Struggling with developing or evaluating tablet/capsule products/formulations? The following considerations should be helpful

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A drug dissolution test is one of the most critical and important tests used for developing and evaluating tablet/capsule products. However, unfortunately, as conducted at present the test is also perhaps one of the most frustrating and the least value adding tests one would use. The test is often promoted as a quality control test or tool as well, however, without defining or linking to a quality parameter/end-point. It is conducted using apparatuses which have never been validated for the intended purpose or objective, which further adds to the frustration. This article describes reasons for such practices and frustrations, and suggests a simple approach to address the issues and concerns.

For developing or evaluating an oral product such as tablet or capsule, like for any other assessment, one would require an endpoint (parameter with a value) to establish that the product meets certain desirable characteristics or qualities. Therefore, before even one starts a task of product development and/or evaluation, one must first define/establish the criterion/goalpost for quality (or the desired characteristic).

It important to note that at present there is no (scientifically) valid goalpost or quality parameter available for dissolution testing at the product development or evaluation stage, thus it is impossible to develop a product of desired characteristic/quality in a systematic (scientific) way, before proceeding to in vivo (bioavailability/bioequivalence) testing (link). This often causes hardship and frustration as well as significant financial loss.

The following may help in setting up, and achieving, the goalpost/criterion (aka quality attribute) so that an efficient product development and/or evaluation routine may be followed.

The basic principle of establishing and evaluating efficacy and safety of a drug in humans is based on its availability on the site of its action. Often the site of action of a drug is not accessible; therefore, blood circulation is used as a carrier to transport the drug to the site of action. Thus, the expected and reproducible appearance (rate) of amount (extent) of the drug in blood (commonly in plasma) becomes a standard for monitoring efficacy and safety of the drugs. Except for local actions, most drugs are delivered through this (bloodstream) route which is also known as the systemic route.

A drug may be introduced into the blood circulation through many input routes such as intravenous, oral, intramuscular, intraperitoneal, dermal, rectal, vaginal etc. However, the most convenient, thus popular, is the oral route.

In its simplest form, a drug (often a pure chemical compound/entity) can be administered as powder or liquid/solution. However, reproducibility, convenience and stability issues would dictate that solid oral dosage forms such as tablets and capsules be used. For all practical purposes, a tablet or capsule is simply a vehicle or package for the powder/liquid drug to deliver/release it in the GI tract, in particular the intestine from where the drug gets absorbed and appears in blood circulation.

The most critical aspect for manufacturing of such products (table/capsules) from the efficacy and safety aspect, thus quality, is that the product should be capable of releasing the drug and facilitating its unhindered dissolution in the intestinal liquid, as the drug would behave in its native (intrinsic) form. The critical importance of the dissolution step is derived from the fact that for a drug to appear/absorb into the blood it should be in a solution form. Therefore, in vivo drug dissolution becomes the critical quality attribute for drug products, a surrogate of appearance of drugs in the blood/plasma stream (aka efficacy and safety indicator).

The in vivo dissolution of drug can be monitored either by in vivo methods e.g. by obtaining plasma drug concentration-time profiles (aka bioavailability/bioequivalence assessments) or by an in vitro method, commonly known as a drug dissolution test.

In addition, the same in vitro dissolution test is also used as a quality control tool/test i.e. for monitoring dissolution characteristic reflecting potential in vivo behaviour of production batches. It is to be noted that the link of in vitro dissolution test to manufacturing is based on establishing consistency of the production of batches having consistency in dissolution characteristics, and not the operation of the manufacturing plant. Different plant operations between different manufacturers or within the same manufacturer, with same or different ingredients, can produce products having acceptable and/or desired plasma drug concentration-time profiles, thus of acceptable quality. The point being that a dissolution test has no capability or capacity of determining/monitoring the manufacturing operation, but the end results i.e. dissolution results. This is like a thermometer or blood pressure monitor that has no ability of determining whether the temperature or blood pressure is being monitored is that of a man, woman or child, who is sick or healthy. All these instruments (testers) provide is a reading which is used for diagnostic purposes. Similarly, a dissolution test or tester provides a reading which would reflect if the product is capable of delivering expected dissolution results/levels. The test or tester has no sense or capacity to know whether the product tested is from a good plant or a bad one or it is from a small (laboratory) or large production scale facility. All it tells is whether a product is capable of releasing the drug in the expected manner i.e. it has an acceptable quality or not. That is why it is considered or called a quality control/assurance test.

This is precisely the reason that the worldwide regulatory agencies and standard setting organizations (e.g. pharmacopeias) require this test, because they are concerned about the efficacy and safety, thus quality, of the product. Therefore, a dissolution test is in fact goalpost or criterion for establishing or evaluating quality of drug products. This fact should be kept in mind.

In a surprise recent announcement (link), USP declared that their pharmacopeial dissolution tests are not biorelevant. However, a disturbing aspect is that the current, or the same, tests would still be considered and required for establishing quality of the products for human use i.e. the test does not show bio-relevancy but is still expected to show the "quality" of the product for human use. This is not logical at all, therefore, re-evaluation of the requirement of current (pharmacopeial) dissolution tests is certainly warranted.

The immediate impact of such an announcement would be that current practices of dissolution testing for product developments would become useless. It appears that some are promoting that other than lack of bio-relevancy of the pharmacopeial tests, the dissolution test retains its usefulness. This is simply an incorrect opinion as there are practically no differences between the pharmacopeial dissolution tests or testers and those used for product development and/or their quality assessments. In addition, a dissolution test or tester has no other use than to monitor the in vivo (or bio-relevant) dissolution of a product as explained above. Furthermore, it is assumed and/or implied that dissolution tests for pharmacopeial purpose would still be developed/suggested based on results obtained from the product developments stage i.e. relevant to bioavailability testing (clearly not a logical requirement). Such confusing opinions and situations cause the problems of using drug dissolution testing for product evaluations, and are expected to further exacerbate them.

The question is why does the drug dissolution testing causes so many problems that eventually the USP has to clearly and publically state that the pharmacopeial methods should not be considered bio-relevant. The reason is that indeed suggested drug dissolution practices are problematic and one cannot use these for product development and/or evaluation, because:

(i) The recommended pharmacopeial apparatuses have never been validated for their relevance and reproducibility. In fact, it has been shown, based on experimental studies that these apparatuses cannot provide bio-relevant and/or reproducible results.

(ii) From the beginning, it has been promoted that dissolution tests are to be developed/conducted using product dependent experimental conditions. This requirement is not only a violation of basic principles of analytical chemistry, but also physiologically irrelevant. The reasons being: (a) the purpose of any analytical test is to determine an unbiased and true value of the desired parameter, which can only be achieved using independently developed and validated test methods. In current practices of dissolution testing, the methods are developed using the test products themselves. Therefore, it is not possible to obtain true or unbiased dissolution characteristics of any product. (ii) For a bio- or physiological relevant dissolution test, the test must be conducted using a physiologically representative environment as closely as possible. One of the requirements for dissolution testing in this regard is that, as the physiological environment remains the same or constant from product to product, the dissolution testing environment (experimental conditions) must also remain constant or product independent. However, for in vitro dissolution testing, the experimental condition varies from drug to drug, and product to product, which clearly is a non-physiological environment. It is again an operational (scientific) impossibility to obtain relevant and valid results without meeting the physiologically requirements.

Therefore, as a first step, for appropriate drug dissolution testing one should consider addressing the following two deficiencies: (i) the dissolution tests have to be conducted using apparatuses/testers which are capable of providing bio-relevant dissolution results e.g. capable of differentiating dissolution characteristics of products (such as IR vs ER)

reflecting their bio-behavior (link); (ii) the products must be tested using experimental conditions representative of physiology (intestinal) which also must be product independent (link).

Without addressing these shortcomings of current practices, drug dissolution testing will remain a scientifically weak, rather invalid, practice providing irrelevant and useless data and will continue to cause frustrations.

An interesting and comforting part is that a bio-relevant test can easily be developed by improving the stirring within the dissolution vessels (e.g. using a crescent-shape spindle rotating at 25 rpm) (link). Experimental studies have shown validity of this approach. In addition, a simple calculation approach, as suggested in literature, may also be used to convert dissolution results to predict expected plasma concentration-times profiles for convenient comparison with those obtained from in vivo studies i.e. bioavailability evaluations (link).