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White Paper

Improving API Solubility by Salt and Cocrystal Formation

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Ensuring sufficient solubility is critical to the success of small molecule drugs. An active pharmaceutical ingredient (API) must be absorbed by the body and enter the systemic circulation to deliver the desired therapeutic effect. Many APIs, however, suffer from low solubility and if this cannot be addressed, the small molecule may never make it to the market.

The solubility challenge is highlighted in the biopharmaceutics classification system (BCS).[1] The BCS was developed in the 1990s to correlate *in vitro* solubility and permeability with the potential *in vivo* performance of drug molecules (Figure 1). The system was originally used by the United States Food and Drug Administration (FDA) as the basis for biowaiver applications. For instance, BCS Class I molecules exhibit good solubility and good permeability, and are expected to have good absorption in the gastrointestinal tract.

BCS Class II compounds have low solubility and high permeability, while BCS Class III molecules have high solubility and low permeability. The most challenging class of molecules are those categorized as BCS Class IV; these molecules have low solubility and low permeability.

Today, it is estimated that 30–40% of all marketed drugs have low solubility and are categorized as BCS Class II and IV.[2] As high throughput screening and target-oriented drug discovery often result in challenging, poorly water-soluble APIs, this challenge will even further increase in the near future. It is estimated that approximately 70–90% of drugs currently under development are poorly water-soluble (Figure 2), thus requiring new strategies to address this challenge.[2]

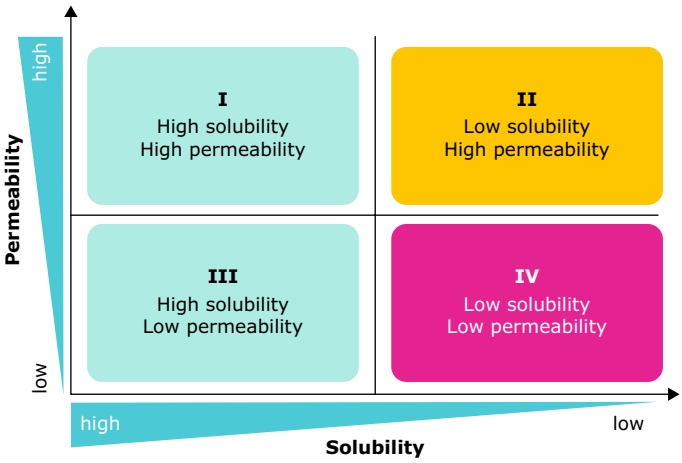

Figure 1.

The Biopharmaceutical Classification System categorizes APIs in terms of permeability and solubility.

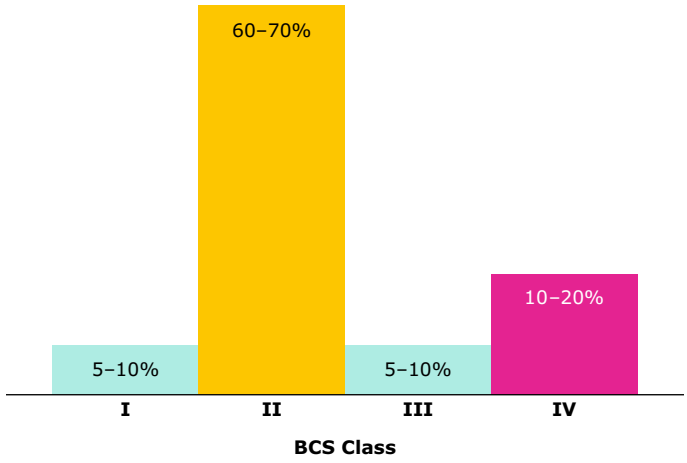

Figure 2.

Drug substances in the pipeline classified in the different BCS classes.

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Determining the Best Approach

Solubility can be addressed with a variety of techniques including API processing and formulation. Formulation is one of the final steps of drug development and involves use of excipients such as liposomes, silica carriers, and cyclodextrins to overcome solubility challenges. Formulation alone, however, might not be sufficient to increase solubility, and because it is one of the last steps of development, a significant investment will have already been made in the API. In contrast, API processing is performed earlier in development and comprises techniques such as polymorph screening, nano-milling as well as salt and cocrystal formation to create the optimal solid-state form of the API.

Salt formation is of particular interest as approximately 50% of all currently marketed APIs are in salt form[3]; this approach, however, can only be applied to ionizable APIs. Cocrystal formation can be an alternative to salt formation and can be applied to nearly every kind of API. Determining whether salt or cocrystal formation is best suited for API processing relies on evaluation of the pK_a of the parent compound (Figure 3). Based on our experience, if the pK_a is greater than or equal to 5.0, salt screening is advised; for compounds with a pK_a of less than 3.0, cocrystal screening is the preferred approach. Screening both options is typically used for APIs that have a pK_a between 3.0 and 5.0. Once the final solid-state form is identified, the process is scaled, followed by the final formulation and prospective pharmacokinetics studies.

Salt Formation

Salt formation is a well-established, simple, cost-effective technique that is accepted by regulatory agencies to influence the solid-state properties of an API. In this technique, the API is ionized by a proton transfer with the aid of an acid or base counterion. Approximately 50% of marketed small molecule APIs are administered in their salt form; approximately 39% are bases and 13% are acids.[3] Table 1 provides examples of marketed drugs in salt form.[4]

Table 1.

Examples of marketed drugs in salt form.

Product	API	Counterion	Company
Clindac (antibiotic)	Clindamycin	Phosphate	Sandoz
Baytril® (antibiotic)	Enrofloxacin	Mesylate	Bayer
Trimeton® (antihistaminic)	Chlor-pheniramine	Maleate	MSD
Escitalopram (antidepressant)	Escitalopram	Oxalate	Hexal
Gastrografin® (contrast agent)	Diatrizoate	Meglumine	Bayer
Ketorol™ (anti-inflammatory)	Ketorolac	Thromethamine	Dr. Reddy's

In addition to enhancing solubility and dissolution rates, salt formation may improve API purity and isolation possibilities, physical and chemical stability, and manufacturability due to its effect on particle size and flowability of the final drug product. For salt formation to be used, however, the API must be ionizable. Table 2 lists some common acids and bases, which are typically used to form salts.

Table 2.

Common salt formers.

Hydrogen chloride	Oxalic acid	Acetic acid
Sulfuric acid	Maleic acid	Other sulfonic acids
Phosphoric acid	L-Malic acid	Meglumine
Fumaric acid	Succinic acid	
L-Lactic acid	L-Tartaric acid	
p-Toluenesulfonic acid	Citric acid	
Methanesulfonic acid	Benzoic acid	

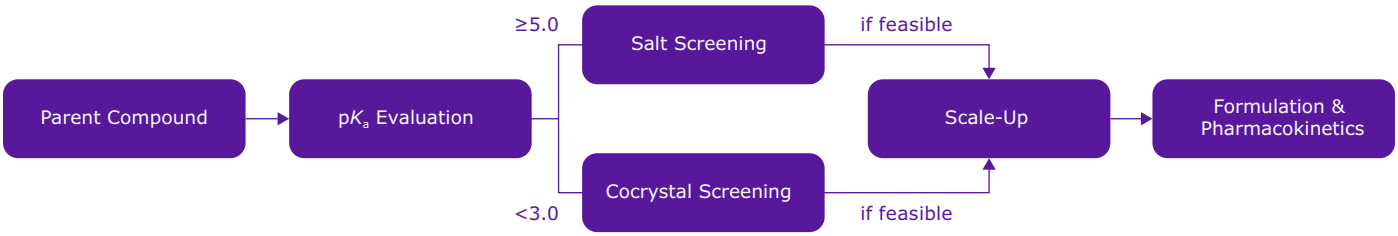

Figure 3.

Salt and cocrystal formation workflow.

Influence of pH on Salt Formation

Salt formation is a pH dependent process. Two solid phases, the salt and the respective free base, coexist in an equilibrium in a saturated solution; adding low amounts of an acid or base will not affect the pH nor the concentration of the drug in solution until the point of maximum solubility (pH_{max}) is reached. As shown in Figure 4, three different salt formers (a, b, and c) result in different pH_{max} values and maximum solubility. The pH range has an impact on potential physical stability of the drug such as disproportionation. For salt former a, a smaller pH range from 0 to 3, whereas for salt former c, a broader range up to pH 5 favors the salt over the free base.[5]

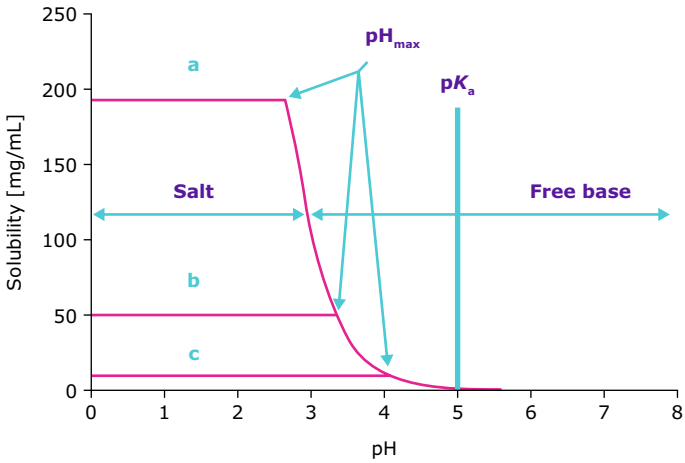

Figure 4.

Solubility diagram of salts of a weak base having an intrinsic solubility of 1 mg/mL and pK_a of 5.0 with salt forms: (a) hydrochloride, (b) sulfate, and (c) tosylate having a solubility of 200, 50, and 10 mg/mL, respectively.

The Common Ion Effect

Addition of common ions (e.g. [Na^+Cl^-] or [H^+]) shift the equilibrium to salt formation (Figure 4) resulting in the precipitation of salts. The same mechanism can be an issue during production during evolution of HCl gas for instance, shifting the reaction in favor of the free base.[5] In addition, the common ion effect may also reduce the solubility of API chloride salts in gastro-intestinal fluids (such as FaSSIF or FeSSIF), due to the fact that these biorelevant media contain substantial amounts of sodium chloride.

The Risk of Disproportionation

Disproportionation is another issue related to salts in terms of their physical stability. This reaction involves the dissociation of the ionic solid into its neutral or weakly basic component and acidic form of its counter ion, causing stability and potential bioavailability issues for the drug product. The pH_{micro} of the microenvironment of the drug relative to its pH_{max} value determines whether disproportionation occurs.

In this situation, incompatibility of the API with excipients can occur; for instance, in case of the HIV drug delavirdine, which is formulated as a mesylate salt, a solid-state reaction to the free form could be observed during development when storing the salt at 40 °C/75% relative humidity for one week.The estimated pH_{max} ~4 of the drug is less than the pH_{micro} for most excipients in tablet formulations resulting in spontaneous disproportionation. Solubility of the salt is around 2,3× higher than for the free base, indicating a substantial free energy gap and consequently, a substantial driving force for the reaction.[5]

Cocrystal Formation

Cocrystal formation is a relatively new approach and provides an alternative for non-ionizable compounds. Nearly all APIs can form cocrystals in which the API and co-former crystallize in one joint crystal lattice interacting via non-ionic forces (e.g. hydrogen bonds). Common crystal formers are shown in Table 4. While there are currently less than ten drugs marketed in cocrystal form (Table 3)[6], this number is expected to grow significantly in the near future due to the upsides that come along with this technique.

Table 3.

Examples of marketed drugs in cocrystal form.

Product	API: Co-former	Company
Suglat®	Ipragliflozin: L-Proline	Astellas/MSD
Entresto®	Valsartan: Sacubitril	Novartis
Steglatro®	Ertugliflozin: Z-Pyroglutamic acid	MSD
Depakote®	Valproic acid: Valproate sodium	Abbott
Beta chlor®	Chloral hydrate: Betaine	Mead Johnson

Table 4.

Common cocrystal formers.

2,4-Dihydroxybenzoic acid	Nicotinamide	L-Proline
3,4-Dihydroxybenzoic acid	Tert-butyl hydroquinone	Maltol
Tartaric acid	Resorcinol	Oxalic acid
Citric acid	Orotic acid	Urea
Fumaric acid	Sorbic acid	Glycerol
Phloroglucinol	L-Tyrosine	Sulfamic acid

The benefits of cocrystal formation are similar to those offered by salt formation including enhancement to bioavailability, purity, isolation, stability and manufacturability.

Unlike salts, cocrystals typically have no counter ion or disproportionation effects and are less prone to hygroscopicity. However, this approach is more challenging with respect to the experimental screening effort needed to identify suitable co-formers for specific APIs. Control of crystallization may be difficult and as this is a newer technique, regulatory acceptance may be more challenging.

Screening

The first step in the process is computational *in silico* screening to predict suitable co-formers. Co-former selection is specific to each API and dependent on several factors including purity of the API, structural features, polymorphic nature, and physical properties such as solubility and thermodynamic state variables. Once the preferred co-formers are selected, a toxicology evaluation is performed followed by solubility and stability studies, scale-up, formulation and pharmacokinetics studies.

There exist many experimental techniques for identifying the right cocrystal-API combination including solvent evaporation, solvent assisted grinding, sublimation, slurrying, and crystallization from the melt. Computational screening is a promising approach and can offer significant cost and time savings as it is important to identify all possible cocrystal combinations that are suitable or possible from a market perspective and then protect them as intellectual property. Table 5 provides a selection of recently published computational approaches for identifying co-formers.

Table 5.

Computational approaches for screening co-formers.

Institution	Approach	Source
3DS BIOVIA (COSMOlogic)	Combination of quantum chemistry and statistical thermodynamics	COSMO-RS Solvation Chemistry Software
CCDC	Molecular complementarity based on statistical CSD analysis	[7]
Oxford University, UK (Wicker *et al.*)	Machine learning	[8]
Radboud University, NL (Devogelaer *et al.*)	Artificial neural network	[9]
Sichuan University, China (Jiang *et al.*)	Feature identification + Graphical neural network	[10, 11]
Western University, Canada (Ahmadi *et al.*)	Molecular electrostatic potential Hydrogen bond energy/propensity Logistic regression (ML)	[12]
Peking University, Shenzhen and XtalPi Inc.	COSMO-RS + Machine Learning	[13] and service

Regulatory Implications

Both the European Medicines Agency (EMA) and the FDA have published perspective and guidance on cocrystals – perspective or guidance on cocrystals respectively. The EMA has stated that there is *"No strict borderline between salt formation in the one end with complete proton transfer and cocrystal formation in the other end with no proton transfer."* They further state that *"Ultimately the resulting material properties are the critical factors that determine the suitability of a developed solid-state form, regardless of the molecular bonding involved."*[14] As described in this white paper, bonding is a major difference between salts and cocrystals.

EMA states that it is more the substance itself and not the bonding that is involved and that salts and cocrystals from a regulatory perspective are not treated differently. This is made clear by subsequent statements which state that *"Dissolution of such different forms of drug substance in the stomach or intestinal canal will lead in the end to the release of the same substance and independent of the form that was taken in."*[14]

The agency further states that *"Cocrystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied."*[13] As with any excipients, co-formers must be pharmaceutically acceptable, and their safety and quality must be ensured. If not previously used, the co-former should be justified and documented in the same manner as a novel excipient.

The FDA published guidance for the industry on cocrystals in 2018.[15] In contrast to the EMA, the FDA states that *"Co-crystals are distinguished from salts because unlike salts, the components that co-exist in the co-crystal lattice with a defined stoichiometry interact non-ionically."*[15] They further state that *"If both API and co-former have ionizable functional groups, a conclusion that the component API and co-former co-exist in the cocrystal which interact non-ionically should be provided."*[15]

The agency further states that *"A co-crystal with a pharmaceutically acceptable co-former that meets the above conditions can be considered to be a pharmaceutical cocrystal and has a regulatory classification similar to that of a polymorph of the API."*[15] Specifically, it is not regarded as a new API: *"Drug products that are designed to contain a new cocrystal are considered analogous to a new polymorph of the API."*[15]

Conclusion

A high percentage of APIs currently in development have shortcomings related to solubility that must be addressed. In addition to formulation strategies, API processing using salt or cocrystal formation is an important part of the toolbox for drug development and can offer a viable solution for these challenging APIs. The key benefit is the ability to intervene at a much earlier stage than other common approaches for solubility enhancement.

Salt formation is an established technique with many benefits for ionizable APIs. However, the technique may cause various stability issues during drug development including disproportionation, high hygroscopicity, and common ion effects.

Cocrystal formation is an emerging technique that can be used for nearly every API and therefore represents a valuable alternative to salt formation. Cocrystals are not subject to disproportionation and common ion effects, and typically show much less hygroscopicity. The process can however be demanding, and because the regulatory landscape continues to evolve, developers may face some uncertainty.

Despite the possible shortcomings of these techniques, both salt and cocrystal formation offer the opportunity to overcome API solubility challenges that may otherwise cause a development program – and a promising new drug – to be abandoned. Given the large percentage of poorly soluble APIs currently in pharmaceutical pipelines, these techniques which address the core issue by improving the physicochemical properties of the active, can be invaluable options for drug developers and should be established as part of the toolbox in small molecule development.

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