. Their large surface areas and capacity for effective drug loading make them a promising and safe approach for drug delivery ^[88].

For instance, Yao et al. developed a novel nanogel using chitosan to load myricetin, a flavonoid. This method significantly increased oral bioavailability by 2.20-fold compared to plain myricetin in rats ^[89]. Similarly, Khan et al. designed a nanogel system to enhance the solubility of olanzapine by up to 38 times compared to the free drug ^[90].

Metal Organic Frameworks (MOFs)

Metal-organic frameworks (MOFs) create porous and crystalline materials by integrating organic ligands with metal ions or complexes, offering molecular structural flexibility ^[91]. Their customizable physiochemical characteristics have made them highly attractive as drug delivery carriers in recent years ^[92].

For example, Wang et al. increased the solubility of quercetin by 100-fold by loading it into γ cyclodextrin metal-organic frameworks (γ -CD-MOFs) ^[93]. Chen et al. addressed isosteviol's insolubility by using cyclodextrin's metal-organic framework (CD-MOF), resulting in a significant increase in solubility and bioavailability ^[94]. Additionally, He et al. successfully enhanced the

solubility of Azilsartan, observing a 340-fold increase when loaded into γ -CD metal-organic frameworks, subsequently increasing bioavailability by 9.7 times in rats ^[95].

Carbon Nanotubes

possess Carbon nanotubes (CNTs) unique electrical, mechanical, chemical, and optical properties, making them a highly promising carrier in nanotechnology. These cylindrical structures represent a distinct allotropic form of carbon. Functional groups are deliberately introduced onto the surfaces of CNTs through a process called functionalization. These groups play a crucial role in fostering better interaction between CNTs and matrices or solvents, ensuring a more uniform dispersion or solubility of CNTs. Surface modification of CNTs becomes imperative to prevent aggregation and enhance their dispersibility, facilitating improved interactions with both matrix materials and polymer matrices [96-97]

Functionalized **CNTs** exhibit high water dispersibility, enabling them to act as nucleation sites for hydrophobic compounds in drugs, thereby augmenting hydrogen bonding in aqueous media. This phenomenon accelerates dissolution rates ^[98]. This enhancement in solubility for weakly watersoluble drugs due to **CNTs** is termed "functionalized partitioning" [99]. In a study by Chen et al., the incorporation of CNTs into hydrophobic drugs-griseofulvin and sulfamethoxazole—during synthesis showed significantly enhanced dissolution rates. For instance, with 4% CNTs in griseofulvin, the dissolution time reduced from 66 to 18 minutes. Similarly, for 5.1% CNTs in sulfamethoxazole, the dissolution time dropped from 67 to 10 minutes, achieving 80% dissolution ^[100].

Additionally, Zhu and colleagues developed a formulation of dipyridamole alongside CNTs, which is a poorly soluble drug. This led to higher drug loading and a conversion of dipyridamole from an amorphous state to a crystalline one. As

the drug loading in carriers increased, the release rate of the drug decreased, alongside a noticeable improvement in the dissolution rate. CNTs have shown promise as effective carriers for loading dipyridamole ^[101].

Mesoporous Silica

Mesoporous silica is widely acknowledged for its capacity to enhance solubility by adsorbing and stabilizing APIs within its porous structure in an amorphous state ^[102-103]. As a result, it is advisable to use mesoporous silica materials (MSMs) as matrices to enhance the apparent solubility and dissolution rate of drug molecules that are poorly soluble in wate. Given that amorphous silica is classified as a 'generally regarded as safe' (GRAS) material, biodegradable via hydrolysis, and easily modifiable on the surface to improve drug loading and subsequent release within the human body, mesoporous silica materials prove to be exceptional candidates for drug delivery ^[104].

The key benefits of mesoporous silica as carriers for poorly water-soluble drugs encompass their pore dimensions, pore structure, and adaptability in altering surface chemistry. The latter facilitates optimized interactions between a drug candidate and the mesoporous silica carrier by altering the pore surfaces ^[105]. However, MSMs are primarily characterized by their pore size, which is within the mesoporous range according to the IUPAC definition, spanning from 2 to 50 nanometers. Notably, Rengajaran et al. deduced that molecules residing in pores less than 10 times their size remain in amorphous forms due to insufficient space for crystallization ^[106]. Exploiting this phenomenon has led to the formulation of orodispersible films (e.g., prednisolone) ^[107], fastdissolving tablets (e.g., tamoxifen) ^[108], and lyophilized tablets (e.g., silvmarin)^[109-110].

Zhang et al. created spherical mesoporous silica nanoparticles (MSNs) in an in vivo investigation to improve the oral bioavailability of telmisartan (TEL) as an oral drug delivery system. Their study on human colon cancer (Caco-2) cell lines showed that the MSNs significantly enhanced the permeability of TEL, while concurrently lowering the rates of drug efflux. Subsequent investigation of the oral bioavailability of TEL-laden ordered MSMs, MSNs, and the commercial drug Micardis in beagle dogs revealed that the TEL-loaded MSNs formulation exhibited a relative bioavailability of 154.4 \pm 28.4%, whereas the TEL-loaded MSMs formulation showed a relative bioavailability of 129.1 \pm 15.6% ^[111].

A parallel study conducted in a clinical setting by Bukara et al. further corroborated these findings, indicating significantly enhanced absorption rates and extents for fenofibrate loaded into MSMs compared to a marketed micronized formulation [¹¹²]. This study served as pioneering evidence for this relatively innovative formulation approach.

CONCLUSIONS

In this assessment, previously established literature and developing technologies related to formulation design are assessed. This encompasses solid particle techniques, prodrug approaches, micronization, solid dispersions, methods for reducing particle size, nanosizing, utilization of cyclodextrins, solid lipid nanoparticles, drug conjugates, colloidal drug delivery systems, nanoemulsion, micelles, and other pertinent methodologies. Numerous emerging drug candidates undergoing development encounter difficulties related to their solubility in water, a critical factor influencing bioavailability, formulation strategies, and therapeutic effectiveness. Nanotechnology offers a promising approach to enhance solubility and has been utilized effectively in nanomedicines, serving as a platform to address this issue.

However, the translation of these nanocarriers from lab to market poses challenges related to production costs, reproducibility of formulation properties, and varied pharmacokinetics affecting their widespread human benefit. Despite these hurdles, ongoing advancements in innovative drug delivery technologies offer undeniable advantages. Nanotechnology offers formulation scientists the chance to broaden their research and development horizons, effectively addressing challenges related to drugs with low solubility, thus improving therapeutic effectiveness.

The successful tackling of these difficulties depends on the characteristics at a molecular level, where both solid dispersions and lipid delivery methods are becoming significantly desirable approaches projected to resolve these issues for a considerable array of drug compounds.

Future Scenarios and Challenges

Scientists have felt increased pressure in recent decades to innovate techniques that improve the bioavailability due to the rising discovery of insoluble APIs. То achieve effective pharmaceutical delivery, exploring diverse approaches becomes formulation crucial in tackling these challenges. While conventional methods exist to elevate bioavailability, further research is imperative to devise practical and efficient approaches. Despite recent focus on solid dispersion and lipid-based nanotechnology, limited utilization because commercial persists of problems with scaling up, physicochemical instability, a brief shelf life, and issues with reproducibility.

Improving the solubility of molecules with low solubility requires utilizing new techniques and additives to enhance solubility trends. Yet, implementing entirely new methodologies proves costly for pharmaceutical the industry, necessitating additional infrastructure and personnel. Simplifying this process and pinpointing optimal approaches involves attention towards molecular modeling. While not presently molecular feasible, progress in dynamic simulations edges closer to determining the most effective excipients or technologies.

An innovative approach for forecasting human oral bioavailability based on chemical structure was introduced by Fagerholm et al. The method

involved comprehensive a technique that incorporated 9 machine learning models, 3 sets of structural alerts, and 2 physiologically based pharmacokinetic models. Using a benchmark dataset consisting of 184 chemicals, their model demonstrated a predictive accuracy (Q2) of 0.50, which is deemed successful in the pharmaceutical sector. This approach exhibits sufficient predictive accuracy for applications in predicting human exposure and dose, optimizing compounds, and decision-making, potentially streamlining drug discovery and development, thereby reducing failures and overexposure in early clinical trials^[113].

Given that oral administration is the most practical drug delivery method, accurate assessment of oral bioavailability during drug discovery is essential. Promising alternatives for early oral bioavailability prediction include Quantitative Structure-Property Relationship (QSPR), Rule-of-Thumb (RoT), and Physiologically Based Pharmacokinetic (PBPK) approaches^[114]. The synergy between artificial intelligence and innovative solubility enhancement technologies holds transformative potential in resolving solubility issues while concurrently curbing R&D costs.

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REFERENCES

- Pavan BR, Mayura K, Jafar S, Abolghasem J. Solubility of Etoricoxib in Aqueous Solutions of Glycerin, Methanol, Polyethylene Glycols 200, 400, 600, and Propylene Glycol at 298.2 K. J.Chem.Eng.Data.2018; 63(2): 321-330.
- 2. Jain S, Patel N, Lin S. Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug Dev Ind Pharm. 2015 Jun; 41(6): 875-87.
- 3. Saal C, Petereit AC. Optimizing solubility: kinetic versus thermodynamic solubility

temptations and risks. Eur J Pharm Sci. 2012 Oct 9; 47(3): 589-95.

- Lu JX, Tupper C, Murray J. Biochemistry, Dissolution and Solubility. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2022 Sep 12;
- 5. Gabor F, Fillafer C, Neutsch L, Ratzinger G, Wirth M. Improving oral delivery. Handb Exp Pharmacol. 2010; (197): 345-398.
- Dixit VB, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. 2022; 10(9): 2055.
- JOSHI J, NAINWAL N, SAHARAN VA. A REVIEW ON HYDROTROPY: A POTENTIAL APPROACH FOR THE SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG. Asian J. Pharm. Clin Res 2019 Oct; 12(10): 19-26.
- Tsume Y, Mudie DM, Langguth P, Amidon GE, Amidon GL. The Biopharmaceutics Classification System: subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC. Eur J Pharm Sci. 2014 Jun 16; 57: 152-63.
- 9. Mostafa N, Authelin JR. Gianola G. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Eur J Pharm Sci. 2014; 9(6): 304-316.
- Kalepu, S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm. Sin. B. 2015; 5(5): 442-453.
- 11. Saxena V, Kesharwani P, Gupta S, Mohammad NA, Sharma V, Khan AD, et al. Hydrotropy: Recent Advancements in of Enhancement Drug Solubility and Formulation Development. Int. J. Drug Deliv. Technol. 2021; 11(3): 1092-1102.

- 12. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. int. sch. res. Notices. 2012; 2012: 195727.
- 13. Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. J Adv Pharm Technol Res. 2011; 2(2): 81-87.
- Prasanna P, Kumar GA. Nanosuspension technology: A review. Int J Pharm Pharm Sci. 2010; 2(4): 35-40.
- 15. Chauhan AS. Dendrimers for Drug Delivery. Molecules. 2018; 23(4): 938.
- Bansal KK, Kakde D, Gupta U, Jain NK. Development and characterization of triazine based dendrimers for delivery of antitumor agent. J Nanosci Nanotechnol. 2010; 10(12): 8395-8404
- Clulow AJ, Barber B, Salim M, Ryan T, Boyd BJ. Synergistic and antagonistic effects of non-ionic surfactants with bile salt + phospholipid mixed micelles on the solubility of poorly water-soluble drugs. Int J Pharm. 2020 Oct 15; 588: 119762.
- Mishra V, Bansal KK, Verma A, Yadav N, Thakur S, Sudhakar K, Rosenholm JM. Solid Lipid Nanoparticles: Emerging Colloidal Nano Drug Delivery Systems. Pharmaceutics. 2018 Oct 18; 10(4): 191.
- Yin X, Luo L, Li W, Yang J, Zhu C, Jiang M, et al. A cabazitaxel liposome for increased solubility, enhanced antitumor effect and reduced systemic toxicity. Asian J Pharm Sci. 2019 Nov; 14(6): 658-667.
- 20. Wang Y, Zhang Z, Zheng C, Zhao X, Zheng Y, Liu Q, et al. Multistage Adaptive Nanoparticle Overcomes Biological Barriers for Effective Chemotherapy. Small. 2021 Aug; 17(31): e2100578.
- 21. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and

dissolution rates. Adv Drug Deliv Rev. 2007 Jul 30; 59(7): 617-30.

- 22. Vandana KR, Prasanna RY, Chowdary HV, Sushma M, Vijay KN. An overview on in situ micronization technique - An emerging novel concept in advanced drug delivery. Saudi Pharm J. 2014 Sep; 22(4): 283-289.
- Sherje AP, Jadhav M. β-Cyclodextrin-based inclusion complexes and nanocomposites of rivaroxaban for solubility enhancement. J Mater Sci Mater Med. 2018; 29 (12): 186.
- Semcheddine F, Guissi NI, Liu X, Wu Z, Wang B. Effects of the Preparation Method on the Formation of True Nimodipine SBE-β-CD/HP-β-CD Inclusion Complexes and Their Dissolution Rates Enhancement. AAPS PharmSciTech. 2015; 16(3): 704-715.
- 25. Argade PS, Magar DD, Saudagar RB, Solid dispersion: solubility enhancement technique for poorly water soluble drugs. J. Adv. Pharm. Edu. & Res. 20123; 3(4): 427-439.
- 26. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. Pak J Pharm Sci. 2009 Apr; 22(2): 234-246
- 27. Cid AG, Simonazzi A, Palma SD, Bermúdez JM. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. Ther Deliv. 2019 Jun 1; 10(6): 363-382.
- 28. Devhare, Lalchand, Kore PK. A recent review on bioavailability and solubility enhancement of poorly soluble drugs by physical and chemical modifications. Res. Chron. Health Sci. 2016; 2(5): 299-308.
- 29. Muniandy A., Huei LW, Pichika MR. Investigation of hyperbranched Poly (glycerol esteramide) as potential drug carrier in solid dispersion for solubility enhancement of lovastatin. Drug Deliv. Sci. Technol. 2021; 61:102237.

- 30. Jatwani, S, Singh G, agarwaal G. Solubility and dissolution enhancement of simvastatin using synergistic effect of hydrophilic carriers. Der Pharm Lett. 2011 jan; 3(6): 280-93.
- 31. Gao N, Guo M, Fu Q, He Z. Application of hot melt extrusion to enhance the dissolution and oral bioavailability of oleanolic acid. Asian J Pharm Sci. 2017; 12(1):66-72.
- 32. Ying Chen. Preparation and characterization of emulsified solid dispersions containing docetaxel. Arch Pharm Res. 2011; 34:1909-1917.
- Herbrink M, Schellens JHM, Beijnen JH, Nuijen B. Improving the solubility of nilotinib through novel spray-dried solid dispersions. Int J Pharm. 2017; 529(1-2):294-302.
- 34. Chamsai B, Limmatvapirat S, Sungthongjeen S, Sriamornsak P. Enhancement of solubility and oral bioavailability of manidipine by formation of ternary solid dispersion with d-α-tocopherol polyethylene glycol 1000 succinate and copovidone. Drug Dev Ind Pharm. 2017;43(12):2064-2075
- 35. Aller MR, Davy G, Veuthey GL, Robert G. Strategies for formulating and delivering poorly water-soluble drugs. J Drug Deliv Sci Technol. 2015; 30:342-351.
- Jornada DH, dos SFGF, Chiba DE, de Melo TR, dos Santos JL, Chung MC. The Prodrug Approach: A Successful Tool for Improving Drug Solubility. Molecules. 2015 Dec 29; 21(1):42.
- 37. Beaulieu PL, De Marte J, Garneau M, Luo L, Stammers T, Telang C, et al. A prodrug strategy for the oral delivery of a poorly soluble HCV NS5B thumb pocket 1 polymerase inhibitor using self-emulsifying drug delivery systems (SEDDS). Bioorg Med Chem Lett. 2015 Jan 15; 25(2):210-5.
- 38. Qurratul AS, Shama P. An overview on various approaches used for solubilization of

poorly soluble drugs. Pharma Res. 2009; 2:84-104.

- 39. Karagianni A, Malamatari M, Kachrimanis K. Pharmaceutical Cocrystals: New Solid Phase Modification Approaches for the Formulation of APIs. Pharmaceutics. 2018 Jan 25; 10(1):18.
- 40. Kumari S, Santanu K, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by a cocrystal engineering technique. Cryst Growth Des. 2014; 14(9) :4475-4486.
- Kankala RK, Zhang YS, Wang SB, Lee CH, Chen AZ. Supercritical Fluid Technology: An Emphasis on Drug Delivery and Related Biomedical Applications. Adv Healthc Mater. 2017 Aug; 6(16):10.1002/adhm.201700433.
- 42. Deshpande PB, Kumar GA, Kumar AR, Shavi GV, Karthik A, Reddy MS, Udupa N. Supercritical fluid technology: concepts and pharmaceutical applications. PDA J Pharm Sci Technol. 2011 May-Jun; 65(3):333-44.
- 43. Kumar M, Sharma Y, Chahar K, Kumari L, Mishra L, Patel P, Singh D, Kurmi BD. Validation of a Novel Supercritical Fluid Extractor/Dryer Combo Instrument. Assay Drug Dev Technol. 2023 Apr; 21(3):126-136.
- 44. Pasquali I, Bettini R, Giordano F. Supercritical fluid technologies: an innovative approach for manipulating the solid-state of pharmaceuticals. Adv Drug Deliv Rev. 2008 Feb 14; 60(3):399-410.
- 45. Girotra P, Singh SK, Nagpal K. Supercritical fluid technology: a promising approach in pharmaceutical research. Pharm Dev Technol. 2013 Feb; 18(1):22-38.
- 46. Misra SK, Pathak K. Supercritical fluid technology for solubilization of poorly water soluble drugs via micro- and naonosized particle generation. ADMET DMPK. 2020 Jun 29; 8(4):355-374.
- 47. Pablo GS. Aguiar. Micronization of transresveratrol by supercritical fluid: Dissolution,

solubility and in vitro antioxidant activity. Ind Crops Prod. 2018; 112: 1-5.

- Seedher N, Kanojia M. Micellar solubilization of some poorly soluble antidiabetic drugs: a technical note. AAPS PharmSciTech. 2008; 9(2):431-6.
- 49. Vinarov Z, Katev V, Radeva D, Tcholakova S, Denkov ND. Micellar solubilization of poorly water-soluble drugs: effect of surfactant and solubilizate molecular structure. Drug Dev Ind Pharm. 2018 Apr; 44(4):677-686.
- 50. Chen J. Preparation of Doxorubicin Liposomes by Remote Loading Method. Methods Mol Biol. 2023; 2622:95-101.
- Mufamadi MS, Pillay V, Choonara YE, Du Toit LC, Modi G, Naidoo D, Ndesendo VM. A review on composite liposomal technologies for specialized drug delivery. J Drug Deliv. 2011; 2011:939851.
- Torchilin VP, Weissig V, eds. Liposomes: A Practical Approach. Oxford University Press; 2003
- 53. Jin GZ, Chakraborty A, Lee JH, Knowles JC, Kim HW. Targeting with nanoparticles for the therapeutic treatment of brain diseases. J Tissue Eng. 2020 Mar 4; 11:2041731419897460.
- 54. Lee MK. Liposomes for Enhanced Bioavailability of Water-Insoluble Drugs: In Vivo Evidence and Recent Approaches. Pharmaceutics. 2020 Mar 13; 12(3):264.
- 55. Chaudhary S, Garg T, Murthy RS, Rath G, Goyal AK. Recent approaches of lipid-based delivery system for lymphatic targeting via oral route. J Drug Target. 2014 Dec; 22(10):871-82.
- 56. Monica RP Rao, Laxmi S. B. Liposomal Drug Delivery for Solubility and Bioavailability Enhancement of Efavirenz. Indian J Pharm Sci. 2018; 80(6):

- 57. Telange DR, Patil AT, Pethe AM, Fegade H, Anand S, Dave VS. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. Eur J Pharm Sci. 2017 Oct 15; 108:36-49.
- Choudhary S, Gupta L, Rani S, Dave K, Gupta U. Impact of Dendrimers on Solubility of Hydrophobic Drug Molecules. Front Pharmacol. 2017 May 16; 8:261.
- Emanuele D A, Attwood D. Dendrimer-drug interactions. Adv Drug Deliv Rev. 2005; 57(15):2147-2162.
- 60. Mignani S, El Kazzouli S, Bousmina M, Majoral JP. Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: a concise overview. Adv Drug Deliv Rev. 2013; 65(10): 1316-1330.
- 61. Yellepeddi VK, Ghandehari H. Poly (amido amine) dendrimers in oral delivery. Tissue Barriers. 2016; 4(2): e1173773.
- 62. Patel J, Garala K, Basu B, Raval M, Dharamsi A. Solubility of aceclofenac in polyamidoamine dendrimer solutions. Int J Pharm Investig. 2011; 1(3): 135-138.
- 63. Hanafy NAN, El-Kemary M, Leporatti S. Micelles Structure Development as a Strategy to Improve Smart Cancer Therapy. Cancers (Basel). 2018 Jul 20; 10(7): 238.
- 64. Xu W, Ling P, Zhang T. Polymeric micelles, a promising drug delivery system to enhance bioavailability of poorly water-soluble drugs. J Drug Deliv. 2013; 2013: 340315.
- 65. Jhaveri AM, Torchilin VP. Multifunctional polymeric micelles for delivery of drugs and siRNA. Front Pharmacol. 2014 Apr 25; 5: 77.
- 66. Aliabadi HM, Lavasanifar A. Polymeric micelles for drug delivery. Expert Opin Drug Deliv. 2006 Jan; 3(1): 139-62.

- Bansal KK, Ali AA, Rahma M, Sjöholm E, Wilén CE, Rosenholm JM. Evaluation of solubilizing potential of functionalpoly (jasmine lactone) micelles for hydrophobic drugs: A comparison with commercially available polymers. Int. J. Polym. Mater.Polym. Biomater. 2022; 72(16): 1–9.
- 68. Ali A, Bhadane R, Asl AA, Wilén CE, Salo-Ahen O, Rosenholm JM, et al. Functional block copolymer micelles based on poly (jasmine lactone) for improving the loading efficiency of weakly basic drugs. RSC Adv. 2022 Sep 21; 12(41): 26763-26775.
- 69. Zhou Z, Forbes RT, Emanuele AD. Preparation of core-crosslinked lineardendritic copolymer micelles with enhanced stability and their application for drug solubilisation. Int J Pharm. 2017 May 15; 523(1): 260-269.
- Naseri N, Valizadeh H, Zakeri-Milani P. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: Structure, Preparation and Application. Adv Pharm Bull. 2015 Sep; 5(3): 305-13
- Das S, Chaudhury A. Recent advances in lipid nanoparticle formulations with solid matrix for oral drug delivery. AAPS PharmSciTech. 2011; 12(1): 62-76.
- Hu L, Tang X, Cui F. Solid lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs. J Pharm Pharmacol. 2004; 56(12): 1527-1535.
- 73. Khan S, Shaharyar M, Fazil M, Hassan MQ, Baboota S, Ali J. Tacrolimus-loaded nanostructured lipid carriers for oral deliveryin vivo bioavailability enhancement. Eur J Pharm Biopharm. 2016; 109: 149-157.
- 74. Abuzar SM, Hyun SM, Kim JH, et al. Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent (SAS) process. Int J Pharm. 2018; 538(1-2):1-13.

- 75. Sinha B, Müller RH, Möschwitzer JP. Bottom-up approaches for preparing drug nanocrystals: formulations and factors affecting particle size. Int J Pharm. 2013; 453(1):126-141.
- 76. Francob P, De Marco I. Supercritical Antisolvent Process for Pharmaceutical Applications: A Review. Processes 2020; 8: 938.
- 77. Park J, Cho W, Cha KH, Ahn J, Han K, Hwang SJ. Solubilization of the poorly water soluble drug, telmisartan, using supercritical anti-solvent (SAS) process. Int J Pharm. 2013; 441(1-2): 50-55.
- 78. Park HJ, Kim MS, Lee S, Kim JS, Woo JS, Hwang SJ et al. Recrystallization of fluconazole using the supercritical antisolvent (SAS) process. Int J Pharm. 2007 Jan 10; 328(2): 152-60.
- 79. Tayeb HH, Felimban R, Almaghrabi S, Hasaballah N. Nanoemulsions: Formulation, characterization, biological fate, and potential role against COVID-19 and other viral outbreaks. Colloid Interface Sci Commun. 2021; 45: 100533.
- Pandey P, Gulati N, Makhija M, Purohit D, Dureja H. Nanoemulsion: A Novel Drug Delivery Approach for Enhancement of Bioavailability. Recent Pat Nanotechnol. 2020 Dec 24; 14(4): 276-293
- Kanke PK, Pathan IB, Jadhav A, Usman MRM. Formulation and evaluation of febuxostat nanoemulsion for transdermal drug delivery. J Pharm BioSci. 2019; 7(1): 1-7.
- 82. Wik J, Bansal KK, Assmuth T, Rosling A, Rosenholm JM. Facile methodology of nanoemulsion preparation using oily polymer for the delivery of poorly soluble drugs. Drug Deliv Transl Res. 2020;10(5):1228-1240.
- Pyrhönen J, Bansal K, Bhadane R, Wilen CE, Salo-Ahen O, Rosenholm J. Molecular

Dynamics Prediction Verified by Experimental Evaluation of the Solubility of Different Drugs in Poly (decalactone) for the Fabrication of Polymeric Nanoemulsions. Adv NanoBiomed Res. 2022; 2(1): 2100072.

- Kendre PN, Satav TS. Current trends and concepts in the design and development of nanogel carrier systems. Polymer Bulletin. 2019; 76: 1595-1617.
- Zhang Y, Andrén OCJ, Nordström R, et al. Off-Stoichiometric Thiol-Ene Chemistry to Dendritic Nanogel Therapeutics. Adv Funct Mater. 2019; 29(18):1806693.
- 86. Sharma A, Garg T, Aman A, Panchal K, Sharma R, Kumar S, Markandeywar T. Nanogel--an advanced drug delivery tool: Current and future. Artif Cells Nanomed Biotechnol. 2016; 44(1): 165-77.
- Kaewruethai T, Laomeephol C, Pan Y, Luckanagul JA. Multifunctional Polymeric Nanogels for Biomedical Applications. Gels. 2021 Nov 23; 7(4): 228.
- 88. Soni G, Yadav KS. Nanogels as potential nanomedicine carrier for treatment of cancer: A mini review of the state of the art. Saudi Pharm J. 2016 Mar; 24(2):133-9.
- Yao Y, Xia M, Wang H, Li G, Shen H, Ji G, et al. Preparation and evaluation of chitosanbased nanogels/gels for oral delivery of myricetin. Eur J Pharm Sci. 2016 Aug 25; 91:144-53.
- 90. Khan KU, Akhtar N, Minhas MU. Poloxamer-407-Co-Poly (2-Acrylamido-2-Methylpropane Sulfonic Acid) Cross-linked Nanogels for Solubility Enhancement of Olanzapine: Synthesis, Characterization, and Toxicity Evaluation. AAPS PharmSciTech. 2020 May 17; 21(5):141.
- 91. He S, Wu L, Li X, Sun H, Xiong T, Liu J, Huang C, Xu H, Sun H, Chen W, Gref R, Zhang J. Metal-organic frameworks for

advanced drug delivery. Acta Pharm Sin B. 2021 Aug; 11(8):2362-2395.

- 92. Lawson S, Newport K, Pederniera N, Rownaghi AA, Rezaei F. Curcumin Delivery on Metal-Organic Frameworks: The Effect of the Metal Center on Pharmacokinetics within the M-MOF-74 Family. ACS Appl Bio Mater. 2021 Apr 19; 4(4):3423-3432.
- 93. Wang Z, Ma Y, Jiang Y, Zhou F, Wu Y, Jiang H, et al. Encapsulating quercetin in cyclodextrin metal-organic frameworks improved its solubility and bioavailability. J Sci Food Agric. 2022 Jul; 102(9):3887-3896.
- 94. Chen X, Guo T, Zhang K, et al. Simultaneous improvement to solubility and bioavailability of active natural compound isosteviol using cyclodextrin metal-organic frameworks. Acta Pharm Sin B. 2021; 11(9):2914-2923.
- 95. He Y, Zhang W, Guo T, Zhang G, Qin W, Zhang L, et al. Drug nanoclusters formed in confined nano-cages of CD-MOF: dramatic enhancement of solubility and bioavailability of azilsartan. Acta Pharm Sin B. 2019 Jan; 9(1):97-106
- 96. Dubey R, Dutta D, Sarkar A, Chattopadhyay P. Functionalized carbon nanotubes: synthesis, properties and applications in water purification, drug delivery, and material and biomedical sciences. Nanoscale Adv. 2021; 3(20):5722-5744.
- 97. Mahor A, Singh PP, Bharadwaj P, Sharma N, Yadav S, Rosenholm JM, Bansal KK. Carbon-Based Nanomaterials for Delivery of Biologicals and Therapeutics: A Cutting-Edge Technology. C. 2021; 7(1):19.
- Gomez-Gualdrón DA, Burgos JC, Yu J, Balbuena PB. Carbon nanotubes: engineering biomedical applications. Prog Mol Biol Transl Sci. 2011; 104: 175-245.
- 99. Zhang W, Zhang Z, Zhang Y. The application of carbon nanotubes in target drug delivery

systems for cancer therapies. Nanoscale Res Lett. 2011; 6(1):555.

- 100.Chen K. Mitra S. Incorporation of functionalized carbon nanotubes into hydrophobic drug crystals for enhancing aqueous dissolution. Colloids Surf В Biointerfaces. 2019 Jan 1; 173: 386-391.
- 101.Zhu W, Huang H, Dong Y, Han C, Sui X, Jian B. Multi-walled carbon nanotube-based systems for improving the controlled release of insoluble drug dipyridamole. Exp Ther Med. 2019 Jun; 17(6):4610-4616.
- 102.Vialpando M, Martens JA, Van den Mooter G. Potential of ordered mesoporous silica for oral delivery of poorly soluble drugs. Ther Deliv. 2011 Aug;2(8):1079-91.
- 103.Lainé AL, Price D, Davis J, Roberts D, Hudson R, Back, et al. Enhanced oral delivery of celecoxib via the development of a supersaturable amorphous formulation utilising mesoporous silica and co-loaded HPMCAS. Int J Pharm. 2016 Oct 15; 512(1):118-125.
- 104.Maleki A, Kettiger H, Schoubben A, Rosenholm JM, Ambrogi V, Hamidi M. Mesoporous silica materials: From physicochemical properties to enhanced dissolution of poorly water-soluble drugs. J Control Release. 2017 Sep 28; 262:329-347.
- 105.Bremmell KE, Prestidge CA. Enhancing oral bioavailability of poorly soluble drugs with mesoporous silica based systems: opportunities and challenges. Drug Dev Ind Pharm. 2019 Mar; 45(3):349-358.
- 106.Rengarajan GT. Stabilization of the amorphous state of pharmaceuticals in nanopores. J Mater Chem. 2008; 18(22):2537-2539.
- 107.Sen KD, Patrignani G, Rosqvist E, Smått JH, Orłowska A, Mustafa R, et al. Mesoporous silica nanoparticles facilitating the dissolution

of poorly soluble drugs in orodispersible films. Eur J Pharm Sci. 2018 Sep 15; 122:152-159.

- 108.V. V. Jadhav. Formulation and Evaluation of Mesoporous Silica Nanoparticle Loaded Fast Dissolving Tablet of Tamoxifen. Indian J Pharm Sci. 2021;83(1):
- 109. Ibrahim AH, Rosqvist E, Smått JH, Ibrahim HM. Ismael HR, Afouna MI, et al. Formulation and optimization of lyophilized nanosuspension tablets to improve the physicochemical properties and provide immediate release of silymarin. Int J Pharm. 2019 May 30; 563:217-227.
- 110.Ibrahim AH, Smått JH, Govardhanam NP, Ibrahim HM, Ismael HR, Afouna MI, et al. Formulation and optimization of drug-loaded mesoporous silica nanoparticle-based tablets to improve the dissolution rate of the poorly water-soluble drug silymarin. Eur J Pharm Sci. 2020 Jan 15; 142:105103
- 111.Zhang Y, Wang J, Bai X, Jiang T, Zhang Q, Wang S. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. Mol Pharm. 2012 Mar 5; 9(3): 505-13.
- 112.Bukara K, Schueller L, Rosier J, Martens MA, Daems T, Verheyden L, et al. Ordered mesoporous silica to enhance the bioavailability of poorly water-soluble drugs: Proof of concept in man. Eur J Pharm Biopharm. 2016 Nov; 108:220-225.
- 113.Fagerholm U, Hellberg S, Spjuth O. Advances in Predictions of Oral Bioavailability of Candidate Drugs in Man with New Machine Learning Methodology. Molecules. 2021 Apr 28; 26(9):2572.
- 114.Cabrera-Pérez MÁ, Pham-The H.
 Computational modeling of human oral bioavailability: what will be next? Expert Opin Drug Discov. 2018 Jun; 13(6):509-521.