A Simple and Unique Approach for Developing and Evaluating Products

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Commonly pharmaceutical products are evaluated and developed based on four "quality" parameters/measurements: (1) Identity, to show that a product contains the expected drug; (2) assay, to show that a product contains expected amount of drug (dose); (3) Content Uniformity (CU), to establish that the dose or drug content in each unit varies within an expected range; (4) Dissolution/release, to show that the drug will be released from the product in an expected manner.

All these tests are simple chemical tests based on solvent extractions, i.e. the drug is extracted from the product and measured using any of the quantitative techniques such as spectrophotometeric or chromatographic. At present, there are no specific requirements for the use of an extraction procedure. Often, it is expected that the drug be ground and extracted by shaking, vortexing, blending etc., with a suitable solvent, filtered and then measured.

Consider the extraction step in a slightly different way. Rather than using the currently used practices of vortexing, shaking or blending, use a dissolution apparatus **without calling it a dissolution apparatus but an ordinary extractor** for the extraction of the drug from the product **for determining assay and CU only**. The extractions are to be performed using: (1) distilled water as the solvent, which is maintained at 37 ºC and; (2) The stirring rod will be the crescent-shaped spindle set at 25 rpm. The solution samples are withdrawn at different time intervals to measure drug concentrations in solution until a plateau is reached.

Plot the extraction of drug (amount as cumulative percentages) against time using graph paper or Excel spreadsheet. Note that the extraction with time is in fact a dissolution/release profile of the product. There is no need for conducting an extra test just for dissolution testing.

Before evaluating these results further, the following explanation is provided for potential queries in using this approach. For example: if a drug is not soluble in water then how should one proceed? In this case, one should first establish, before starting the extraction step, whether the drug will be soluble in water alone or with the use of some type of solublizer (e.g. SLS). The requirement is that the extraction solvent should be water, with or without a solublizer depending on the nature of the drug. Why should one use the crescent-shaped spindle and not the more commonly used stirrers such as Paddle/Basket? The reason is that the Paddle and Basket do not provide appropriate stirring therefore extraction would not be efficient and accurate. Why should the test not be performed at higher speeds (rpm) to complete the experiment in a shorter time? The reason is that there is an interest in monitoring the difference between extraction profiles of different formulations of the same drug and/or different products, thus a softer/milder extraction process in beneficial.

The data set for the last sampling time represents the complete extraction of the drug, and its values should be on average around 100% of the dose. This result would represent the assay/potency of the product. As the test is conducted in multiple units 6 or 12 then the range of individual values or its %RSD values would represent CU. As the quantitation is conducted using UV or chromatographic techniques, then the matching spectra/peak retention time establishes the identity of the drug in the product.

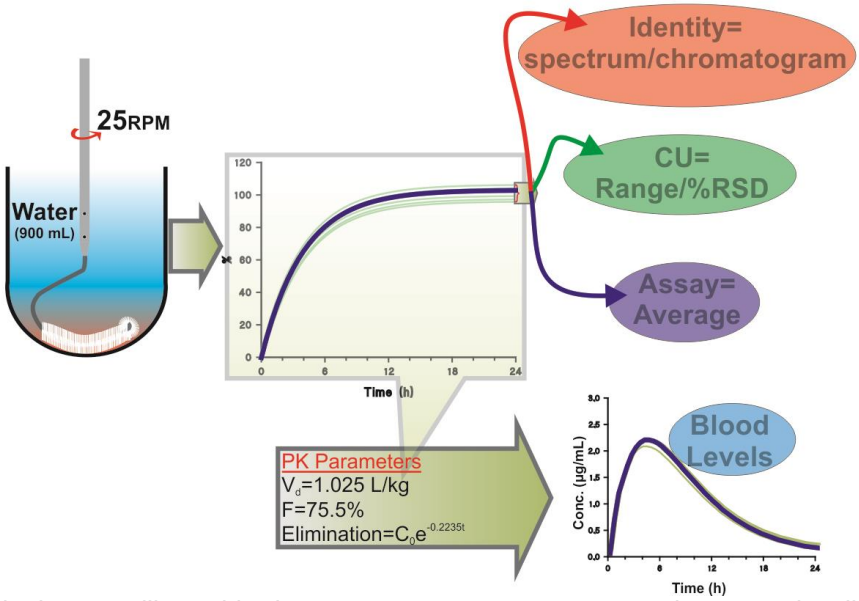
As a whole, the data set would represent extraction/release characteristics of the product and would reflect the dissolution characteristics of the product. There is no need for conducting a separate dissolution test. These results may further be manipulated mathematically using pharmaco-kinetic parameters of the drug to estimate the potential drug levels in humans as described

in literature. A schematic representation of this concept is described in the figure 1 as well.

Figure 1

Schematic representation of an approach of determining assay, CU, identity and dissolution from a *single extraction step.* Drug blood levels can also be estimated from the same results.
(Illustration is for a 500-mg acetaminophen ER product)

Text provides description of the approach.



In short, a single test will provide the answer to all of the four parameters which, at present, commonly require 3 or 4 separate tests. In addition, there would not be any need for conducting additional testing for IVIVC purposes. As the testing is conducted using bio-relevant conditions, these data can directly be used for estimating blood-levels. Apart from simplicity and time/money savings, the approach provides the following additional advantages.

- As assay, CU, identity and dissolution results using this approach are obtained from the same units (tablets/capsules), therefore, the approach provides improved overall evaluation of product characterization and quality.
- The extraction solvent is distilled water, thus, offers significant experimental simplicity and physiological relevancy. The suggested approach eliminates the need for conducting separate bio-relevant or IVIVC studies.
- Experimental conditions are product independent which can provide the required comparison of results (quality) within and between products.
- The approach provides freedom from using Paddle/Basket apparatus which are known for their flaws and requirements of meeting unnecessary and irrelevant large set of specifications.

If further information/detail is required in this regard, an on-site training/demonstration can be arranged. Post-graduate students and post-doctoral fellows who are interested in evaluating the use of crescent-shaped spindle for their on-going research projects may request samples. Please contact us by sending an email to sales@pharmacomechanics.com.

Relevant references and links

- A new crescent-shaped spindle for drug dissolution testing - but why a new spindle? *Dissolution Technol* 2004;11:13-18. (Link)

- Applications of a new device (spindle) for improved characterization of drug release (dissolution) of pharmaceutical products. *Eur J Pharm Sci* 2003;22:291-297. (Link).

- Drug dissolution testing: Selecting a dissolution medium for solid oral products. *Am Pharm Rev* 2009:12;18-23. (Link)

- A simple and economical approach/concept to evaluate quality of pharmaceutical products based on an improved dissolution testing methodology. *Open Drug Delivery J*. 2008:2;33-37.(Link)

- Application of a dissolution test using crescent-shaped spindle (css) to evaluate assay and uniformity of dosage unit parameters. (Link)

- Limitations of Some Commonly Described Practices in Drug Dissolution Testing and Suggestions to Address These. *Am Pharm Rev. 2011: (Jan/Feb), 44-49*. **(**Link**).**

- Determining blood concentration-time (C-t) profiles from in vitro dissolution results and product evaluation – carbamazepine.(Link)

- *In Vitro-In Vivo* Correlation (IVIVC) and Determining Drug Concentrations in Blood from Dissolution Testing – A Simple and Practical Approach. *The Open Drug Delivery Journal,* 2010: *4,* 38-47. *(*Link*)*