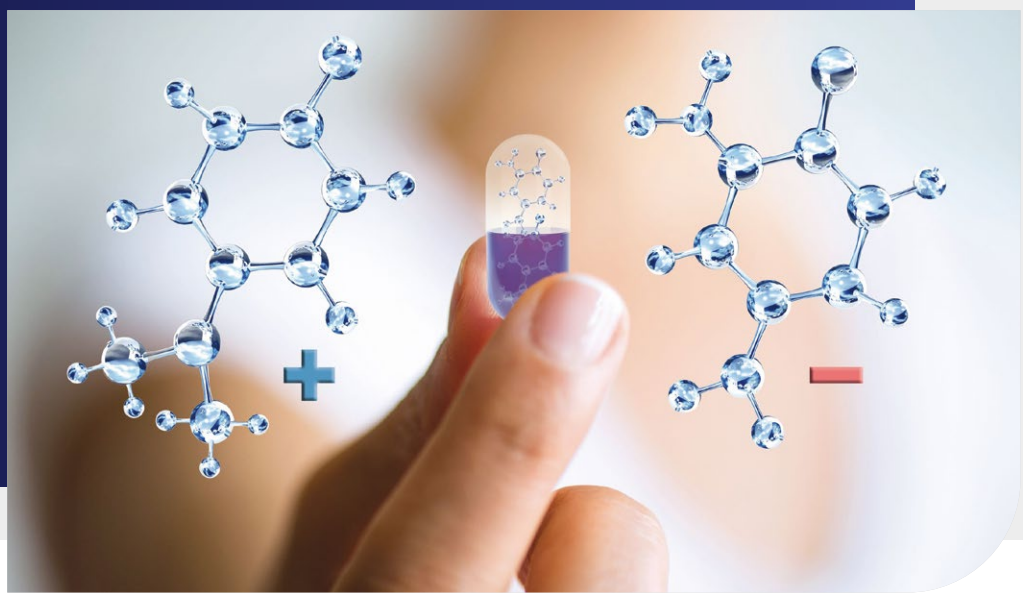


SALT SCREENING WITH THE CRYSTAL16: DESIGN AND CONSIDERATIONS

Most approved APIs are salts

The term pharmaceutical salt is used to refer to an ionizable drug that has been combined with a counter-ion to form a neutral complex. More than half of all drug molecules on the market are salts. The main reason behind this is that in general salts have more desirable aqueous solubility (and implicitly bioavailability) profiles compared to the free acid or the free base API (Active Pharmaceutical Ingredient). Transforming an API into a salt has several other benefits, with different physico-chemical and mechanical properties available, such as dissolution profile, stability, and manufacturability in solid formulations. The difference between the physico-chemical properties of different salts of the same API can be so great, that it has been said that 'changing the salt is changing the drug'. This is true in the legal context as well, as new API salts are patentable. Therefore, salt screenings have become increasingly important for protecting your intellectual property, and not only as a way of improving and tuning your APIs properties.

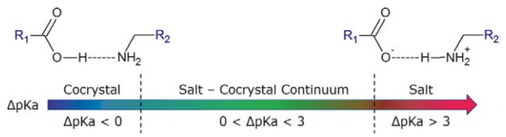
Why formulate APIs as salts

- Improved bioavailability (solubility, dissolution)
- Distinct physico-chemical properties (melting point, hygroscopicity and solid form stability)
- Enhanced manufacturability (chemical stability, drug product stability, flow and compressibility)

Salt Screening Challenges

Strong acids and bases readily form salts with one another. This is not the case however with pharmaceutical compounds, which most are weak acids, weak bases or even have a zwitterionic character. In this case it is recommended that the difference between the pKa of the compound and counter ion is higher or equal to 3 to guarantee salt formation. If the difference is between 0 and 3, then the resulting solid form can be either a salt or a cocrystal, depending on each individual chemical system. This is especially true when dealing with weak organic acids or bases, and in many such cases other analyses are required to confirm if the new solid form is indeed a salt.

Figure 1. Salt-cocrystal continuum as a function of ΔpKa



While this pKa rule is a good starting point for designing a salt screen, chemists should take into account that most pKa values reported in literature are for aqueous solutions. The acidity/basicity of any compound is highly solvent dependent, and the same salt formation experiment performed in water and in isopropanol can yield very different results, and salts can be missed as protonation has not fully completed. Furthermore, the counterions available are limited to those found on the Generally Regarded As Safe (GRAS) list when dealing with pharmaceutical compounds. In Table 1 we present a series of commonly used acids, bases and solvents typically employed in salt screenings. This should be taken only as a suggestion, and you should always tailor the salt screening to your specific API structure (acid or base, hydrophobicity etc.) and formulation, manufacturing and regulatory requirements (stability, trace solvent limits etc.).

Finally, as each salt is on its own a different chemical entity, it also presents its own characteristic solid form landscape, with the same salt crystallizing as several polymorphs and solvates.

The current state of the art in salt screening methodology has moved away from high-throughput screening, towards a more focused medium-throughput approach relying on a rational design of experiments. The pKa rule and API and counterion solubilities are good starting points for designing a rational salt screening DoE, but one must always keep chemical diversity in mind. In practice, this translates to testing several counter-ions in several solvents, and every successful salt screening should cover as much of the chemical and solid form landscape as possible.

Table 1. Examples of some of the most widely used acids and bases

Acids	Bases
1,5-Naphthalenedisulfonic acid	t-Butyl amine
Fumaric acid	Tromethamine
Phosphoric acid	L-Lysine
Hydrobromic acid (HBr)	Piperazine
L-Tartaric acid	Lithium hydroxide
Hydrochloric acid (HCl)	Sodium hydroxide
Sulfuric acid	Potassium hydroxide
Oxalic acid	Cesium Hydroxide
Benzenesulfonic acid (BSA)	Calcium(II) Acetate
p-Toluenesulfonic acid (pTSA)	Tetramethylammonium hydroxide
Citric acid	Dicyclohexylamine
S-Camphorsulfonic acid	Zinc(II) Acetate
Succinic acid	Diethanolamine
Maleic acid	L-Arginine
Boric acid	Ammonia
R-Mandelic acid	Imidazole
Ethanesulfonic acid (ESA)	Triisobutylamine
Methanesulfonic acid (MSA)	4-Methylmorpholine
Salicylic acid	Dibutylamine
L-Malic acid	Dehydroabietylamine
Acetic acid	Ethanolamine
Benzoic acid	N-Methyldicyclohexylamine
Dichloroacetic acid	Diethylamine
Trifluoroacetic acid	Diisopropylethylamine
Fluoroboric acid	Diisopropylamine

Salt screening methods

We present some common salt screening methodologies described in literature, each method having its own advantages and disadvantages. All fundamentally rely on mixing stoichiometric amounts of API and counterion and performing a combinatorial solution or slurry screening. The size of the salt screening depends on the size of the chemical space which should be explored, i.e. the number of counterions and solvent systems which need to tested. All these methods can be performed on the ***Crystal16*** instrument several orders of magnitude faster and reliably controlling the temperature than performing the same experiments by hand.

In-situ salt screening

In the in-situ salt screening an amount of solid API is dosed in each vial and to it a stoichiometric amount of aqueous solution of acid/base is added. The slurries are aged under stirring for several days by using the ***Crystal16*** instrument, at one temperature or with temperature cycling, and then the solids are harvested by centrifugation and analyzed. The solute is also analyzed for API concentration. In-situ salt screening has the advantage of assessing salt formation directly in an aqueous environment and offering information about solubility of the salt form obtained.

This strategy can be applied using the ***Crystal16*** by simultaneously testing 16 different acids or bases, while accurately controlling the temperature, the stirring rate, and monitoring any potential dissolution events by making use of the transmissivity technology. The ***Crystal16*** combines automation with integrated turbidity measurement to determine cloud and clear points and is ideally suited to acquire crystallization related data at an early stage using only minimal amounts of sample.

Saturated solution method

Rational salt-screening approach relies on mixing stoichiometric saturated solutions of API and counterion and ageing the clear solution obtained. Any precipitates are harvested and analyzed and, after ageing for a given amount of time, the solutions are cooled. A key piece of information used in this approach is the solubility of your API in several solvents, as well as that of each counterion. This approach has the benefit of covering a very large chemical space, testing several counterions in several solvents at the same time. This of course translates into potentially more solid forms discoverable in the screening.

The ***Crystal16*** is ideally suited for such a combinatorial study: the device allows for the monitoring of 16 individual crystallization reactors, arranged in a 4x4 matrix. This means testing 4 different counterions in 4 different solvents at the same time at your desired heating and cooling rate.

Cooling evaporative method

In this last method, stoichiometric amounts of API and acid/base are dosed as solids in each vial, to which an appropriate amount of solvent is added. The resulting slurries can be aged at different temperatures or thermocycled. If solids are not observed, the solutions are subsequently evaporated.

The main advantage of using the ***Crystal16*** for such a screening is the ability to track any dissolution or crystallization events with temperature in real time.

Salt screening methods

- In-situ Salt Screening
- Saturated Solution Method
- Cooling Evaporative Method

Figure 2. In-situ Salt Screening diagram

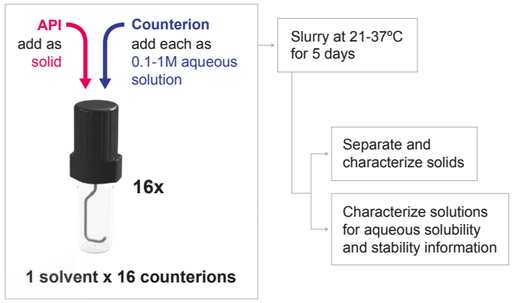


Figure 3. Saturated Solution Method diagram

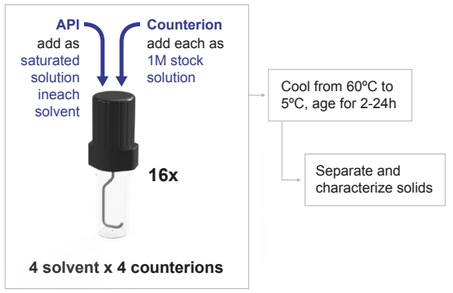
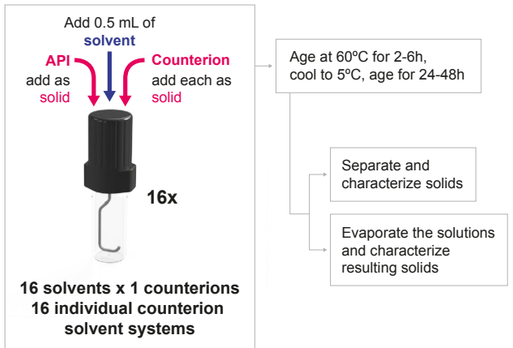


Figure 4. Cooling Evaporative Method diagram



Characterizing your salts

Having obtained a new salt, confirmed by single crystal or powder X-ray diffraction, you need to characterize its solubility in aqueous solutions or in the relevant aqueous medium, a given buffer or simulated gastric or intestinal fluid. Here also, the ***Crystal16*** can greatly speed up your development process, allowing you to obtain 4 solubility curves simultaneously.

Conclusion

Salt screening is more than mixing your API and counterion together. Although apparently simple, in a salt formation reaction one should consider not only the API properties, but also those of the counterion, the solvent involved, together with many other experimental conditions, such as temperature and stirring rate. Several salt screening methodologies can help to cover as much of the chemical space as possible, and using rational approaches also reduces the number of experiments which need to be performed. In any case, the ***Crystal16*** device, having 4 individually temperature and stir controlled zones, 16 reactors each with individual in-line transmissivity analytics, is ideally suited to help you navigate the solid form salt landscape of any API.

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