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The determination of the dissolution properties of pharmaceutical products has become one of the most important *in vitro* tests used throughout the lifecycle of all types of formulations. Traditionally used to measure the release rate of drugs from tablet and capsule formulations, it is now an essential tool for assessing the performance of products for all routes of administration including patches and semi-solids such as ointments and creams for transdermal application, suppositories, pessaries, buccal tablets, chewing gums, suspensions, implants for subcutaneous or intramuscular release, and surgical products such as bone cement and drug-eluting stents for repairing damaged blood vessels.

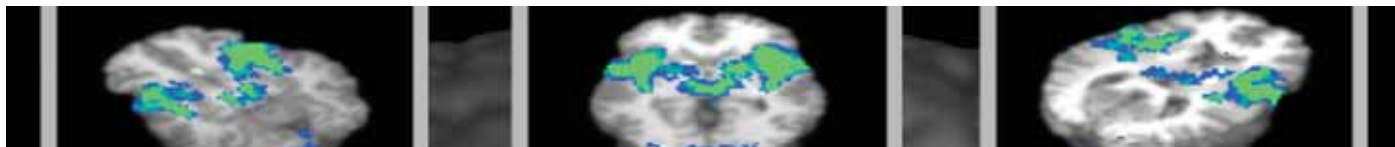


A Basic Guide to **DISSOLUTION TESTING** *for pharmaceutical products*



Dissolution testing was introduced as a routine testing procedure back in the 1960s for two main reasons. Firstly, there were some well-founded concerns about the bioequivalence of supposedly similar products. Different sources of some products often resulted in different *in vivo* responses and a simple comparative test that could be carried out in the laboratory was needed to investigate some of the possible reasons for these differences. Secondly, an *in vitro* means of assessing dissolution rates of emerging modified release formulations was required. For some drug substances, it is advantageous to control either the rate of release or the location of release in the gastrointestinal tract. Enteric coated tablets, for example, are resistant to stomach acid and only release their product in the higher pH conditions of the intestines. This property may be used to control the position of release in the treatment of ulcerative colitis, to prevent gastric irritation, or to prevent the drug substance from being rendered inactive through degradation in the acidic environment of the stomach. Once-a-day dosage regimes from controlled release formulations are often preferred for chronic conditions and this property can be extended to long-term release from transdermal patches or implants.

These days dissolution testing is a regulatory requirement for all pharmaceutical products delivering drug substances



and its prime function is as an *in vitro* control of bioequivalence. It is necessary to demonstrate bioequivalence between products from different manufacturers (e.g. branded Vs generic), different formulations, multiple sources of raw materials, varying manufacturing processes or sites of manufacture, or simply batch to batch variation. The most important purpose of dissolution testing is to ensure that the patient receives a reliable and consistent product.

The dissolution test should not be considered as an absolute analytical procedure. It is always comparative, whether as a bioequivalence test assessing different formulations, as a stability test comparing stored product with the original product, or as a quality control test comparing different batches against previously established limits. As a comparative test procedure, the consistency and reproducibility of

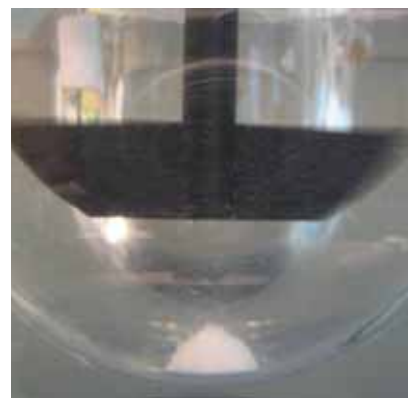


both the analytical equipment itself and the techniques used are essential, and this requirement continuously occupies the minds of those involved in practical dissolution testing.

Over the years many different types of dissolution apparatus have been developed, but a limited number of standardised procedures are now used with only minor differences seen throughout the world. These procedures are documented in the major pharmacopoeias and controlled through the international pharmaceutical regulatory bodies.

The procedures can be divided into categories according to the method used to establish the fundamental hydrodynamic conditions essential for dissolution; that is the conditions whereby the medium containing dissolved material is continuously removed from the region in which dissolution is taking place (i.e. at the surface of the undissolved material).

The most widely used equipment is the standard dissolution tester with a rotating device to cause continual motion, usually a paddle or a mesh basket assembly for solid products or, a cylinder for transdermal products. These apparatus are used for the evaluation of a wide range of formulations under a range of conditions and for periods of time ranging from minutes to days. The speed of rotation can vary over a typical range from 25 rpm to 150 rpm. The volume of the dissolution vessel (a universally adopted cylindrical vessel with a hemispherical bottom) can range from 100 ml to 4 L with a volume of 900 ml of a relevant dissolution medium contained in a 1 L vessel being the most common set-up. An alternative method which is gaining popularity uses a glass cylinder with a mesh to retain the product under test which is reciprocated inside a flat-bottomed tube containing the dissolution medium (usual volume 250 ml). An advantage of this method is that instruments are constructed to facilitate transfer of the product under test through a series of dissolution media which can vary in composition so as to reflect more closely the changing conditions found throughout the gastrointestinal system. Modifications of this apparatus are used (e.g. USP Apparatus 7) for the testing of a wide variety of specialised dosage forms including osmotic pumps, transdermal formulations,



implants and stents. A compendial method with completely different hydrodynamic properties to the continual motion set-up is the continuous flow procedure. In this apparatus, the test material is contained within a small chamber (volume 10-20 ml) with fresh dissolution medium continuously pumped through the chamber. This set-up has the effect of continuously removing dissolved material from the vicinity of the dissolving product, which is advantageous for drugs with poor solubility.

To establish the release rate of a product by whichever method is chosen, it is usually necessary to test at least six individual dosage units. The dosage units are always tested individually and never in multiples. The dissolution procedure itself does not actually generate any results; as it is simply a sample preparation process. A complete dissolution test involves a multi-stage procedure, with each stage having specific requirements and controls. Firstly, the apparatus must be maintained to conform to the required standards and the medium into which the product will dissolve must be carefully prepared (e.g. removal of dissolved gases from the medium). The test must be monitored to ensure controlled conditions and samples of the medium are taken under specified conditions at appropriate intervals. Further sample preparation may involve filtration and dilution prior to analysis to determine the actual concentration of drug in solution from which the release rate can be calculated. Analysis of the dissolution samples is usually carried out by either direct ultraviolet spectrophotometry or high performance liquid chromatography. Since there are often numerous samples to test and analyse, automation of one or more stages of the whole dissolution test procedure, especially the sampling and analysis, is not uncommon.