Application of Dissolution Testing for API Quality Characterization

by Samir Haddouchi

Dissolution testing is an extremely powerful tool to acquire knowledge about pharmaceutical products. Unfortunately, dissolution profiles are often used without a complete understanding of their meaning and are often considered only when the regulatory agencies require us to provide data for a submission or to demonstrate appropriate batch-to-batch consistency. Alternatively, one can use the dissolution technique in order to learn more about the properties of the Active Pharmaceutical Ingredient, the composition of the formulation as well as the route of administration. The scientist should drive to adapt the testing conditions, keeping in mind the aim of the in vitro dissolution method (e.g., formulation development, IVIVC, or Quality Control).

The in vitro profiles can represent either the dissolution rate of the active ingredient or the release rate from the finished formulation. A more frequent use of API characterization tools such as intrinsic and apparent dissolution (Eur. Ph. §2.9.29 and 2.9.43, respectively) can be of great help in achieving such a goal.

The intrinsic dissolution relies on testing the dissolution rate from a known and controlled surface, from pure API, with a theoretically null porosity. This allows to have a comparison without consideration of the physical properties of the powder.

The apparent dissolution is using the flow though cell dissolution concept (known as USP4) which has been used for many years for testing different dosage forms such as tablets and capsules. It is also known as the method of choice for extended release and poorly soluble drugs. Nowadays the flow through cell technology is used widely for testing API with respect to its rate of dissolution.

Using the flow through cell, one can easily compare the biopharmaceutical properties of different batches of a drug substance, considering their physical properties.

Here is an example of a case study: Acetaminophen.

- **Acetaminophen powder**
- **Acetaminophen crystal grade**
- **Acetaminophen capsule grade**
- **Acetaminophen fine powder**
- **Acetaminophen micronized**
- **Acetaminophen microcaps**

When measuring the physical properties of the various batches (surface area and the particle size), the following results were obtained:

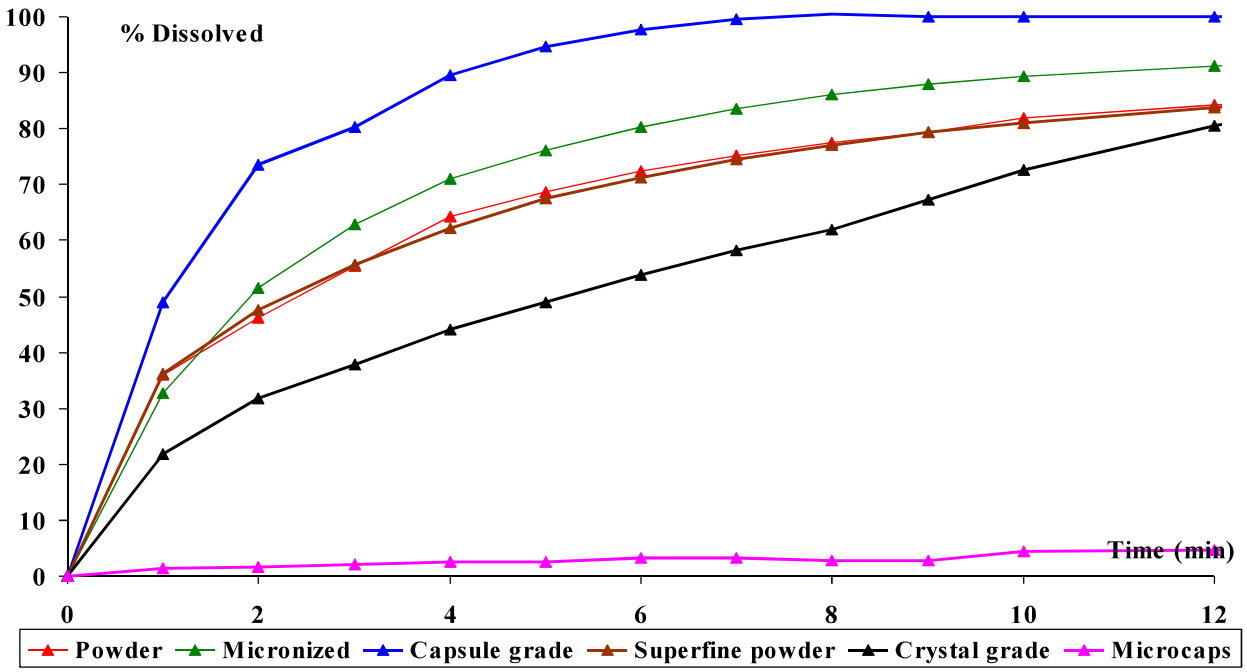
Product	Surface area (m^2/g)	Mean diameter (µm)
powder	0.16	88.45
capsule grade	0.53	394.4
crystal grade	0.33	58.86
fine powder	0.38	48.36
micronized	0.68	34.82
microcaps	---	419.8

All batches were tested using Intrinsic Dissolution Rate, with an amount of 100 mg per replicate, with a pH 5.8 aqueous buffer and 3 determinations per batch. The results obtained were very similar:

Product	K (h-1)
powder	1.8
capsule grade	1.7
crystal grade	1.8
fine powder	1.8
micronized	1.8
microcaps	---

Indeed, for Acetaminophen, there was no difference expected with regards to solid-state (polymorphism, hydrates, etc). Thus, intrinsic dissolution rate was expected to be similar, despite the difference of physical properties.

The same batches were tested using Apparent Dissolution Rate being done with the Flow-through Cell dissolution system (USP4), using cells for powder, in a closed system, with the same pH 5.8 aqueous buffer, with a flow rate of 16 mL/min and 100 mg per replicate. The results obtained show the different curves below.



Conclusions

The results above demonstrate that it is possible to characterize the biopharmaceutical properties of active pharmaceutical ingredients. Having such knowledge allows for example to investigate the root cause of bio-inequivalence and to proceed with a more systematic approach for drug product optimization. Both intrinsic and apparent dissolution testing bring different information about the API tested but, overall, it is of importance to proceed with such API characterization. Such knowledge may obviously guide the development of a new formulation but can also be very valuable during the life cycle of any product, when considering post approval changes such as new sources/ suppliers of raw material and its possible impact on the performance of the drug product.

Author Biography

Prior to joining SPS Pharma Services in 2005, Samir spent more than 10 years in the pharmaceutical industry. As a chemist, he started working on the analytical development of agrochemical compounds at Sandoz Agro in the region of Basel (Switzerland). During the Novartis merger, he moved to Orléans (France) in 1998 to join the analytical group in the technical development department where he became responsible for dissolution. In 2005, he resigned from Novartis to create SPS Pharma Services in Clermont Ferrand which is the first and only CRO specialized in Dissolution and Release Testing. Since then, Samir manages SPS facility and is in charge of projects management. Samir is regularly invited as speaker in international conferences as well as expert for various organizations (scientific societies and Health Authorities).

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