VERANOVA™

Physicochemical characterization services

Helping you understand the properties of your API and identifying your development options

The physchem services at Veranova provide comprehensive physicochemical characterization for your compound using small quantities of material, enabling you to:

- Obtain measured pKa values as a precursor for salt screening studies
- Better understand and predict *in vivo* behaviors of an API
- Compare the performance of various different free form salt, cocrystal and polymorphic forms
- Find the most compatible surfactants and excipients to improve bioavailability in poorly soluble compounds
- Aid in troubleshooting batch to batch variability
- Completing data packages in preparation for IND application

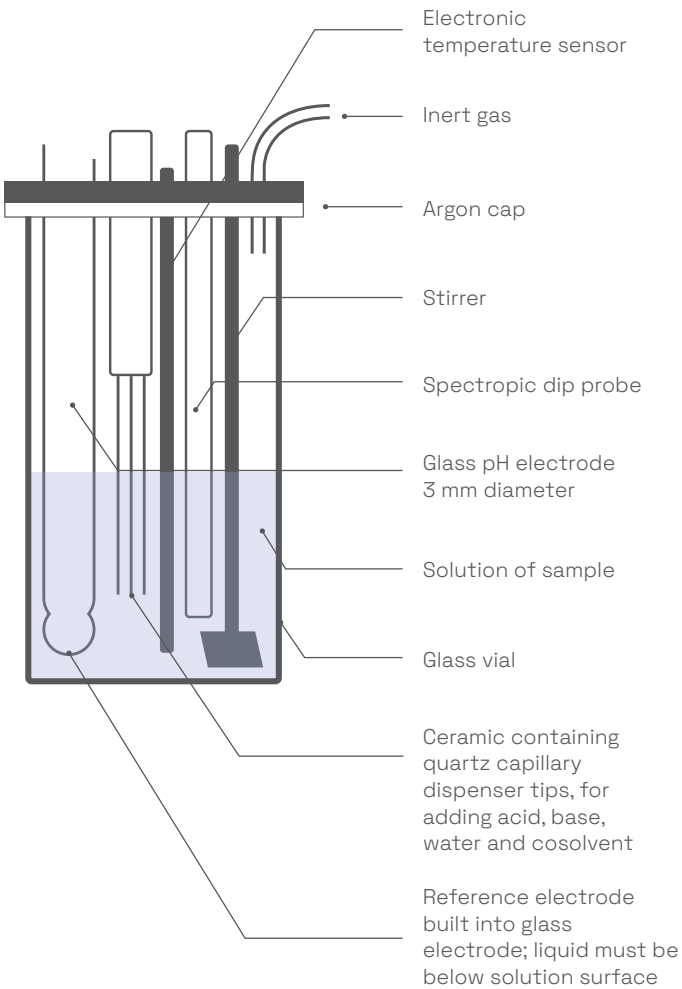
At Veranova, we leverage our longstanding expertise in solid form science and physchem to help you fully understand how solid forms may behave *in vivo.* This is achieved through a flexible approach to experimental design and utilizing strong relationships between the solid form and analytical service groups.

Leading technology

We use highly specialized instruments for compound screening and preparing physchem profiles. The SiriusT3 machine has a 192 place autosampler capable of running high numbers of samples in sequence, at a small scale.

Similarly, the dissolution apparatus used in-house is capable of running up to 10 dissolution assays in sequence, and the *in situ* UV probes allow for online monitoring, both reducing analysis time and sample requirements. Traditional dissolution apparatus can use in excess of 500 mg material. Using the inForm platform, dissolution data can be performed on as little as 50 mg of material.

Diagram of the titrator vessel for high throughput analysis



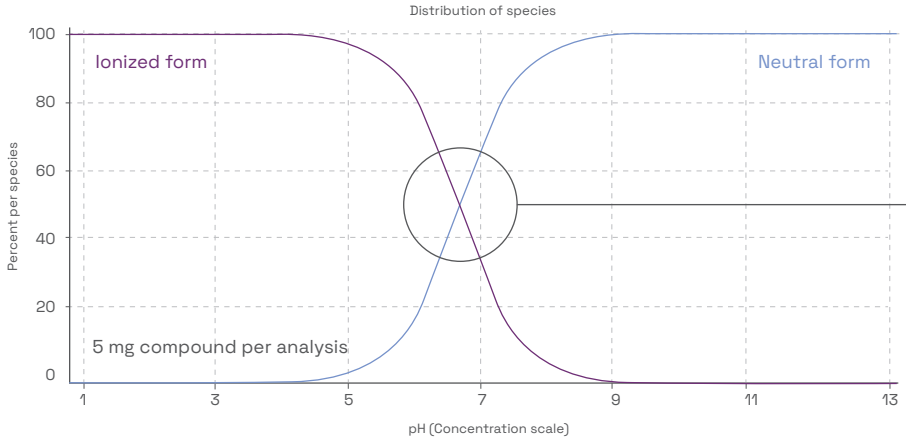
Pion's inForm machine allows us to precisely control pH monitoring, enabling dissolution studies under conditions that mimic *in vivo* conditions.

We use the SiriusT3 machine for analyzing pure single-component organic chemicals and their salts.

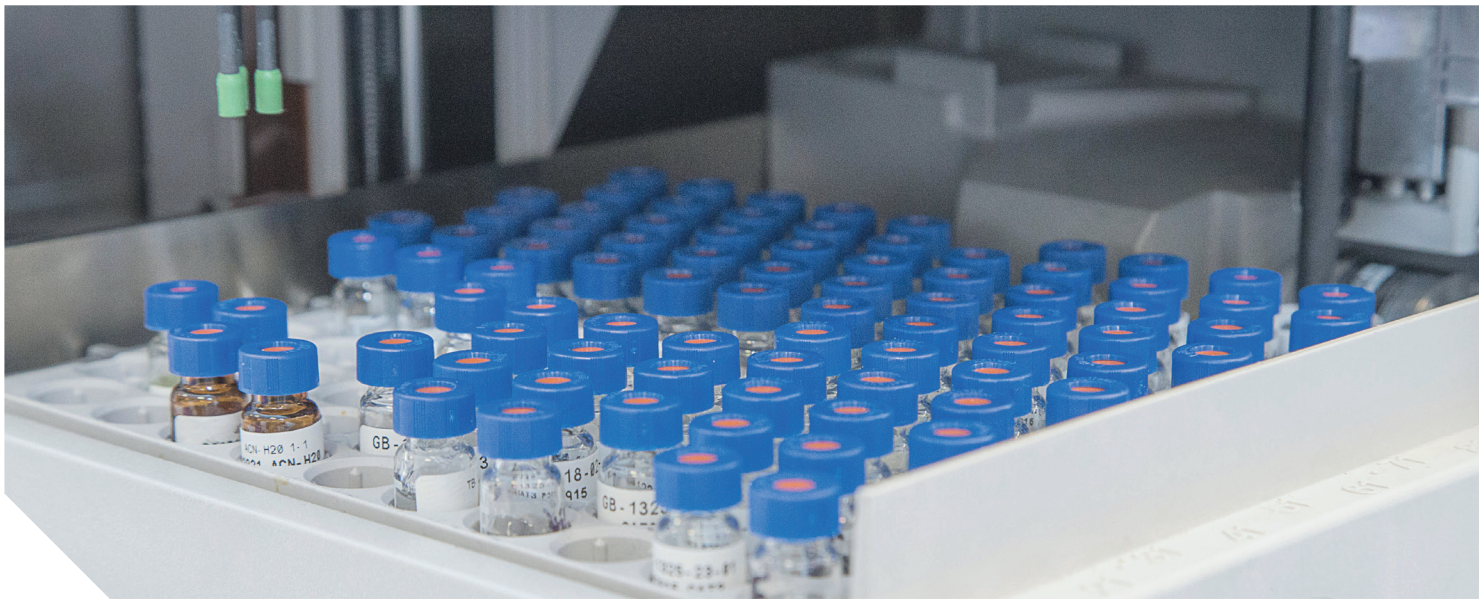
T3 - pKa data obtained by UV (*circa* 5 mg)

pKa determinations are useful for helping us to identify the degree of ionization across the pH scale. In relation to oral dosage forms, a pKa value of between 6-8 is desirable as this provides optimum conditions for absorption. This is because an equilibrium exists between the neutral and charged species, so you have the benefit of the increased solubility of the ionized species, and enough of the neutral species present for absorption; the equilibrium then continues to drive the compound across the biological barrier.

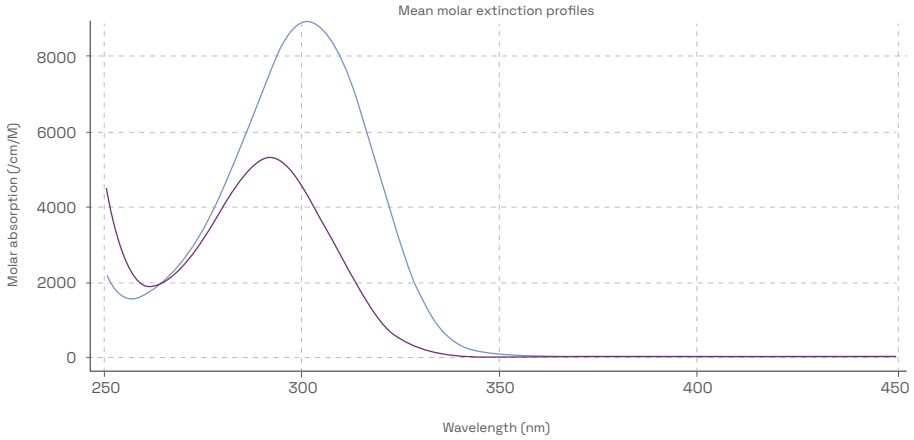
Distribution of species for a basic compound – What species is present over the pH range?



The point at which the curves cross is where the compound is present at 50% of the protonated and 50% of the deprotonated species (also known as the pKa).



Molar Extinction Coefficient profile (MEC) – How strongly light is absorbed at a given wavelength



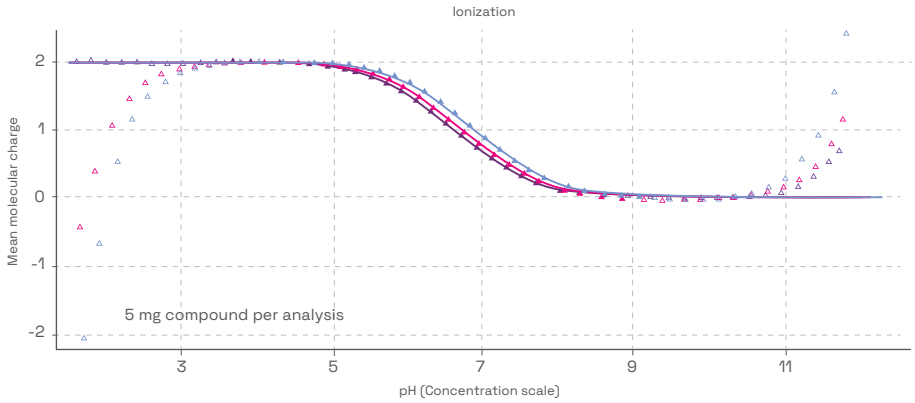
MEC data is important as UV profiles may change across the physiological pH range. In fact this is how pKas are detected using the UV method. MEC data sets are also run and used to convert the raw UV absorbance, measured *in situ* during dissolution assays, into concentration.

This compound has one pKa at 6.7. This means that two different species are present, and the two different species are represented by the two different colored lines. Each species will have a different UV absorption associated with different UV chromophores (or molar extinction profile).

pKa data obtained by potentiometry (*circa* 5 mg)

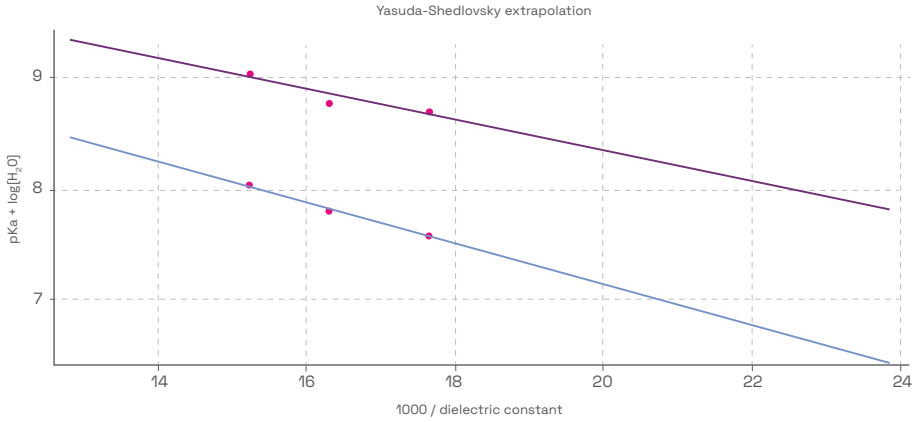
We often deal with highly insoluble compounds. This can cause issues for pKa determinations as the compound has to be in solution in order to obtain good quality data for accurate pKa measurements. For both UV and potentiometric titrations, co-solvent assays can be performed to aid dissolution of the sample. Since the pKa shifts in organic solvent, triple titrations are required in varying ratios of the co-solvent (typically ISA MeOH at 50:40:30%) in order to extrapolate back to the aqueous pKa. This type of analysis is known as Yasuda-Shedlovsky extrapolation.

Ionization graph – What is the degree of ionization of the sample over the pH range?



This compound has two mid-range pKas at 6.7 and 7.6 – the ionization plot shows two steps in the mean molecular charge which is indicative of two pKas.

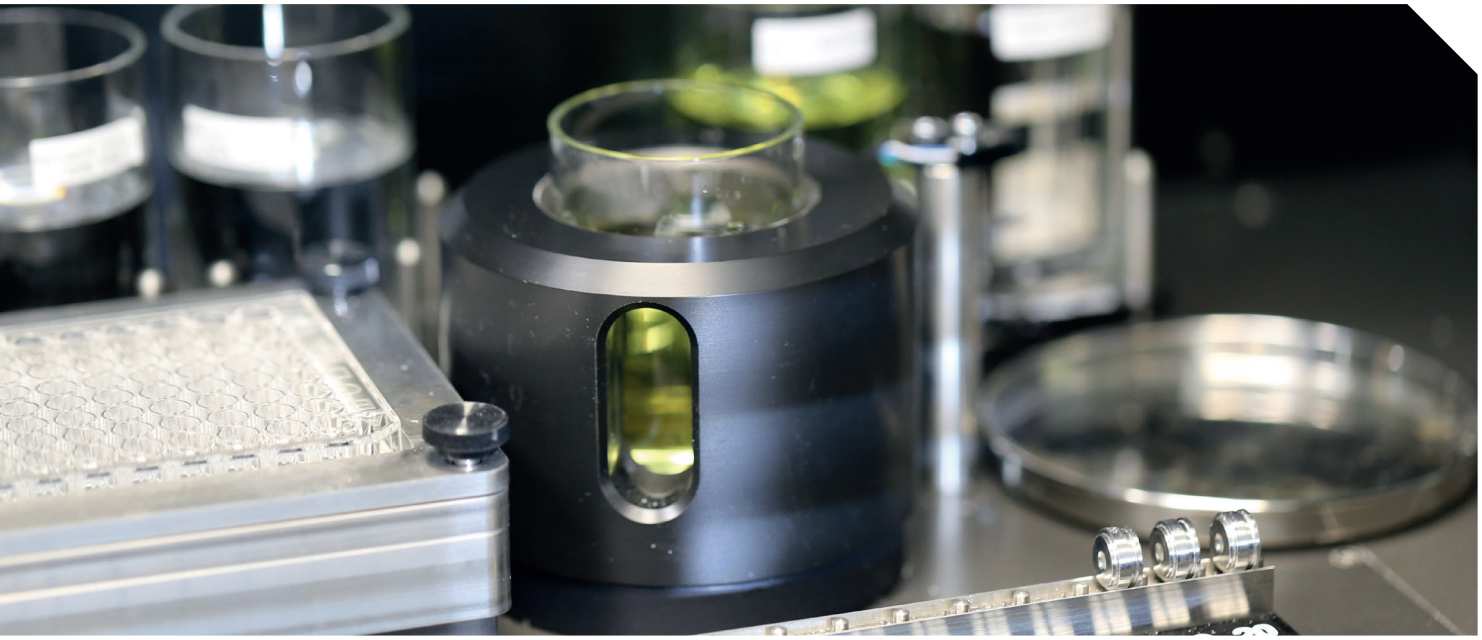
Yasuda-Shedlovsky extrapolation – How do we calculate the aqueous pKa of a highly insoluble compound?

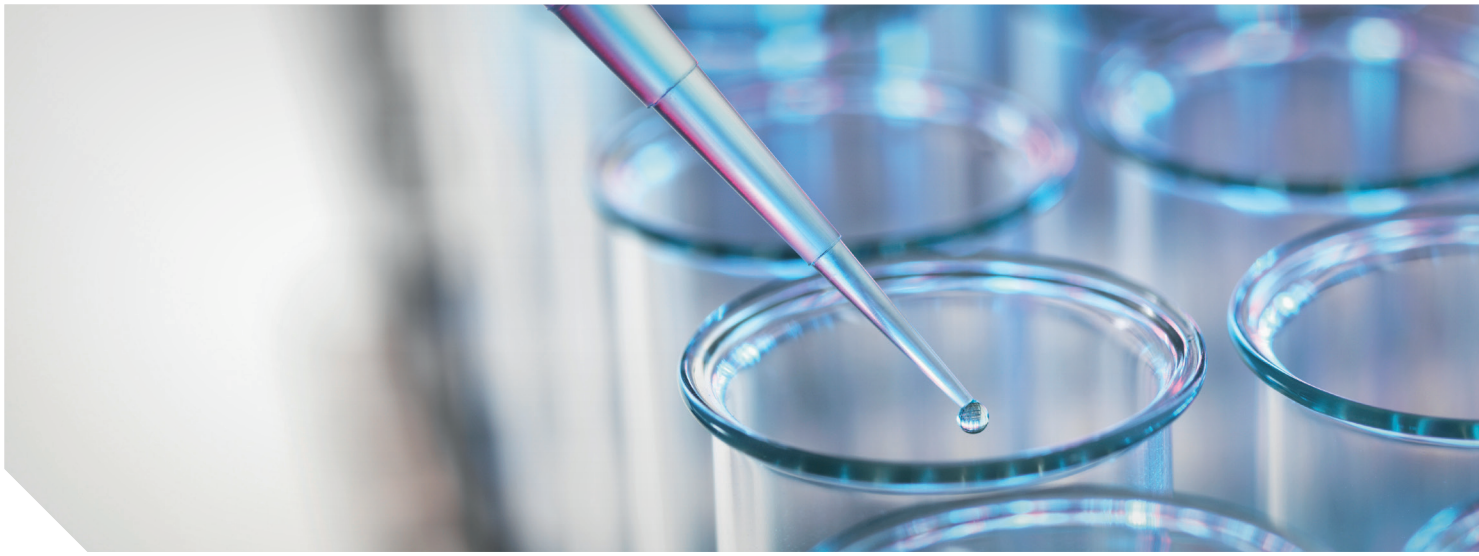


Here the two colored lines represent two pKas. The negative slope indicates that there are two basic pKas present.

pKa 1: 0% Solvent at 25.0°C

pKa 2: 0% Solvent at 25.0°C

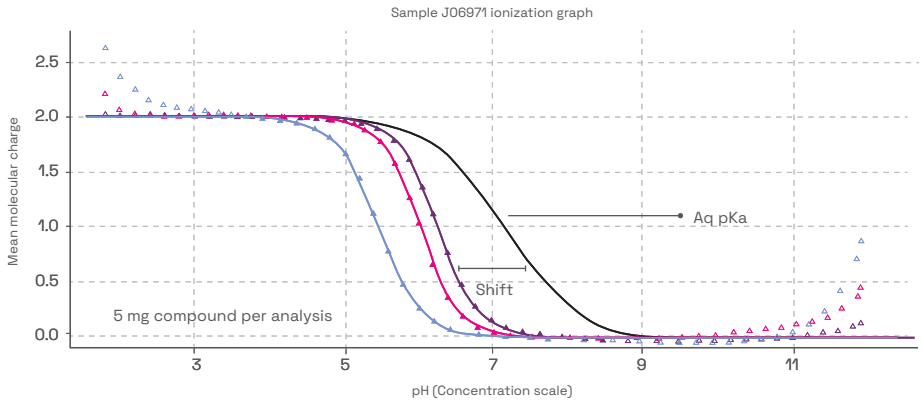




LogP data obtained by potentiometry (*circa* 5 mg)

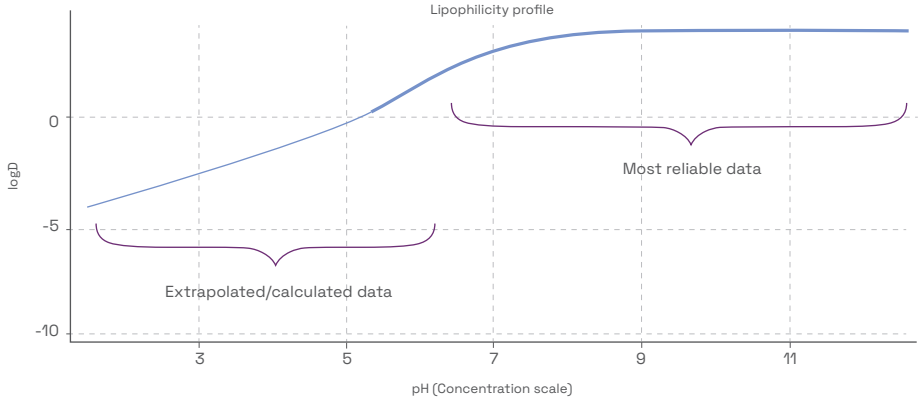
LogP data allows us to assess how hydrophilic or hydrophobic an API might be, which in turn provides useful information on how a drug might distribute itself in the body. For example, a compound with a high LogP (hydrophobic) is likely to be more concentrated in the lipid bilayers or proteins of cells rather than in the highly aqueous blood serum due to its affinity for the organic/lipid phase. The reverse is found for APIs with a low LogP. LogP is defined as the partition coefficient of the neutral species; this makes LogP measurement difficult for zwitterionic compounds. In these cases, the 'shake-flask' LogD method would be used.

Ionization graph



Here a downwards shift in the pKa is observed. This is typical of basic compounds and the reverse is found for acidic compounds. Increasing degrees of shift are seen due to the increasing ratios of octanol/water used.

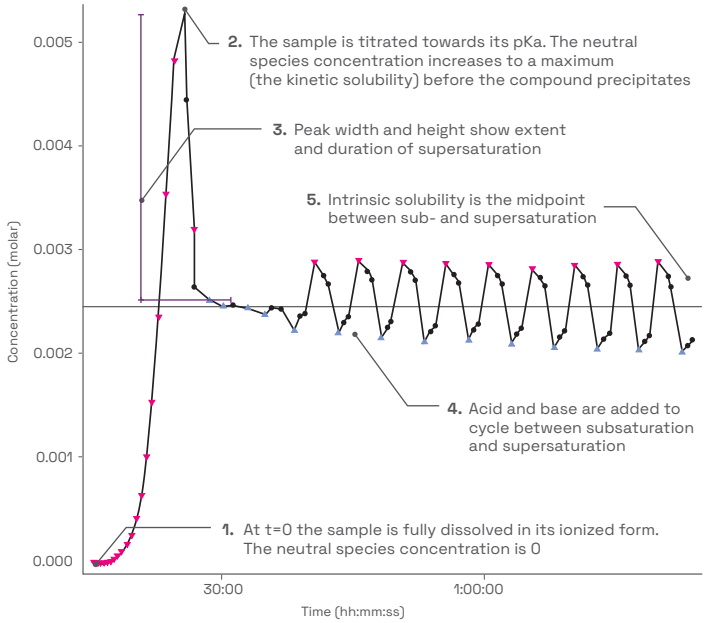
Lipophilicity profile – What is the LogP at any given pH?



Small scale solubility analysis (*circa* 2 mg per compound)

Solubility analysis in the physchem suite can be used as a screening tool during characterization to maximize the information obtained from one assay where compound availability is low. This method uses far less material than traditional shake-flask methods (*circa* 5 mg although this is compound dependent), and will provide thermodynamic and kinetic solubility values as well as a full pH profile.

Neutral species concentration time profile



Intrinsic solubility

Concentration of the neutral form of an ionizable compound in a saturated solution when excess solid is present and the solid and solution are at equilibrium.

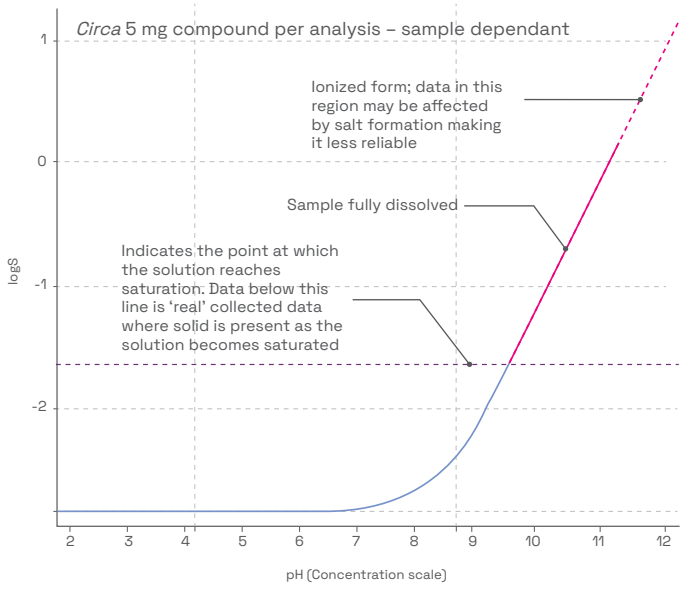
Kinetic solubility

Concentration of the compound in solution when an induced precipitate first appears.

Natural solubility

Thermodynamic solubility at the natural pH of the compound.

Solubility versus pH profile



Solubility analysis is much faster on the T3 than the traditional shake-flask method (no HPLC) and uses less material (*circa* 5 mg) to provide much more information. The standard solubility does not provide differentiation between salts because it is the neutral species that is measured. In order to obtain solubility data, the compound in question must have a mid-range pKa, as the assay titrates towards the first pKa to induce a precipitate and then adds small amounts of acid and base to transcend between a super-saturated and sub-saturated solution.

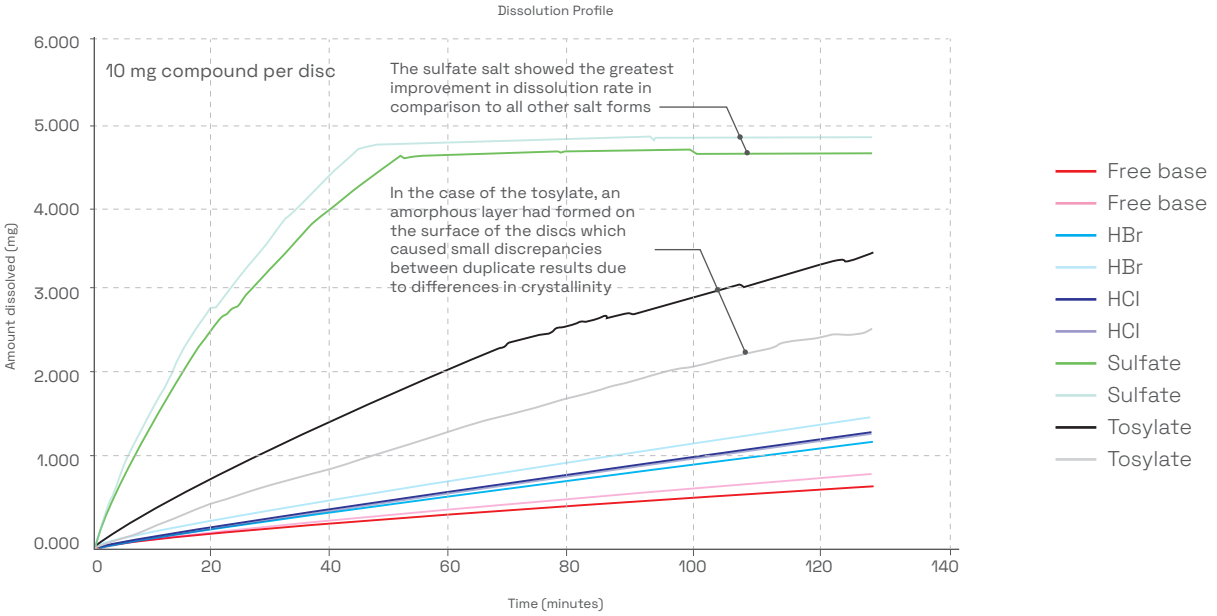
Whilst free powder solubility is a valuable tool in understanding the physicochemical properties of your API, these types of experiments are heavily influenced by morphology, and particle shape and size will have a huge impact on solubility. To truly differentiate between forms, the best method for use is Intrinsic Dissolution Rate or IDR.

Small scale comparative dissolution (*circa* 20 mg per compound)

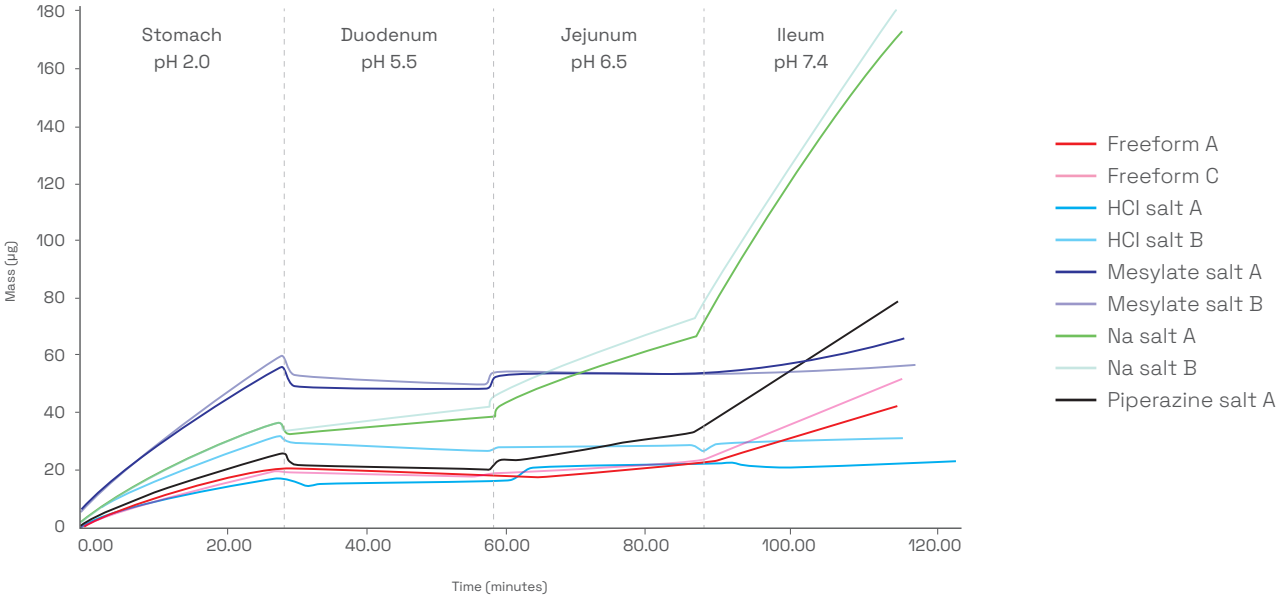
Controlling the surface area provides a much more meaningful comparison of dissolution performance between potential lead candidates. This is as a result of fixing the surface area which eliminates any influence of sample morphology (shape/size) on the dissolution profiles. This can be done on a much smaller scale than the traditional USP dissolution apparatus. Discs are formed using 10-80 mg of material and analysis is performed in duplicate. Dissolution testing can be performed in any aqueous media in addition to collecting a dissolution profile over varying pHs. For example, the GI dissolution assay is performed in the GI dissolution buffer (phosphate buffer) which is designed to maintain a steady pH during individual pH sectors, but also to enable the pH to be adjusted between sectors. The dissolution rate is then measured over 4 different sectors to mimic the GI tract, thus enabling us to assess the solubility of a drug that is intended for oral dosing.

NB: Other assays can be designed to suit your needs including multiple methods of sample introduction (tablets, capsules, free powder, suspensions), specific formulation media and observations made for precipitation studies and extended release formulations.

Single sector dissolution testing in SGF media



GI tract dissolution testing in GI buffer over four different pH sectors



Evaluation of changes in form by XRPD

To confirm the solid form and whether or not any evidence of dissociation has been observed, we run XRPD analysis before and after dissolution analysis. It is not unusual for some APIs to change form under compression, and we need to understand which form we are observing.

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