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DISSOLUTION TEST FOR SOLID ORAL DOSAGE FORMS: MORE THAN JUST A TEST, AN ART

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ABSTRACT

Solid dosage forms, such as tablets and hard gelatine capsules have been on the market for a very long time. Despite the growth of biological molecules that are mainly given though parenteral routes (implying in a lot of cases, the need for a professional in health sciences) solid oral dosage form will remain very successful for several reasons: Their low cost of goods (compared to injectables) and the patient's compliance. Furthermore, it can be said that the oral route is and will remain the *Royal route*.

KEYWORDS: capsules, injectables, biological molecules.

Dissolution is an in vitro test carried out in a dissolution apparatus composed of a thermostated bath, paddles, baskets, or capsules sinkers that will rotate under programmed speed, in a vessel composed of buffers which should mimic physiological conditions. Thus, a system is proposed to mimic the physiological and hydrodynamic conditions over which a tablet or a capsule will have to go through to demonstrate that once swallowed, the solid dosage form will start disintegrating and will initiate dissolution of the active pharmaceutical ingredient (API). However, any person will recognize that a dissolution apparatus does not represent neither a stomach nor a gut, therefore in vitro/in vivo correlations may become hazardous to forecast and are more interesting from an academic standpoint. Authors of these short communications gather more than 50 years of experience in pharmaceutical development and will try to explain why dissolution is not considered just a wet chemistry test but an art. Furthermore, they will try to illustrate that dissolution tests should be considered a reliable quality control test when well-developed but not entirely reliable to predict bioequivalence between two oral dosage forms.

In 1897, Noyes and Whitney[1] reported in the literature the first dissolution study by immersing in a water glass vessel two compounds: Namely benzoic acid, and lead chloride. In the 1970's, 1980's and 1990's were introduced through different types of dissolution apparatus[2] with dedicated sections in the USP. In 1997, four FDA guidance were released, and dissolution became closely connected from a regulatory standpoints, including formulation and analytical

development, release, and stability specifications.[3-6] The first guidance[3] illustrated, with statistical formula on how two dissolution profiles could be compared and whether they would show equivalence between them. In fact, dissolution has been used and is mandatory for both release and stability specifications, for any kind of oral dosage forms.

Strengths of dissolution profiles

- Different types from USP 1 to 5, depending on the oral dosage forms.
- Different medium can be used such as SGF (Simulated Gastric Fluid), FaSSIF and FeSSIF (Fasted/Fed State Simulated Intestinal Fluid), with or without enzymes.
- During R&D, non-compendial dissolution media such as organic solvents (acetonitrile, isopropyl alcohol) when solubility is an issue, or ethyl alcohol for abuse deterring/tamper-resistant formulation to have an idea of how the dosage form will behave in alcoholic environment.
- From a regulatory standpoint, it is very useful for bioequivalence study, especially for BCS 1 and 3 small molecules since the dissolution test may allow to waive the carrying out of a bioequivalence study on healthy volunteers to get a generic on the market.[7]
- Will assure consistency from batch to batch and should be able to monitor any physico-chemical changes over time of development and when dosage forms are under different conditions of temperature and humidity.
- Different volumes of media could be used, such as 500 ml to 900 ml.
- Different hydrodynamic conditions could be used, from 50 to 100 rpm.

Weaknesses of dissolution profiles

- The cost of a complete equipment may be expensive for start-up companies.
- The understanding of sink conditions, the generation of a discriminating dissolution medium may be difficult to achieve.
- Seasoned people showing a proven track records in analytical development represent the crux of the matter. A lot of qualified people in quality control are available however, people showing development skills are becoming increasingly rare.
- Dissolution apparatus/test should not be considered an *in vitro* device that represents the gastrointestinal tractus, even though it can mimic physiological conditions.
- It may be challenging to generate a profile with oily active pharmaceutical ingredients once soft gelatin capsules are disintegrated, the use of surfacting agent may biased the dissolution phenomenon.
- It is difficult to generate dissolution profiles of different solid dosages forms taken at the same time and since numerous patients are polymedicated, sink conditions of each drug substance may not be respected in the vessel of the dissolution apparatus.
- Some dosage form, such as orally disintegrating film or tablets are dissolving so fast, 1) it becomes very difficult to generate a profile since in less than 5 minutes, everything is disintegrated (even though disintegration is not discriminatory of dissolution) and 2) it does not mimic at all the real life, where these kind of drug delivery are located on the tongue, with nothing “above” them (no saliva, nor gastric/intestinal media).

How to generate a robust, reliable and stability indicating dissolution method

First and foremost, this is a discussion for solid-state chemists and formulators. The data generated by solid-state chemists such as polymorphism, pKa determination and solubility data of the active pharmaceutical ingredient (API) are critical. This will be a determining factor in the development of a robust dissolution method. There is no need to start from square one.

One must remember that dissolution failures are the number one cause of product recalls in the pharmaceutical industry. Hence the importance of developing a solid and robust dissolution method.

The first step in developing a dissolution method is determining the sink conditions. Those are defined as 3 times the intended highest finished product form, and ideally 10 times. The studies are performed in 6 different media: Water, 0.01N HCl, 0.1N HCL, pH 4.5 buffer, pH 6.8 buffer and pH 7.2 buffer. Dissolution media containing a surfactant or alcohol can be used but needs to be justified. As an example, for a finished dosage form containing 100 mg of API, the co-author's preferred way of performing the sink conditions determination would be to weigh 1000 mg of API and transfer to an empty dissolution vessels. Pre-heated media would then be added to the vessels and the paddles rotating at 100 rpm. Adding the dissolution media in the vessels helps prevent the drug substance from floating and accumulating around the paddle shaft. The concentration of the API in each dissolution medium is then determined by either UV or HPLC.

The next step is to perform dissolution experiments based on the data generated by the solid-state chemists and sink conditions results. The apparatus chosen depends on the selected finished dosage form (this should be evaluated in a development report). Working along with formulators, aberrant tablets should be manufactured on a small scale to determine the discriminating power of the dissolution method recently developed. Aberrant tablets can be described as a formulation that has been purposely modified by varying the amount of the excipients, while keeping the same dosage strength.

The most commonly used dissolution apparatus are apparatus 1 (baskets) and apparatus 2 (paddles). Those are used mainly for immediate release dosage forms. Apparatus 3 and 4 should not be ignored for delayed or sustained release formulations. The advantage of apparatus 3 and 4 is that the dissolution media are easily interchangeable without manipulating the dosage form during the test.

If the dosage form has a propensity to float, a sinker should be used. There are several types of sinkers available from manufacturers. The type of sinker selected should be documented in the dissolution method.

Based on a recent experience in development of a delayed release dosage form, in vivo in vitro correlation could not be determined but apparatus 3 was not evaluated during drug development. Decent dissolution profiles had been obtained using apparatus 2 but the API was not absorbed in the intestinal tract at pH 6.8. Evaluating apparatus 3 would have been useful in evaluating the dissolution profile in different media such as 0.1N HCl, pH 4.5 acetate buffer followed by phosphate 6.8 and 7.2 buffers.

The quantitation method should be either UV or HPLC. HPLC is preferred since it is more specific, meaning that degradation products can be identified, as opposed to UV. It is important to develop a method which has a short acquisition time since when performing dissolution profiles, large number of samples need to be quantified.

Once the dissolution method has been selected, it must be validated. The ICH guidelines are very useful in developing the validation protocol. Parameters such as those described below should be evaluated:

- Rotating speed for apparatus 1 and 2. Dip rate for apparatus 3 and flow rate for apparatus 4.
- Buffer concentration and pH variations in the dissolution medium.
- Accuracy in the 70-130% range.
- Linearity.
- Ideally, stress testing should be performed to determine if the quantitation method is stability-indicating, and this is performed by measuring peak purity by HPLC.

CONCLUSION

- One must remember that the dissolution test is the number one cause of product recalls by the regulatory agencies so the dissolution method should be robust and reliable.
- Dissolution should not be considered a reliable tool for in vitro in vivo correlation but could be very helpful as a quality control test to monitor the physico -chemical behavior during stability studies. Of course, a reliable, robust, and discriminatory dissolution method, as described above, will have to be developed in order to achieve such a goal.

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