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Strategies for Improving Solubility and Dissolution of Poorly Water-Soluble Drugs: Current Developments and Pharmaceutical Applications

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Abstract

Poor aqueous solubility is a significant hurdle in the development of Biopharmaceutics Classification System (BCS) Class 2 and 4 candidates, which often leads to poor dissolution, poor gastrointestinal absorption and poor oral bioavailability. This review makes an effort to examine in detail the inherent and extrinsic factors that affects solubility, taking consideration of such aspects as molecular architecture, crystalline lattice enthalpy, ionisation behaviour, hydrogen bonding potential, the pH gradient through the gastrointestinal tract and the occurrence of endogenous surfactants as well as the complexities of the supersaturation permeability interplay. Conventional strategies based on particle size reduction, pH regulation, salt formation, co-solvent system, solubilization mediated by surfactants and complexation of cyclodextrins provide foundation that is often found to have limitations in terms of physicochemical stability, limitations related to scaleup and precipitation phenomena in case of dilution. Recent advances in nanotechnology and materials science have introduced high efficacious strategies, represented by amorphous solid dispersions, nanocrystals, polymeric and lipid based carriers along with mesoporous carriers and supercritical fluid processing. Emerging platforms, especially co-amorphous formulations, deep eutectic solvents, ionic liquids, hybrid nanostructures and 3D printing of dosage units increases solubility and bioavailability even more. Collectively, these innovations supported by AI enabled predictive modeling are promising giants toward the realization of strong patient centric solutions for poorly water soluble therapeutics.

Keywords: Solubility enhancement; Amorphous solid dispersions; Nanotechnology; Lipid based drug delivery; Poorly water soluble drugs

Introduction

The rapid growth and expansion of modern drug discovery have resulted in more and more highly potent lipophilic drug candidates moving through the drug development pipelines. Nearly forty to seventy percent of new chemical entities (NCEs) that are Biopharmaceutics Classification System (BCS) Classes II and IV have poor aqueous solubility, which leads to poor absorption and poor oral bioavailability. These solubility problems create major formulation challenges, which often lead to erratic pharmacokinetics, high inter patient variability and lack of therapeutic efficacy resulting in later stage clinical failures or the exclusion of promising candidates. Therefore, improving solubility and dissolution performance has become a crucial element in the early formulation design, pharmaceutical development and translation research [1].

Drug solubility is intrinsically governed by molecular properties such as lipophilicity, crystalline lattice energy, pKa, hydrogen bonding potential and polymorphism. Externally solubility is affected by pH, solvent system, concentrations of surfactant, particle size and microenvironmental conditions within the gastrointestinal tract. There is a need to understand these physicochemical and biopharmaceutical determinants for choosing rational enhancement approaches. Traditional approaches, such as particle size reduction, pH adjustment, salt formation, co solvency, solubilization driven by surfactants and cyclodextrin complexation have for many years been very common frontier techniques because of their relative simplicity and familiarity from industrial applications [2]. However, it is common that these methods deliver limited improvements or restricted by physicochemical incompatibilities, precipitation when diluted or the inability to be scaled up.

Advances in materials science and nanotechnology outcomes in solubility enhancement have produced manipulation of drug physicochemical states at the molecular level. Technologies, like amorphous solid dispersions, drug nanocrystals, polymeric nanoparticles, lipid and drug delivery systems, mesoporous carriers and supercritical fluid engineering, provide significant improvements in apparent solubility, dissolution rate and stability. These modern systems promote supersaturation maintenance, better gastrointestinal permeation, and lymphatic transportation, which promote better bioavailability of molecule with high insolubility [3].

Furthermore, there are hybrid approaches, for example, co amorphous materials, deep eutectic solvents, ionic liquids, and 3D printed dosage forms that offer novel platforms for personalized and precision oriented therapeutics. With the ongoing development of artificial intelligence, machine learning, and predictive modelling, formulation scientists can design solubility optimized systems with increasing speed and accuracy [4]. Therefore, an integrated knowledge and comprehension of classical and contemporary solubility enhancement methods is critical to fulfil the demand for safe, effective and patient centrical pharmaceuticals products. This review shows an in depth study concerning the current developments and future horizons on solubility enhancement of poorly water soluble drugs.

Physicochemical and Biopharmaceutical Determinants of Solubility

The solubility of a pharmaceutical entity depends on a complex balance of the intrinsic molecular properties of the entity and extrinsic biopharmaceutical conditions that the drug will experience during gastrointestinal passage [5]. A mechanistic understanding of these determinants allows rational design of formulations to improve solubility and allows for a better prediction of the *in vivo* dissolution behavior.

Intrinsic Physicochemical Determinants

Molecular Architecture and Lipophilic Density

Structural features such as aromatic ring systems, halogen atoms and long, spontaneously hydrophobic regions cause a higher li-

pophilic density and hence lead to lower affinity to aqueous media. Molecules with high partition coefficients (log P) tend to have a limited hydration capacity and low solute-solvent interactions and this tends to manifest itself as a low aqueous solubility [6].

Crystalline Lattice Strength and Solid-State Arrangement

The crystalline form of a drug is its lowest energy state, which has very strong packing of the molecules rich in intermolecular bonds and is very difficult to dissolve in a solvent. Polymorphic transitions, the formation of hydrates and the presence of metastable forms can have a significant impact on solubility. On the other hand, amorphous solids being with higher free energy and higher molecule mobility, usually exhibit better apparent solubility and faster dissolution profiles [7].

Ionization Behavior (pKa) and Microenvironmental pH

Ionizable pharmaceuticals have pH dependent solubility that is determined by their pKa values. The ionized species are usually clearer in aqueous solubility; therefore, strategic adjustment of the micro environmental pH of a dosage form can be used to increase dissolution efficiency [8].

Hydrogen Bonding Capacity and Steric Modulation

The tendency of drug to form hydrogen bonds or dipolar interaction with water molecules has a critical effect on solubility. Bulky substituents or molecular conformations that are rigid are often obstructing the accessibility of solvent reducing solubility [9].

Biopharmaceutical Determinants
GI Physiological Environment

Solubility changes dynamically along the gastrointestinal tract due to changes in the pH, ionic strength and buffer capacity. Weak bases are represented as being more soluble in the acid environment of the stomach and weak acids are represented as being more soluble in the more alkaline pH of the small intestine [10].

Endogenous Solubilizing Agents

Bile salts, phospholipids and dietary lipids promote solubilization through the formation of mixed micelles and liquid crystalline structures, which enable the promotion of lipophilic compound dissolution [11].

Particle Size, Wettability, and Interfacial Behavior

Reducing particle size has the effect of increasing the surface area and interfacial energy which in turn accelerates the rate of dissolution. Enhanced wettability in the form of surfactants or hydrophilic polymers better improve the penetration of a solvent [12].

Supersaturation and Permeability Interdependence

Controlled induction and maintenance of supersaturation on the other hand provides a transient driving force for absorption. The combination of solubility, precipitation kinetics and membrane permeability is ultimately determines overall bioavailability [13].

Traditional Approaches for Solubility Enhancement

The older theories of solubility enhancement are the building blocks of pharmaceutical formulation science. Although conceptually classical, these approaches are still highly relevant in particularly in the early stages of development, because of their simplicity, regulatory familiarity, and scalability [14]. Their success comes from the manipulation of basic principles of dissolution kinetics, ionization, and intermolecular interactions.

Category	*Determinant*	*Key Description*	*Impact on Solubility*
Physicochemical Factors	Molecular Structure & Lipophilicity	Presence of hydrophobic groups, aromatic rings, and bulky substituents have an effect on polarity and solvency.	High lipophilicity has a drawback of poor aqueous solubility through poor drug-water interaction
	Crystalline Form, Polymorphism & Amorphicity	Solid-state Arrangement, League and existence of metastable or amorphous States.	Strong crystalline lattice reduces solubility, amorphous systems exhibit an enhanced apparent solubility.
	Ionization & pKa	Extent to which ionized at different pH.	Ionized are better soluble. pH changes throughout the GI tract.
	Hydrogen Bonding & Intermolecular Forces	Ability to enter into hydrogen bonds and dipolar interactions with water.	Increases in the strength of the interactions with the water will increase the solubility of solvation: steric hindrance will decrease the solvation.
Biopharmaceutical Factors	Gastrointestinal pH & Buffer Capacity	Varying pH environments between stomach and intestine of ionizable drugs.	Weak Bases dissolve more in acidic pH- Weak Acids more soluble in alkaline pH.
	Bile Salts & Endogenous Surfactants	Natural solubilizers GI fluids micelles & mixed micelles	Increase solubility of lipophilic drugs by the solubilization effect of micelles.
	Particle Size & Surface Area	Drug particle size, wettability and the internal contact.	Smaller particles dissolve at a faster rate because of the available surface area and better wetting.
	Permeability & Supersaturation characteristics	Balance between solubility, rate of dissolution and transport through the membrane.	Maintain supersaturation: Reduce the rapidity of the precipitation to increase benefits of solubility.

Table 1: Physiochemical and Biopharmaceutical properties affecting the solubility.

Particle Size Engineering: Micronization and Comminution

Particle size reduction is one of the first and most important methods for dissolution rate improvement that is universally applied. By reducing the particle size, the surface area available to the dissolution medium increases, which increases the rate of release of drug as per the Noyes-Whitney equation. Techniques such as jet milling, ball milling and micronization continue to be industry standards. However, their effectiveness is often limited to moderate improvements as the dissolution (thermodynamic) in itself is not that much enhanced [15, 16].

pH Manipulation and Microenvironmental Modification

The solubility of many weakly acid or basic drugs is pH dependent. Classical pH adjustment by addition of an alkalizer, acidifier, or buffer system improves the ionization and dissolution. Microenvironmental pH modulation in solid dosage forms and its localised solubility advantage is of particular value for poorly ionizable molecules [17].

Salt Formation: Lattice Disruption for Better Solubilization

The formation of salt is one of the most successful of traditional ways in order to reduce the lattice energy and increase the solvation. Numerous commercial preparations are based on the salt form (e.g. diclofenac potassium or omeprazole sodium). While effective, salt

forms can potentially get stability issues (hygroscopicity, disproportionation etc.) [18].

Co-Solvency and Hydrotropy

Co solvents such as ethanol, PEG or propylene glycol act to improve solubility by reducing the solvent polarity. Hydrotropic agents some other molecules enhance solubilisation by the effect of enhanced solute solvent interactions, such as sodium benzoate, nicotinamide. These methods are used widely in parenteral and oral liquids but are in risk of precipitating on dilution [19].

Surfactant-Mediated Solubilization

Surfactants can lead to the formation of micelles, and they encapsulate the hydrophobic drug molecules to improve the apparent solubility. Non ionic surfactants such as Tween or poloxamers are still the ones of choice because they are biocompatible [20].

Complexation and Cyclodextrin Chemistry

Complex formation using cyclodextrins or hydrophilic polymers enhances drug-wettability as well as stability Inclusion complexes provide flexibility in the dosage form and are still a mainstay in improving solubility orally [21, 22].

Modern Advanced Solubility Enhancement Technologies

Advances in formulation science have led to the development of a new generation of solubility enhancement technologies designed to overcome the shortcomings of traditional approaches. These modern systems make use of nanoengineering, supramolecular chemistry, as well as high energy solid state transformations in order to achieve maximum dissolution performances, maintain supersaturation and enhance bioavailability of poorly water-soluble drugs [23].

Amorphous Solid Dispersions (ASDs): High-Energy Molecular Engineering

Amorphous Solid Dispersions have become a mainstay of modern solubility enhancement strategies because they have the capacity to transform crystalline formulations into high energy amorphous formulations that have superior apparent solubility. Through techniques such as hot melt extrusion (HME) spam drying, freeze drying, and processing using the advanced KineticSol technology the drugs are molecularly dispersed inside polymeric carriers such as HPMC-AS, PVP or Soluplus. These carriers inhibit nucleation and recrystallization, prolong supersaturation in gastrointestinal conditions and significantly improve *in vivo* absorption. The scalability, continuous manufacturing capability, and acceptance of ASDs by regulators have aided in the widespread adoption of ASDs in current drug development [24].

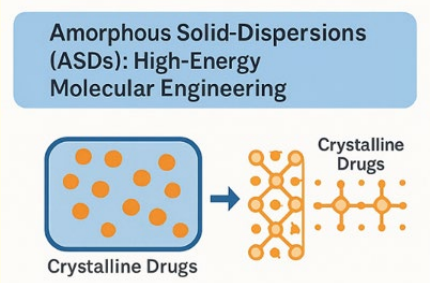

Figure 1: Amorphous solid Dispersion.

Nanotechnology-Enabled Drug Delivery Systems

Nanotechnology offers novel and accurate control of particle dimension, charge at surface and surface morphology and results in a profound shift in solubility and dissolution behaviour. Nanocrystals are nanosized particles based on pure drug, and deliver quick dissolution from immense surface area and increased saturation solubility. Polymeric nanoparticles (PLGA, PCL, PLA) are used for encapsulating the drug which increases solubilization, protection against destruction, and targeted delivery. Lipid-based nanocarriers are solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) which include solubilization and controlled release and increased permeability. These nanosystems can facilitate lymph absorption and bypass the liver metabolism, which increases the bio-availability of highly hydrophobic molecules [25, 26].

Lipid Based Drug Delivery Systems (LBDDS)

Lipid based formulations, such as SEDDS, SMEDDS, microemulsions and nanoemulsions are especially effective for the formulation of BCS Class II drugs. Upon contact with the gastrointestinal fluids, these systems spontaneously aggregate to form fine emulsions or mixed micelles, solubilize drugs, inhibit drug precipitation, and promote drug absorption. Their capacity to imitate physiological fat digestion and the use of the endogenous bile constituents decisively contributes to an improved performance. LBDDS are still some of the most successful advanced oral delivery technologies, with a number of marketed products [27].

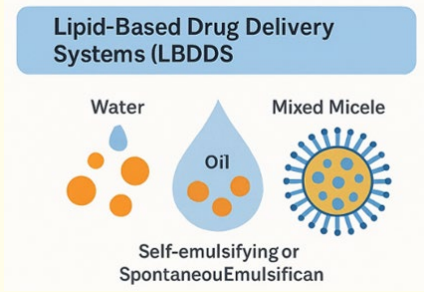

Figure 2: Lipid Drug Delivery.

Supercritical Fluid (SCF) Processing: Precision Particle Engineering

SCF technologies allow solvent free particle engineering with tight control over particle size and morphology. Processes like RESS, SAS, and PGSS produce micron or nanometer scale sized particles having better wettability and dissolution and avoiding thermal and solvents-related degradation [28].

Mesoporous Carriers and Nanoconfinement Strategies

Mesoporous materials such as MCM-41 and SBA-15 have regular sized nanopores which allow the immobilization of drug molecules in amorphous state. This nanoconfinement avoids recrystallization, and provides exceptionally rapid release and are therefore attractive platforms of next generation solubility enhancement [29].

Hybrid and Next-Generation Formulation Strategies

The increasing complexities of poorly water soluble drug molecules have given rise to the accelerated changes in formulations to hybrid and new generation of formulating approach based on combination of principles of nanotechnology, molecular engineering, supramolecular chemistry and sophisticated manufacturing. These emerging strategies overcome limitations of traditional solubility technologies through their improved stability, release kinetics, patient specific adaptability and improved bioperformance [30, 31].

Co-Amorphous Drug Systems: Synergistic Stabilization

Synergistic Stabilization Co amorphous systems are a new generation evolution of amorphous solid dispersions. Instead of polymeric carriers, two or more components of low molecular weight (drug - drug or drug-coformer) are co-amorphized. This synergistic molecular interaction causes disruption of the crystallinity with enhancing the physical stability and prevention of recrystallization. Amino acids, organic acids and small molecule stabilizers (e.g. nicotinamide) are coformers, which increase the solubility and dissolution rate. Co-amorphous systems offer higher drug loading, lower excipients burden and storage stability advantages as compared to traditional ASDs [32].

Deep Eutectic Solvents and Novel Liquid-Phase Carriers

Deep eutectic solvents and therapeutic deep eutectic systems have become new ground breaking solubilizing environments. Formed by hydrogen bond interactions between a drug and a eutectic forming agent, these systems can have a dramatic effect on melting points as well as result in liquid bearing phases with enhanced solubilization capacity. DES can simultaneously act as solvent, stabilizer and permeation enhancer which make them potential platform for transdermal, oral, and injectable delivery [33, 34].

Ionic Liquids and API-Ionic Liquid Systems

Pharmaceutical ionic liquids transform drugs into liquid salts so they are completely devoid of crystallinity. This way it offers exceptional solubility, adjustable viscosity, enhanced thermal stability, and tunability of permeability. By choosing the right counterions, performance of drugs can be made specific for their route of administration. These systems also have diminished polymorphic tendency and may be solubilizing excipients of hybrid nanosystems [35].

3D Printing and Additive Manufacturing of Solubility-Enhanced Dosage Forms

Additive manufacturing introduces unprecedented flexibility in designing dosage forms with tailored solubility profiles. Techniques like fused deposition modelling (FDM), selective laser sintering (SLS), and binder jetting can build solubility enhancement techniques (ASDs, nanocarriers or porous matrices) into targeted geometries. 3D printing enables a sigma dose personalized dosing, rapid disintegration platforms and on demand 3D printing is the essential next generation tool for creating patient centric medicines [36, 37].

Multifunctional Hybrid Nanoplatforms

Combining these principles for solubility enhancement is one of the distinguishing characteristics of next generation design. Hybrid systems can include nanocrystals in lipid matrices, ASDs according to polymeric nanoparticles, or mesoporous according to co amorphous drug pairs. These multifunctional constructs can provide controlled supersaturation, enhanced permeability, synergistic stabilization, and targeted delivery for extremely insoluble molecules to provide better performance [38].

AI Guided Formulation and Predictive Optimization

Artificial intelligence and machine learning models are playing an increasingly significant role in formulation design and prediction of solubility behavior, the optimal excipient combinations, the supersaturation kinetics, and the long term stability. This method is data driven, which means it helps in increasing the speed of developing a product and reducing the trial and error method of empiricism. Together, these hybrid techniques and next generation technologies represent a transformative shift in solubility enhancement from conventional and single mechanism strategies toward intelligent multifunctional and personalized pharmaceutical systems [39, 40].

Pharmaceutical Applications

Modern solubility enhancement technologies have opened new horizons over the therapeutic potential of poorly water-soluble drugs, in several dosage forms and therapeutic domains. Amorphous solid dispersions are widely used in oral tablets and capsules as a way of enhancing the bioavailability of BCS Class II compounds such as itraconazole, efavirenz and posaconazole. Nanocrystal

based formulations have offered fast acting formulations such as Onaject injectionable nano suspension like paliperidone palmitate. Lipid-based drug delivery systems (LBDDS including SEDDS and SMEDDS) are used in commercially available products like Neoral or Fortovase to improve uptake from lymphatics and variability of using highly lipophilic drugs [41, 42, 43].

Mesoporous carriers and polymeric nanoparticles have the advantage in targeted delivery, especially in the field of oncology (where solubility is beneficial for improving intracellular uptake of chemotherapeutics such as paclitaxel and docetaxel). Supercritical fluid technology is beneficial for manufacturing inhalation powders and controlled release oral systems of higher uniformity and dissolution performance. Additionally, new hybrid methods like deep eutectic solvents and ionic liquids, are finding application in transdermal and parenteral formulations for which extra permeability and stability is needed. Collectively, these solubilitynenhancing strategies make the delivery of drugs efficient, from better patient outcome and to allowing the clinical use of challenging drug molecules [44, 45].

Regulatory and Stability Considerations

All aspects of regulatory and stability considerations are critical for the development, approval, and lifecycle management of solubility enhanced formulations. Because the physicochemical state of the drug is fundamentally changed by modern technologies (amorphous solid dispersions, nanocarriers, lipid-based systems, ionic liquids), regulatory bodies insist on the comprehensive characterization, good quality control and long term performance evaluation. From a regulation point of view, needed to be strictly evaluated by regulatory agencies such as FDA and EMA critical quality attributes (CQAs) like particle size distribution, polymorphic purity, residual solvent, amorphicity, excipient interactions, and physical stability. For nano-enabled systems, special guidance requires evaluation of the surface charge, surface morphology, aggregation behaviour and possible immunogenicity [46, 47].

The ICH guidelines (Q8-Q11) guide the use of Quality by Design (QbD) and risk based approaches to ensure reproducibility and controlled manufacturing of high energy or nanostructured drug products. Stability considerations are equally important. High energy formulations such as ASDs and co amorphous systems are susceptible to physical instability: recrystallization, uptake of moisture, phase separation and relaxation of polymer system. Nanotechnology based systems may have challenges with particle aggregation, Ostwald ripening or surfactant degradation. Lipid based systems necessitate monitoring of lipid oxidation, drug precipitation and drift of droplet sizes in the storage condition. To ensure long term stability formulation mechanisms are often used such as polymeric stabilization, moisture protective packaging, antioxidants and crystalline inhibitors. In addition, regulatory evaluation of new types of excipients (e.g., ionic liquids, DES, advanced polymers) have to be toxicological justification and safety profiling. Accelerated stability studies under ICH Q1A conditions are still necessary to predict shelf-life and shelf-stability of the product, and ensure that the therapy remains consistent. Overall, regulatory and stability assessments are an integral process in the effort to ensure the necessary safe, reproducible and clinically reliable performance of solubility enhanced pharmaceutical products [48].

Future Perspectives

Future solubility enhancement strategies will include ever more of the elements of advanced material science, intelligent formulation design, and personalized medicine. Artificial intelligence and machine learning models are expected to advance formulation development by several decade by predicting optimal excipients combinations, supersaturation profiles, and long term stability with a high level of accuracy by significantly reducing the workload for experimental work [49].

Hybrid systems, i.e. nano amorphous systems, mesoporous carrier and multifunctional polymeric matrix, will offer improved stability and controlled release for highly insoluble compounds. Emerging platforms such as those based on ionic liquids, deep eutectics solvents and therapeutic eutectic systems provide adaptive solubilization environments of enhanced biocompatibility. Furthermore, 3D and 4D printing technologies will allow dosage forms specifically designed for the patient with customizable dissolution characteristics and ready-on-demand manufacturing. Sustainability based strategies, solvent free processing and use of biodegradable excipients, will also come into the foreground. Collectively, future innovations will enlist the establishment of faster development, increased clinical efficiency, and more personalized solutions for poorly water soluble drugs [50, 51].

Conclusion

Poor aqueous solubility also poses a huge challenge in the successful development of many pharmaceutical drug molecule, especially drug molecules listed under BCS Class II and IV. This review shows that a complete knowledge of physicochemical and biopharmaceutical determinants is necessary to the choice of effective solubility enhancement strategies. Traditional methods such as particle size reduction, pH modification, salt formation, and complexation still render potential foundation benefits, but the recent new technologies like the amorphous solid dispersion, nanotechnology-based systems, lipid systems, and supercritical fluid processing give a considerable supplement in dissolution and bioavailability. Emerging hybrid strategies, ionic liquids, deep eutectic solvents, and additive manufacturing create additional, extensive opportunities for, personalized and high-performance formulations. Looking forward, formulation design using AI and technologies that focus on sustainability will play a key role in driving the development and improving clinical outcomes. Collectively, these advancements represent a solid pathway to address solubility issues and maximize therapy effectiveness.

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