Q&A with Ardena Experts

The importance of API Intrinsic Dissolution Rate and how to determine it

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Why is solubility determination important in API development?

One of the main problems that can arise during the development of APIs is the low solubility of API in aqueous media. Even very promising APIs with limited solubility and therefore bioavailability have a high risk of failure in late-stage development.

What is the difference between thermodynamic and kinetic solubility?

The solubility of a drug substance is typically investigated during the early preformulation stage.

Thermodynamic solubility represents the equilibrium solubility (maximum amount of API in solution).

Kinetic solubility represents the rate at which an API dissolves in an aqueous buffer system or bio-relevant medium. At Ardena, we use state-of-the-art equipment to measure the intrinsic dissolution rate of APIs.

What are the limitations of IDR measurements?

For accurate measurements, the minimal thermodynamic solubility of the solid form in the selected medium must be approximately 20 µg/mL. Moreover, the API needs to be UV-active in order to monitor its concentration by the in-line UV probes. IDR measurements can be disturbed if the dissolution medium contains UV-active ingredients interfering with the API UV spectrum.

What is IDR, and how is it measured?

IDR stands for Intrinsic Dissolution Rate and is expressed as µg/min/cm^2. The dissolution rate describes how fast the molecules of an API are released from a solid form into solution and is normalized for the surface area of the API. During the IDR measurement, the surface area of the API, stirring speed, pH and ionic strength of the dissolution medium are kept constant. The surface area of the compound is well defined in contrast to a regular dissolution rate measurement. To ensure a well-defined surface area, the API is pressed into a tablet with a known surface area. The measurements are typically performed in aqueous buffer solutions at a given pH value.

How does information from IDR measurements benefit API development?

Information obtained from IDR measurements in the pre-formulation stage aids the selection of the API solid form optimal for further development.

Different solid forms of an API, including polymorphs, salts, and co-crystals, may exhibit different dissolution profiles. Depending on the intended administration route, the fastest or slowest dissolving form may be the most suitable form. Alternatively, if two polymorphs are energetically very similar and production of a pure phase is very challenging, investigation of the difference in dissolution rate profiles of two polymorphs becomes essential. In case of similar dissolution rate profiles, the phase purity of the final drug substance may be of less importance.

During IDR measurements, the influence of particle morphology and size is minimal on dissolution rates.

The suitability of a very poorly soluble compound can be justified for further development if the IDR is fast. With a fast IDR the bioavailability of an API may still be sufficient.

Can you describe the equipment used for measuring IDR?

The MicroDiss Profiler™ with Rainbow R6 is an innovative in-situ fiber optic UV monitoring system, specifically designed to monitor concentrations in real-time from small volume dissolution assays (vessel volume is 20 mL). The measurements are performed on as little as 10 mg of API. The individual Diode Array Spectrophotometer collects UV-spectra in the range of 200 – 720 nm from six channels at regular intervals.

What services does Ardena offer related to IDR?

Thermodynamic solubility determination is our daily routine task and a part of the dissolution rate investigation.

At Ardena we can measure the IDR of pure APIs (polymorphs), salts, cocrystals and amorphous solid dispersions (ASDs). In our solid-state lab we perform screening, selection and scale-up of the best candidates for further investigation. We can compare the IDR performance of salts to that of the parent API. IDR can be measured in buffer solutions or biorelevant media (SGF/SIF, and FaSSGF/FaSSIF/FeSSIF).

What are the limitations of IDR measurements?

For accurate measurements, the minimal thermodynamic solubility of the solid form in the selected medium must be approximately 20 µg/mL. Moreover, the API needs to be UV-active in order to monitor its concentration by the in-line UV probes. IDR measurements can be disturbed if the dissolution medium contains UV-active ingredients interfering with the API UV spectrum.

Could you provide examples of IDR applications?

Figure 1 below shows the dissolution profile of a model API.

The blue line indicates the slope of the dissolution curve. The intrinsic dissolution rate is calculated from this slope. In the example, the highest solubility value is achieved approximately 30 minutes from the start of the experiment. Shortly thereafter, the solubility curve showed a significant decrease in API concentration. After 4-hours, the API concentration decreased by three times with respect to the maximum value.

Figure 1

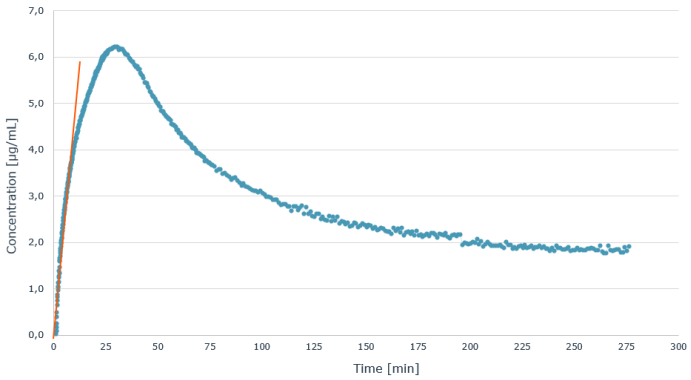
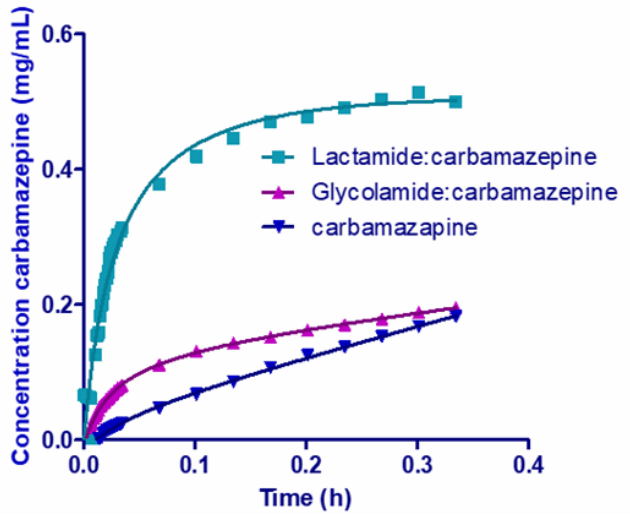


Figure 2 shows the dissolution profiles of carbamazepine cocrystals with lactamide (green line) and glycolamide (purple line) compared to the dissolution rate of pure API (carbamazepine). Both cocrystals showed improvement in dissolution rate compared to pure API. However, the lactamide:carbamazepine cocrystal demonstrated significantly faster API release than the glycolamide:carbamazepine cocrystal.

Therefore, based on the dissolution rate profile, the lactamide:carbamazepine cocrystal can be recommended for further development (after careful evaluation of solid-state properties).

Figure 2



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