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Impact of Poor Solubility on Drug Development

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1.1 Introduction

Poor aqueous solubility remains one of the most significant challenges in modern drug development, impacting nearly every stage of the pharmaceutical product development pipeline. A significantly large proportion of drugs (commonly referred to as active pharmaceutical ingredients [APIs]/new chemical entities [NCEs], lead molecules, etc.), identified through high-throughput screening, exhibit poor solubility, which in turn limits their bioavailability and therapeutic efficacy. This challenge begins as early as the candidate selection phase, where compounds with inadequate solubility may be selected due to their strong and potent pharmacological activity. As development progresses into preclinical and clinical studies, insufficient solubility complicates formulation design, dosing accuracy, and pharmacokinetic profiles, thereby delaying development timelines and increasing costs. Even in post-clinical stages, poor drug solubility can affect long-term storage stability, scalability, etc. (e.g. particle size ripening due to poor drug solubility, loss of product stability due to drug precipitation on storage). This may possibly result in product recalls and, in some cases, complete product withdrawal from the market, hindering the commercial success of the final product.

Over the past decades, numerous strategies have been explored to overcome solubility limitations. These include drug material engineering (salt formation, co-crystallization, prodrugs, etc.), formulation strategies (solubilization techniques, solid dispersions, nanocrystals, lipid-based formulations, cyclodextrin inclusion complexes, etc.), or a combination of them. Selection of the most appropriate solubility enhancement technique, however, is highly dependent on the target product profile, physicochemical properties of the drug, intended route of administration, therapeutic indication, and commercial considerations.

This book gives an in-depth account of such approaches and provides a comprehensive summary of the current strategies available to address poor drug solubility, highlighting their principles, commercial success, advantages, and limitations.

This introductory chapter focuses on understanding the solubility concept and its impact on drug performance. Followed by a brief outline of important and widely reported solubility enhancement strategies. Further, the chapter proposes a possible roadmap to aid researchers and formulators in the systematic selection of solubility enhancement approaches best suited for specific drug candidates. With meticulous integration of these strategies early in development, it is possible to achieve drug bioenhancement, reduce product failures/attrition rates, and ultimately enhance the likelihood of successful translation of the safe, effective, and stable drug product to the market.

1.2 Drug Solubility

Solubility can be defined as the highest amount of solute dissolved in a given solvent to form a homogeneous one-phase saturated solution. Fundamentally, saturation solubility depends innately on the solute (physicochemical properties), solvent (physicochemical properties, composition, volume), and other parameters (temperature, pressure), which are summarized in Figure 1.1 [1, 2].

According to the International Union of Pure and Applied Chemistry (IUPAC), solubility is defined as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. In literature, the solubility for a given solute–solvent system is represented by various units, including

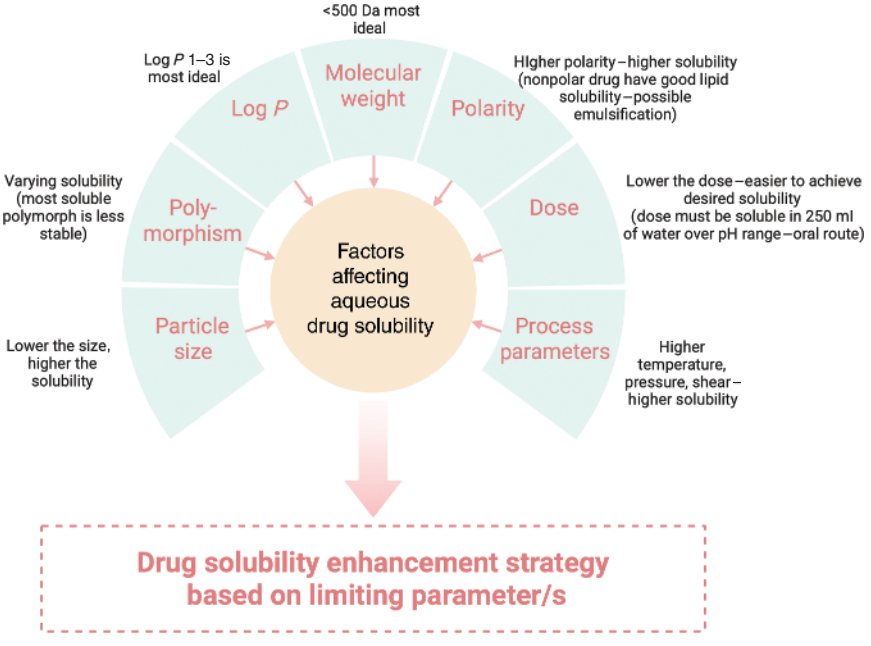

Figure 1.1 Schematic of key factors affecting drug aqueous solubility as well as the possible strategies to address the same.

but not limited to concentration (weight and volume ratio), molality, mole fraction, mole ratio, etc. [1].

Solubility, the commonly described and well-known physical chemistry concept explained above, plays a significant role in the journey of the lead molecule becoming a clinically available drug. Specifically, the overall solubility profile of the drug, more critically, their aqueous solubility exhibits a crucial impact on every stage of drug development, including drug discovery, pharmaceutical product development, and preclinical and clinical success. In simple terms, how a drug moves and/or works in the body depends on how well it dissolves in the body fluids. Good drug solubility in the gastrointestinal (GI) tract enables better absorption, distribution, metabolism, excretion, and toxicity regulation (ADME/Tox). This, in turn, affects the drug safety, bioavailability, effectiveness, and ability to reach the target receptor to produce the desired pharmacological effect.

In this context, knowledge of solubility from a pharmacopoeial perspective and understanding of the Biopharmaceutical Classification System (BCS) are of key importance. The United States Pharmacopoeia (USP) and the British Pharmacopoeia (BP) describe and categorize solubility potential as the saturation solubility of a solute in the given solvent, as described in Table 1.1 [3]. However, for a drug candidate, the solubility concept needs further consideration in relation to its dose. For example, a hypothetical drug candidate "A" that is sparingly soluble but highly potent and administered at a low dose may still dissolve adequately in the GI tract after oral administration. In contrast, a drug candidate "B" that is also sparingly soluble but requires a high dose may not fully dissolve in GI fluids, creating a barrier to absorption.

Furthermore, overall drug absorption is a dynamic process that is not only influenced by drug solubility but also by drug permeability. Drug absorption involves the overall movement of the drug from its site of administration to the systemic circulation. For an orally administered drug, this means that the rate of absorption depends on both the rate and extent of drug dissolution in GI fluids, as well as the ability of the drug to permeate the GI membrane. To amalgamate

Table 1.1 Solubility description per the United States Pharmacopoeia (USP) and the British Pharmacopoeia (BP).

Description forms	Parts of solvent required for one part of solute	Solubility range (mg/ml)
Very soluble (VS)	<1	>1000
Freely soluble (FS)	From 1 to 10	100–1000
Soluble	From 10 to 30	33–100
Sparingly soluble (SPS)	From 30 to 100	10–33
Slightly soluble (SS)	From 100 to 1000	1–10
Very slightly soluble (VSS)	From 1000 to 10,000	0.1–1
Practically insoluble (PI)	>10,000	<0.1

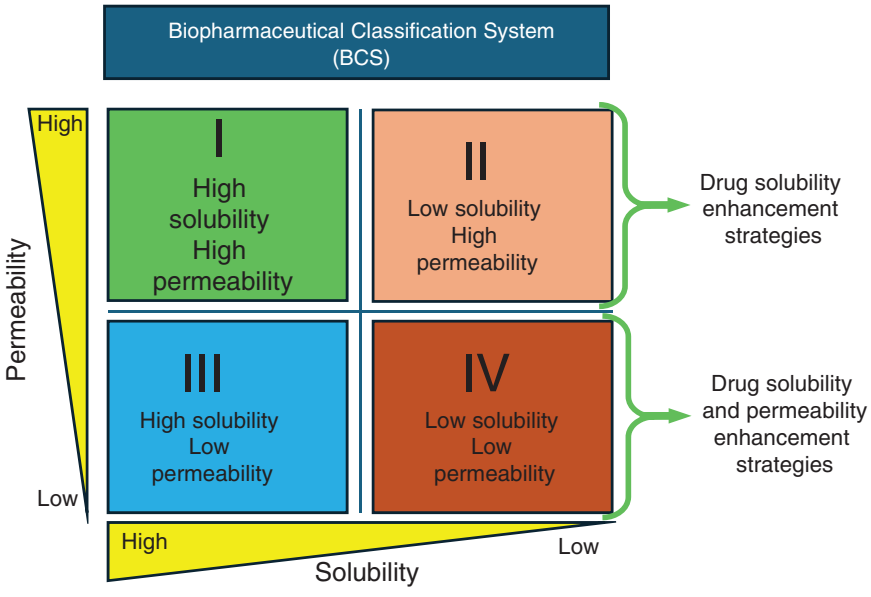

Figure 1.2 Schematic of Biopharmaceutical Classification System (BCS) and the rationale to enhance bioavailability of poorly soluble BCS Class II and IV drugs.

these solubility and permeability parameters, the BCS was established. Per BCS, drug solubility is the ability of a drug to dissolve in an aqueous phase. For oral medications, this is the capacity of the drug to dissolve in GI fluids. As per the classification system, a drug is considered highly soluble if its highest dose dissolves completely in 250 ml of water across the physiological pH range of 1.0–6.8 at 37 ± 1 °C (encompassing the lowest volume and pH variation across the GI tract). The BCS explains drug permeability as the ability of a drug to pass across the biological membranes (e.g. GI membrane), entering the systemic circulation. As per the classification system, a drug is considered highly permeable if ≥85% of it is absorbed into the systemic circulation. In a nutshell, effective drug absorption requires both high solubility and permeability. Based on variability in solubility and permeability, the drugs are broadly classified into four BCS classes, viz., Class I (high solubility, high permeability), Class II (high permeability, low solubility), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability) (depicted in Figure 1.2) [4].

1.3 Impact of Poor Drug Solubility on Drug-Like Properties

Drug-like properties represent suitable physicochemical and biological characteristics of a lead compound, which make it a potential candidate for consideration as a safe and effective therapeutic drug. For a lead candidate with a potent target effect (pharmacological efficacy), the widely used tool to assess drug-likeness is

Lipinski's rule of 5, which focuses on and describes physicochemical aspects of an orally active molecule to be drug-like based on four parameters, viz., molecular weight less than 500 Da, *n*-octanol/water partition coefficient (Log *P*) not exceeding 5, no more than 5 hydrogen bond donors, and no more than 10 hydrogen bond acceptors [5, 6]. Drug candidates that follow this rule exhibit an acceptable solubility and permeability profile, translating to an advantageous ADME/Tox profile, enhanced drug absorption, and bioavailability.

The challenge of low drug solubility has become increasingly prominent in recent years, with widely preferred screening methods of identifying and shortlisting lead candidates based on high potency at the biological target receptor (drug–ligand interaction). While drug potency will always be a priority, adopting a balanced approach of additionally scrutinizing drug-like properties (ensuring satisfactory ADME/Tox properties) and drugability (potential for commercial translation) will be helpful. Advances in combinatorial chemistry, high-throughput screening, and artificial intelligence-driven drug lead identification have further reinforced this trend, as they often emphasize the discovery of high-potency lead candidates that naturally have higher molecular weight and lipophilicity. This has resulted in the growing prevalence of drug leads with poor aqueous solubility, posing significant challenges to successful drug development and clinical drug product realization. Statistically, this trend is on a significant rise, and as per a report published in 2024, it is estimated that approximately 80–90% of lead drugs under development exhibit poor water solubility (BCS Class II and IV), in contrast to only about 40% of currently marketed oral drugs [7].

The high-risk journey of the drug from discovery to clinic is long and expensive (~10–15 years; ~$1.8–2.2 billion USD) with a high clinical development failure rate of ~90%. Based on analysis of clinical studies conducted between 2010 and 2017, a report published in 2022 states that 40–50% of failures resulted from suboptimal clinical efficacy, 30% from unmanageable toxicity, 10–15% from unacceptable drug-like properties, and 10% due to low commercial need or strategic failure. An increasing number of drugs with poor solubility (BCS Class II and IV) can be a key reason for clinical failure, as poor solubility can negatively impact clinical efficacy, safety (high toxicity), and poor drug-like properties. Hence, it is of key importance to ensure satisfactory drug solubility early on in the drug development process to reduce the rate of attrition and failure during product development and clinical trials. The key considerations to assess the underlying reasons for poor drug aqueous solubility and strategies to address the same are depicted in Figure 1.1.

1.4 Addressing Poor Drug Solubility Challenge

Various approaches have been explored to overcome the challenge of poor aqueous solubility to ensure successful product development. They can be broadly classified into two categories, viz., drug material engineering and formulation approaches, which are described in subsequent sections [4, 8–11].

1.4.1 Drug Material Engineering

The physicochemical properties of the drug itself can be modified to overcome the poor solubility challenge. This approach involves physical and chemical methods as described in the following subsections.

1.4.1.1 Particle Size Engineering

The solubility of any chemical is intrinsically dependent on the particle size. As particle size reduces, surface area and surface area-to-volume ratio increase, allowing better interaction with the solvent and thereby increasing the rate and extent of dissolution. This approach of particle size reduction has been widely explored as a strategy to develop drugs with enhanced dissolution rate, solubility, and bioavailability. To achieve such size reduction, various top-down (comminution, milling, etc.) and bottom-up techniques (spray drying, nano- and microprecipitation, etc.) are reported.

Micronization is one such commonly used method capable of reducing the size of coarse drug particles (preferably less than 5 μm), resulting in a significant enhancement of drug dissolution. However, in some cases, it offers challenges of drug crystal structure interference due to high-energy size reduction processes like pulverization and milling. As a solution to this problem, the use of spray drying and supercritical fluid technology is on the rise [12–14].

In recent years, advancing on this concept, further reduction in drug particle size under 1 μm has gained wide attention, yielding drug nanoparticles. Such extensive particle size reduction can offer the dual benefit of enhancing the drug solubility by extensive reduction in diffusion layer thickness and permeability enhancement due to high proclivity to cross biological membranes (e.g. GI tract lining). Thus, drug nanonization can result in significant bioavailability enhancement compared to drug micronization. For example, danazol, a BCS Class II drug used as a synthetic steroid, exhibited ~13-fold bioavailability improvement using the drug nanoform (size: ~180 nm) compared to the unmilled drug (size: 8 μm) [12–15]. However, particle size reduction to the nanoscale comes with the challenge of stabilizing and maintaining the reduced particle size. Therefore, the drug particle size reduction approach is generally combined with a suitable formulation strategy (nanocrystal, nanosuspensions, solid dispersion, etc.) that is capable of stabilizing the reduced particle size over the product stability period, ensuring retention of low particle size, enhanced solubility, and bioavailability. For a detailed description of this approach, refer to Section 1.4.2.2 and Chapter 3.

1.4.1.2 Modulating Drug Properties: Salts, Solvates, Polymorphs, and Co-crystals

This approach for drug solubility modulation utilized both physical and chemical methods like the development of salts, solvates, specific polymorph selection, and co-crystal technology.

Use of drug salts for poorly soluble drugs is the most widely used and industrially favored approach. This requires an ionizable drug (cationic/anionic/zwitterionic)

capable of ionic linking to the counterion. The first salt form of a drug approved by the US Food and Drug Administration (US FDA) back in 1939 was heparin sodium, and since then, over 50% of US FDA-approved drugs are salts. Among these, hydrochloride salts are the most common. This is an interesting approach as the developed salts are ionic in nature, which increases the apparent aqueous solubility but retains the efficacy of the drug without chemical modification [12, 16]. For example, chlorpromazine, a BCS Class IV drug, showed high potency as an antipsychotic, but the original base form was insoluble in water. To overcome the challenge, the drug was converted to chlorpromazine hydrochloride (salt form), which showed enhanced solubility and bioavailability. The drug salt form was successfully translated to a clinically available product (Thorazine®). Further, it was also reported that the crystalline salt form not only increased the solubility and bioavailability but also conferred better stability to the product [17, 18].

Selection of an appropriate polymorph (different crystalline forms), pseudopolymorphs (solvates, hydrates—the US FDA recognized them as polymorphs), or amorphous (non-crystalline) form can also critically modulate the drug solubility. This is one of the key approaches, as 80% of the pharmaceutical compounds are polymorphic in nature [19]. Interestingly, it is reported that the polymorph with low stability (high internal energy) tends to exhibit the highest solubility/dissolution. Therefore, if such a highly soluble polymorph is selected for product development, it comes with a challenge of transformation to a stable polymorph (less soluble) upon storage. Hence, to maintain the highly soluble polymorphic state of a drug (often unstable), a combination with an appropriate drug stabilizing formulation strategy is necessary. The classic example for this is the well-known story of ritonavir (Norvir®), a blockbuster anti-human immunodeficiency virus (anti-HIV) drug that was introduced in the market, wherein the poor drug solubility was enhanced by using a more soluble drug polymorph I. However, upon storage, the drug transformed into stable but less soluble polymorph II, failing to elicit the desired bioavailability and efficacy. Hence, the product was withdrawn from the market, which not only impacted the patients relying on the treatment but also caused severe financial loss to the company. Ultimately, the product was reintroduced in the market by reformulating it with a newer excipient composition that was able to stabilize and retain the soluble polymorph I. This highlights the critical need to approach solubility enhancement strategy through a lens of long-term stability [20].

The new emerging approach in this context is the development of drug co-crystals, which are multimolecular crystalline structures resulting from non-covalent/nonionic interactions. The approach involves the development of a drug–excipient or drug–drug co-crystal for enhancement. Many products (Seglentis®, Depakote®, Entresto®, Lexapro®, etc.) developed with this approach are already available in the market. Seglentis® is a unique drug–drug co-crystal for the co-delivery of two drugs, celecoxib and tramadol, for acute pain in adults. The results indicate enhanced bioperformance, overcoming the individual drug solubility challenge and pharmacokinetic variation [21]. For a detailed description of this approach, refer to Chapter 4.

1.4.1.3 Prodrugs

The concept of prodrugs was first introduced in the late 1950s. A prodrug is a chemically modified derivative of the parent drug. The prodrug is designed with an objective to optimize the physicochemical properties of the parent drug, which, upon administration, can be subsequently converted back to the active parent drug via biotransformation. This unique strategy has been explored for a multitude of drugs and accounts for over 50 US FDA approvals in a 10-year period of 2012–2022 (~13% of US FDA-approved small molecule drugs) [22, 23]. Many such prodrug-based formulations designed for solubility and bioavailability enhancement are available in the market, including Cerebyx®, Solu-Medrol®, Sivextro®, etc. One of the well-known examples of improving drug solubility through a prodrug approach is isavuconazonium sulfate (Cresemba®), a medication prescribed for severe fungal infections (invasive aspergillosis, mucormycosis). Isavuconazole (BCS Class II), the parent drug, exhibited high antifungal potency, but the challenge was to make the drug soluble for intravenous administration. For this, a prodrug, isavuconazonium sulfate, showing significant improvement in solubility, was developed for intravenous use. Interestingly, the solubility enhancement was so significant that ultimately it also enabled the development of an oral version. The prodrug was meticulously designed to be biotransformed in blood (mainly by the enzyme butyrylcholinesterase) upon intravenous administration, while upon oral administration, it is rapidly biotransformed in the gut, liver, and blood. In both cases, the biotransformation to the active drug was highly efficient (about 98% bioavailability) [24]. It is important to note that, for the success of this approach, meticulous design of the prodrug is very important in a way that it should ideally ensure higher solubility and absorption (high bioavailability) followed by prompt biotransformation in systemic circulation to elicit a pharmacological response via the parent drug.

The challenge in this strategy is the possible rapid hydrolysis of such prodrugs prior to absorption. In such a scenario, this transformation would release the water-insoluble parent drug prematurely, resulting in limited absorption and bioavailability. One such example is oral hetacillin (Hetacin®), a prodrug of the widely known antibiotic ampicillin. The prodrug hetacillin showed significant solubility enhancement and was clinically approved for use, but later it was observed that the prodrug was unstable in water, with very quick chemical conversion to ampicillin, and hence did not show significant efficacy enhancement compared to ampicillin itself. Further, during breakdown, it was reported to produce formaldehyde in the GI tract, raising safety concerns. In view of this, the product was withdrawn from the market for human use. However, it is still being used for veterinary purposes via intramammary administration to treat mastitis in cows (PolyMast®). In this context, recently, a new technology, "Sol-Moiety," has been introduced that is capable of delaying and controlling the prodrug hydrolysis, ensuring sufficient solubilization and absorption, leading to enhanced bioavailability [25]. For a detailed description of this approach, refer to Chapter 8.

Overall, poor drug solubility raises issues in product development, but the solubility enhancement strategies based on drug material engineering, chemical form

modification, and optimization of crystal form must be explored with caution, ensuring feasibility, efficacy, safety, and stability as pragmatic endpoints.

1.4.2 Drug Formulation Approaches

Drug material engineering offers exceptional approaches to enhancing drug intrinsic solubility. However, stabilization of engineered drugs becomes a key challenge that can be resolved by strategic formulation approaches. Furthermore, unique and novel formulations capable of enhancing drug solubility and permeability are widely reported in the literature with successful clinical translation. These are discussed below.

1.4.2.1 Cosolvency, Hydrotrophy, and Solubilizing Agents

The use of cosolvents is a simple, effective, and widely adopted approach to enhance the solubility of drugs. In simple terms, a cosolvent can be viewed as a bridge between the drug and the aqueous phase. Cosolvents are water-miscible solvents that possess a unique ability to dissolve poorly water-soluble drugs, thereby increasing their solubility in the aqueous phase. The key is to identify a suitable solvent for the given drug, ensuring that it can be used safely at the required dose for the intended route of administration. Further, it is important to critically understand the impact of cosolvent dilution on drug solubility, because upon administration, the drug may precipitate if a poor cosolvent with limited cosolvency and/or miscibility is used.

In this context, several modeling methods such as Hansen solubility parameters, Hildebrand solubility parameters, thermodynamic modeling, and artificial neural networks have been employed as effective tools for identifying suitable cosolvents [26–29].

This strategy is particularly effective with nonionizable drugs having a moderate partition coefficient (log *P*-value: 1–3). Therefore, highly lipophilic drugs may not be suitable candidates for this approach. The use of cosolvency-based formulations of poorly soluble drugs is common in both oral and parenteral products. Well-known examples include Ativan®, Valium®, Nembutal®, Lanoxin®, etc. For instance, Ativan contains lorazepam (a BCS Class II drug, practically insoluble in water), which is dissolved in cosolvents such as propylene glycol, polyethylene glycol, and benzyl alcohol for intravenous and concentrated oral formulations. For a detailed description of this approach, refer to Chapter 10.

Hydrotropes are another category comprising small amphiphilic molecules (nicotinamide, amino acids, sodium benzoate, sodium salicylate, etc.) with small hydrophobic tails (compared to surfactants). Instead of forming micelles like surfactants, hydrotropes form aggregates, reduce water activity, and form complexes with the drug as mechanisms of solubility enhancement [12, 30]. However, the challenge with hydrotropes-based formulations is that they must be used in large amounts, which raises safety concerns. In this context, the new concept of "ionic liquids" is coming into the limelight as powerful, feasible, and safer hydrotropes. In an investigation, ionic liquids of cholinium vanillate, cholinium gallate, and cholinium

salicylate were tested to improve the aqueous solubility of two model drugs, ibuprofen and naproxen. The studies revealed that cholinium vanillate- and cholinium gallate-based ionic liquids increased the ibuprofen solubility by ~500-fold and all three ionic liquids increased naproxen solubility by ~600-fold [31, 32].

The next category is surfactant and/or solubilizing agents that are more widely explored. They have the capability of forming micelles at low concentration, thereby reducing surface tension, which is the predominant mechanism for enhanced drug solubilization. This approach is more meaningful for BCS Class II drugs, wherein the drugs exhibit poor solubility but have good permeability. This strategy, if it were to be explored for BCS Class IV drugs, would require further formulation rationale wherein these solubilizing strategies are used in conjunction with permeability enhancement approaches like the development of nanoformulations, discussed in subsequent sections.

1.4.2.2 Cyclodextrin Inclusion Complexes

Inclusion complexes are the supramolecular complexes wherein a solute (drug in this specific scenario) is encapsulated in a host molecule. From a drug solubility enhancement perspective, the host molecule exhibits a hydrophilic outer surface with hydrophobic pockets capable of encapsulating the drug. The macromolecule complex overall allows higher solubilization capacity by virtue of the high solubility of the host molecule. The most common example in the drug delivery spectrum is cyclodextrin-based inclusion complexes [33], with a few already in the market, Sporanox®, Vfend®, Nitropen®, etc. Sporanox is an antifungal oral solution comprising intraconazole, a water-insoluble drug (BCS Class II) that was formulated as an inclusion complex with hydroxypropyl-β-cyclodextrin, showing clinically significant bioenhancement [34]. For a detailed description of this approach, refer to Chapter 9.

1.4.2.3 Solid Dispersions and Solid Solutions

Solid dispersions are unique formulations that overcome poor drug solubility challenges by mixing the drug with hydrophilic excipients at the molecular level using techniques such as melt fusion, hot melt extrusion, and spray drying.

The mechanisms of solubility enhancement with this approach incorporate a multitude of reasons, including particle size reductions, conversion and stabilization of more soluble drug amorphous form, enhanced wettability, reduced drug aggregation, etc. As per the report, between 2012 and 2023, about 48 products based on amorphous solid dispersions have been approved by the US FDA. The most commonly used polymers for such development are copovidone and hypromellose acetate succinate, and the most commonly used methods are spray drying (~50%) and hot melt extrusion (~35%) [35]. However, as discussed in the polymorphism (Section 1.4.1.2), maintaining the molecular form of the drug in solid dispersions is of key importance as phase separation and drug instability are the main challenges in solid dispersion-based dosage forms. Owing to this challenge, a few marketed products like Rezulin®, Isoptin SR®, Incivek®, and Norvir® were withdrawn from the market due to drug instability (physical instability) and drug recrystallization issues impacting drug dissolution rate and bioperformance [36]. Therefore, though

solid dispersion is a widely sought approach for solubility enhancement, it must be used with caution for highly lipophilic drugs, ensuring drug stabilization. For a detailed description of this approach, refer to Chapter 2.

1.4.2.4 Nanoformulation Spectrum

Picking up on various concepts of physical and chemical approaches to enhance drug solubility, the current ideal and most explored approach is nanoformulations. To visualize, this approach can be looked upon as the amalgamation of multiple drug solubility enhancement approaches discussed thus far, including but not limited to particle size reduction, solubilization/stabilization with surfactants, cosolvency, encapsulation, etc., ultimately rendering a formulation with particle/globule size in the nanometric range. Nanoformulations increase the solubility of the drug and can also enhance permeability if the drug is encapsulated in a suitable nanocarrier, making them suitable for bioenhancement of BCS Class II and IV drugs.

The simplest of this category is nanosuspensions that aim at creating nanoformulations comprising drug nanocrystals that are stabilized using surfactants and/or steric stabilizers to maintain the nanoparticle size and crystal form. As per a report published in 2024, the first nanocrystal-based tablet product Rapamune® (sirolimus) was approved in 2000, and since then, about 20 products based on nanosuspension/nanocrystal technology have been approved by the US FDA. One of the recent ones in this category is Cabenuva® (cabotegravir/rilpivirine), a combination drug nanosuspension for intramuscular injection for the management of HIV-1 infections [37, 38]. One key technology in this arena is Elan's NanoCrystal® technology, which, in partnership, has entered the market with about nine product approvals. Furthermore, this strategy works best for drugs with high doses. Rather than encapsulating high-dose drugs in a nanoexcipient matrix that increases the bulk of the product, nanosuspensions utilize drug nanocrystals themselves, hence allowing accommodation of higher doses while controlling the product bulk for patient-compliant dosage form.

Lipid-based nanoformulations are another common nanoformulation platform explored for poorly soluble drugs. Many such products are already available in the market that include Sandimmune®, Norvir®, Lamprenes®, Elyxyb®, etc. This strategy harnesses the drug lipophilicity by solubilizing the drug in a lipophilic matrix (lipids/oils), followed by emulsification or vesicle formation that is capable of enhancing drug bioavailability. Self-emulsifying drug delivery systems (micro/nano) are an abundant category explored in this context, which utilizes a unique combination of oil, surfactant, and stabilizers to dissolve the drug in the oily phase with a capability of undergoing self-emulsification upon administration, rendering high drug solubility and permeability via colloidal droplet formation [9, 39]. Importantly, the products are prepared and stored as oily one-phase solutions and are therefore more stable than regular biphasic emulsions. Further, they undergo in situ emulsification in body fluids, allowing the benefits of emulsion-based drug bioenhancement. One such example is the US FDA-approved oral solution of celecoxib (Elyxyb®) for the acute treatment of migraine in adults. Celecoxib is a BCS Class II compound with inherently low water solubility, which was formulated as

self-microemulsifying drug delivery system (SMEDDS) to enhance the solubility and bioavailability. This advanced formulation has been clinically proven to enable faster absorption, resulting in a rapid onset of action, which is critically important for patients experiencing sudden and severe migraine attacks. Self-emulsifying systems, though look lucrative and easy to formulate, have the challenge of identifying the uniquely emulsifying oily composition and optimizing drug loading [9, 38, 40]. For a detailed description of this approach, refer to Chapter 5.

Vesicular lipid nanocarriers like liposomes, ethosomes, phytosomes, etc., have also been explored, and their unique feature is the capability of encapsulating both lipophilic and hydrophilic drugs. In the context of enhancing drug solubility, they can be used for both BCS Class II and IV category drugs and can be very advantageous for BCS Class IV drugs. These vesicles have a unique permeability feature owing to their bilayer structure, enabling better bioenhancement for BCS Class IV drugs with both poor solubility and permeability [41, 42]. For a detailed description of this approach, refer to Chapter 6.

Other nanoformulations explored for resolving drug solubility challenges are mesoporous silica-based nanocarriers, dendrimers, drug conjugates, etc., which are used in unique scenarios based on drug physicochemical properties and target product profile. Mesoporous silica has been investigated as an amalgamation of a solid dispersion approach for drug solubility enhancement with nanoformulations, wherein a highly nanoporous excipient like mesoporous silica (mean pore size: 2–50 nm; high surface area: up to 500 m^2/g; high pore volume: >1 cm^3/g) has been used to encapsulate the poorly soluble drug [43]. For a detailed description of this approach, refer to Chapter 7.

A combination of the aforesaid strategies has also been investigated to resolve the challenge of poor drug solubility early on in product development. For example, a study explored a combination of nanocrystal and co-crystal technologies to enhance drug solubility. Co-crystals of itraconazole and indomethacin with various coformers were prepared, and the particle size was reduced to a nanoscale (300–450 nm) using wet milling. Kinetic solubility studies showed that the nano co-crystals significantly increased the solubility compared to raw free drugs and conventional co-crystals. Specifically, the itraconazole–succinic acid nano co-crystal—achieved ~51.5-fold higher solubility compared to the free drug. These results demonstrate that combining multiple formulation strategies can synergistically improve solubility and dissolution, offering a promising approach for enhancing the bioavailability of poorly soluble drugs [44–46]. Further, a choice of drug dissolution enhancement strategy can vary based on the form of the drug, route of administration, etc. For example, Lenacapavir (BCS Class IV) has been approved as Sunlenca® for management of HIV. This unique formulation treatment dose is initiated as an oral therapy comprising a tablet dosage form containing the salt of the drug (lenacapavir sodium) to enhance its oral bioavailability to achieve an initial loading dose. This is followed by a twice-a-year subcutaneous injection given (drug with cosolvent polyethylene glycol depot) to achieve slow and sustained release of the drug over 6 months. Therefore, the dosage form design can vary based on the desired target product profile and therapy regimen [47, 48]. Therefore, the drug solubility

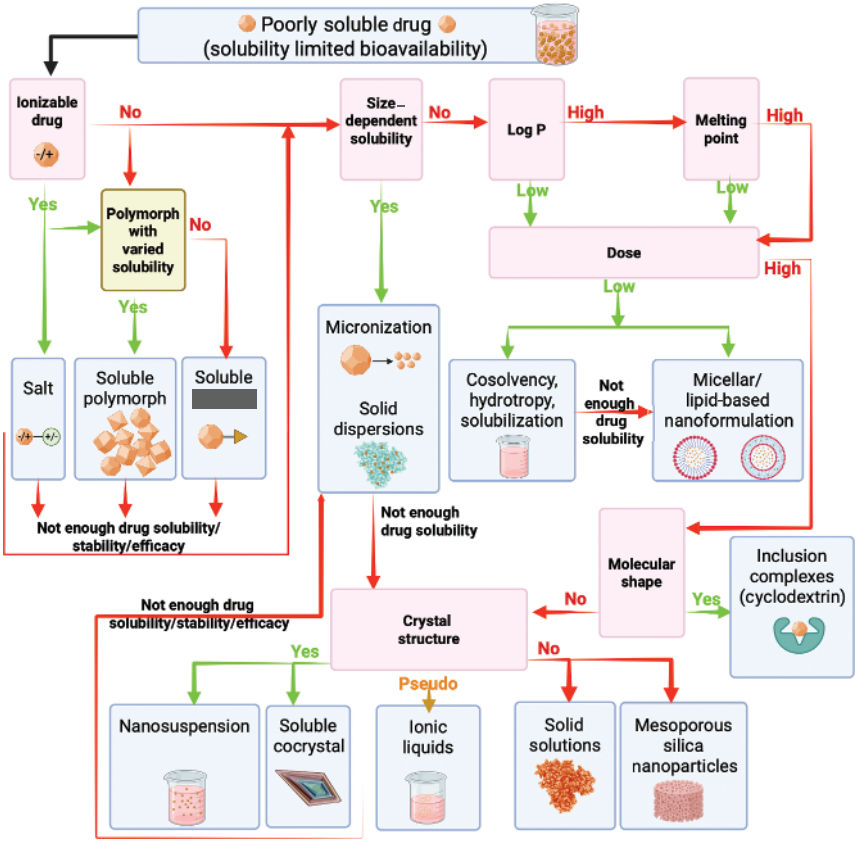

Figure 1.3 Schematic roadmap for selection of appropriate solubility enhancement approaches for successful product development of poorly soluble drugs.

enhancement approach for product development is rather a multipronged approach that requires understanding of the drug profile, dose, dosage form, route of administration, efficacy, stability, and commercial viability. Hence, there is no rule of thumb or a gold standard for the use of a specific drug solubility enhancement strategy. Based on extensive literature analysis and our experience in the field, we have developed a possible roadmap to narrow down amicable approaches for product development of poorly soluble drugs. This approach is mainly based on the drug's physicochemical properties and the desired target product profile, which has been depicted in Figure 1.3.

1.5 Poor Drug Solubility—Is It Always a Challenge?

In most cases, poor drug solubility is broadly considered a challenge or a problem, as it limits drug absorption, bioavailability, and overall efficacy. However, in some cases, it can be looked upon as a double-edged sword, wherein the low drug solubility

can be harnessed for sustained/controlled drug release, localized drug action, and enhancing drug safety. Therefore, in some therapeutic strategies, low drug solubility can be an advantage.

Drugs with poor solubility are beneficial in depot formulations. For instance, Haldol®, an antipsychotic medication prescribed for schizophrenia, comprises an almost water-insoluble (aqueous solubility: 0.01 mg/kg) decanoate ester derivative of haloperidol (haloperidol decanoate). It is commercially available as a sterile injection of haloperidol decanoate in sesame oil with benzyl benzoate as a preservative. Upon intramuscular administration, the Haldol depot formulation results in slow and sustained release of haloperidol due to low drug solubility. Specifically, it shows a gradual increase in haloperidol plasma concentration, reaching C_{max} in ~6 days, with a half-life ($t_{1/2}$) of ~3 weeks. Further, upon once-a-month administration, steady-state plasma concentrations are achieved within 2–4 months [49]. Another example is quarterly shots for birth control, Depo-Provera®, and its low-dose version Depo-SubQ Provera 104®. It comprises a very poorly soluble synthetic progesterone derivative, medroxyprogesterone acetate (BCS Class IV). Hence, low aqueous solubility or high lipophilicity (BCS Class II and IV drugs) can be utilized as an advantage to develop long-acting depot injections [7]. This strategy now not only allows for sustained drug release but also ensures patient compliance for chronic management.

Poor drug solubility can also be an advantage to achieve local action while minimizing systemic absorption. A simple example is the widely used over-the-counter medication, Pepto Bismol®, which contains a poorly water-soluble drug, bismuth subsalicylate (BCS Class IV drug). Poor solubility leads to multiple advantages, wherein the drug is not systemically absorbed but is contained in the gut for a longer duration, forming a coat to protect the GI lining and also elicit an antibacterial effect. Further, low drug solubility can also be advantageous in a topical product desiring local action without systemic absorption. For example, topical antifungal medication like Monistat® contains a low water-soluble drug, miconazole (BCS Class II), allowing prolonged and effective local and topical antifungal effects. Another interesting example will be hetacillin, which was developed as a water-soluble prodrug of the antibiotic ampicillin for oral use, but was later withdrawn due to rapid transformation to the parent drug with no added benefit. This drug, though withdrawn for human use, was repurposed for veterinary use for mastitis in cows (PolyMast), given via intramammary administration as an oil-based gel. The product so developed allows sustained release of the drug, ensuring efficacy [50, 51]. To summarize, it is advised that the corrective action to enhance drug solubility is not always the preferred approach, but a formulation and product design team must take into consideration the route of administration and the target product profile while designing the product and formulation process.

1.6 Conclusion

To summarize, it is evident that poor aqueous solubility represents a critical barrier in overall pharmaceutical development. Poor drug solubility, especially in aqueous

media, plays a vital role in determining ADME/Tox characteristics, thereby influencing therapeutic efficacy and safety and impacting the product stability and commercial success. Multiple strategies have been explored and successfully implemented in developing safe, effective, and stable commercial products of poorly soluble drugs. But there is no single rule of thumb to identify and implement such a strategy. The experts must adopt a multipronged approach of identifying the most suitable drug solubility enhancement approach based on drug physicochemical properties, dose, route of administration, disease state, and commercial feasibility.

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