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A review on discriminative dissolution testing

P Tripurasundari*, G Swetha
RBVRR Women's College of Pharmacy, Hyderabad, Telangana, India

Abstract
In vitro dissolution test means the rate and extent of dissolution i.e. amount of drug dissolves in the medium. A dissolution study of dosage form necessities modification in dissolution medium to increase solubility. Since pH of GIT is 1-8 it is necessary to develop the medium where the drug has maximum solubility and exhibits sink condition. A sink condition occurs when the drug that can be dissolved in the dissolution medium is 6 times greater than the amount of drug to be dissolved. Thus solubility study is carried out and the media in which maximum solubility occurs is selected. A discriminative dissolution method has to be developed to exhibit different results when the manufacture of a product changes. Discrimination in dissolution having dissolution test which will show a difference between one formulation and another. A discriminating medium is one part of discriminating dissolution test. The media should be able to meet sink condition. To determine a good media typically it is but to select study several different pH media, rpm. The dissolution method should be sensitive to variation that can be an impact on the invivo performance of the dosage form. Discriminative method is found to be promising tool for the new drug in the selection of better medium based upon its physico-chemical nature with respect to the body condition.

Keywords: discrimination, physico-chemical, pH media

Introduction

Importance of dissolution testing: Tablets or capsules taken orally remain one of the most effective means of treatment available. The effectiveness of such dosage forms relies on the drug dissolving in the fluids of the gastrointestinal tract prior to absorption into the systemic circulation [1]. The rate of dissolution of the tablet or capsule is therefore crucial. Dissolution is an important test method that is carried out on solid oral dosage forms like capsules, tablets, and oral suspensions. For these dosage forms to be efficacious, the active drug substance must be absorbed into the systemic circulation so that it can be transported to its site of activity. Step one, dissolution, is the process of extracting the drug substance out of the dosage form solid-state matrix into solution within the gastrointestinal tract. Step two, absorption [2, 3], is the process of transporting the drug substance from the gastrointestinal tract into the systemic circulation. Dissolution testing is an in vitro laboratory test method that is designed to demonstrate how efficiently an active drug substance is extracted out of a solid oral dosage form. Therefore, it can provide an indication of the efficiency of in vivo dissolution (step one) but does not provide any information on drug substance absorption (step two), so it can only provide limited information on potential bioavailability. Drug release in the human body can be measured 'in-vivo' by measuring the plasma or urine concentrations in the subject concerned. However, there are certain obvious impracticalities involved in employing such techniques on a routine basis. These difficulties have led to the introduction of official 'in-vitro' tests which are now rigorous and comprehensively defined in the respective Pharmacopoeia.

The principal function of the dissolution test may be summarized as follows:

- Optimizations of therapeutic effectiveness during product development and stability assessment
- Routine assessment of production quality to ensure uniformity between production lots
- Assessment of 'bioequivalence', that is to say, production of the same biological availability from discrete batches of products from one or different manufacturers.
- Prediction of 'in-vivo' availability i.e., bioavailability [4] (where applicable) in vitrodissolution often aids in guiding the selection of prototype formulations. It helps to determine optimum amounts of ingredients needed to achieve requisite drug release profiles. It is one of the most important and useful *in* vitro tests for assuring product quality – batch to batch consistency. Provides information on the impact of changes in composition, process or site of manufacture.

A dissolution test measures the rate of release of the drug. The objective is to develop a discriminatory method that is sensitive to variables that affect the dissolution rate. Such variables may include characteristics of the active pharmaceutical ingredient (API) (*e.g.,* particle size, crystal form, bulk density), drug product composition (*e.g.,* drug loading, and the identity, type, and levels of excipients), the drug product manufacturing process [5] (*e.g.,* compression forces, equipment), and the effects of stability storage conditions (*e.g.,* temperature, humidity). Although it also is desirable to develop a dissolution test that establishes an IVIVC or an IVIVR that kind of correlation between observed changes in in vitrodissolution rate to meaningful *in vivo* product performance quality remains a key challenge.

Characterizing the drug-release mechanism by establishing an *in vitro* dissolution test method (or an appropriate alternative method) to measure product performance is particularly important for poorly soluble compounds. Dissolution testing historically has been a key tool during the development stages of a compound as well as for commercial manufacturing. For a development compound, dissolution testing is used primarily to help develop and evaluate new formulations by evaluating the rate of drug release from dosage forms, evaluating the stability of these formulations, monitoring product consistency, assessing formulation changes, and establishing IVIVRs or IVIVCs. For a commercial product, dissolution testing is used primarily to confirm manufacturing and product consistency, to evaluate the quality of the product during its shelf life, and to assess post approval changes and the need for bioequivalence studies. During the development of a pharmaceutical product [6] dissolution testing is used as a tool to identify formulation factors that are influencing and may have a crucial effect on the bioavailability of the API. As soon as the composition and the manufacturing process are defined dissolution testing is used in the quality control of scale-up and of production batches to ensure batch to batch consistency and that the dissolution profiles remain similar to those of pivotal clinical trial batches. The dissolution test is a vital tool for formulation optimization, method development, formulation changes, manufacturing changes, process modifications to comply with regulatory requirement, US Pharmacopoeia (USP) compliance, in-vitro in-vivo correlation (IVIVC) and Scale Up and Post Approval Changes [7,8] (SUPAC). As the drug moves into production, dissolution test becomes a QC test, which helps to understand outcomes of process and manufacturing changes on dissolution profile. When a new supplier for a certain excipient needs to be selected or when a new lot of excipient is used in the formulation the dissolution profile is investigated. Dissolution test helps in determining whether a drug lot passes or fails as per pharmacopeial standards. Finally as the drug moves into generic arena, dissolution test is one test, which helps to prove bio-equivalence of the generic drug with the patent protected innovative drug in the market. During all these stages, formulation scientists are always looking for ways to find a correlation between the in-vitro dissolution test and in-vivo drug concentration profile [9, 10] (IVIVC). Dissolution studies also provide means to control the quality of many of the parameters of a solid oral dosage form for both batch release and stability testing. This test can provide a much greater amount of value, in addition to providing a metric for quality control and stability testing. The test can be used to investigate a number of critical processing and formulation properties, in order to develop and produce a more robust and better quality drug product.

Different apparatus used in dissolution testing: [11]

- Apparatus 1 (basket apparatus)
- Apparatus 2 (paddle apparatus)
- Apparatus 3 (reciprocating cylinder)
- Apparatus 4 (flow through cell)
- Apparatus 5 (paddle over disk)
- Apparatus 6 (rotating cylinder)
- Apparatus 7 (reciprocating holder)

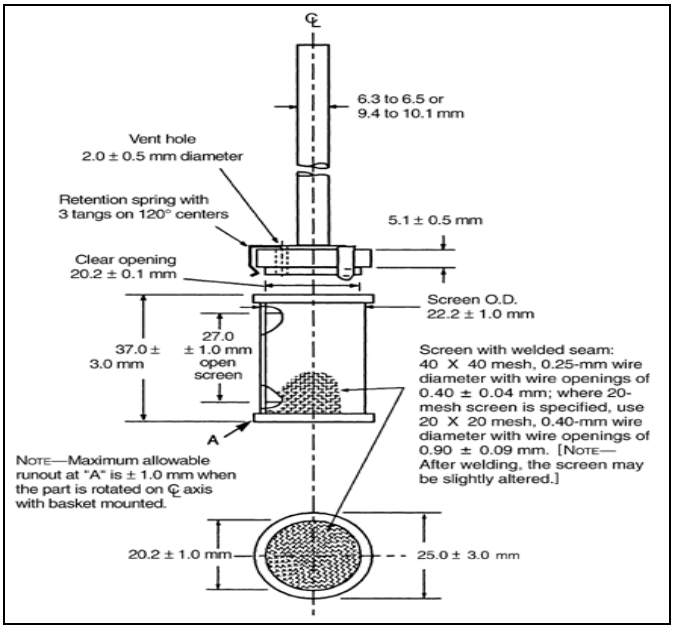

Fig 1: Drug dissolution apparatus-1 USP (Rotating basket)

The rotating basket apparatus [11] (Apparatus 1) consists of a cylindrical basket held by a motor shaft. The basket holds the sample and rotates in a round flask containing the dissolution medium. The entire flask is immersed in a constant-temperature bath set at 37°C. The rotating speed and the position of the basket must meet specific requirements set forth in the current USP. The most common rotating speed for the basket method is 100 rpm. Dissolution calibration standards are available to make sure that these mechanical and operating requirements are met. Calibration tablets containing prednisone are made especially for dissolution tests requiring disintegrating tablets, whereas salicylic acid calibration tablets are used as a standard for non-disintegrating tablets. Apparatus I is generally preferred for capsules and for dosage forms that tend to float or disintegrate slowly.

- Adopted in 1970 the rotating basket method of dissolution testing was the first official method. Essentially it consisted of an approximately 1 inch (25.4mm) × 1 3/8 inch (34.925mm) stainless steel, 40-mesh wire basket rotated at a constant speed between 25 and 150rpm. This method is now called Apparatus 1.
- The apparatus consists a metallic drive shaft connected to the cylindrical basket. The basket is positioned inside a vessel made of glass or other inert, transparent material. The temperature inside the vessel is kept at a constant temperature by being placed inside a water bath or heating jacket. The solution in the vessel is stirred smoothly by the rotating stirring element.
- A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at a specified rate, within ± 4 per cent.
- Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure.
- A basket having a gold coating of about 2.5 µm (0.0001 inch) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test.

- The distance between the inside bottom of the vessel and the bottom of the basket is maintained at 25 ± 2 mm during the test.
- Other types of basket exist for specific applications. For example, suppository baskets are normally manufactured from plastic and have vertical slits to facilitate the dissolution.
- Japanese baskets are sometimes confused with dissolution baskets although they are actually sinkers. Products manufactured under the JP may require the use of this basket.
- This apparatus is used mainly for testing of uncoated tablets, Enteric coated tablets, Sublingual tablets, hard gelatin capsules and Soft gelatin capsules.

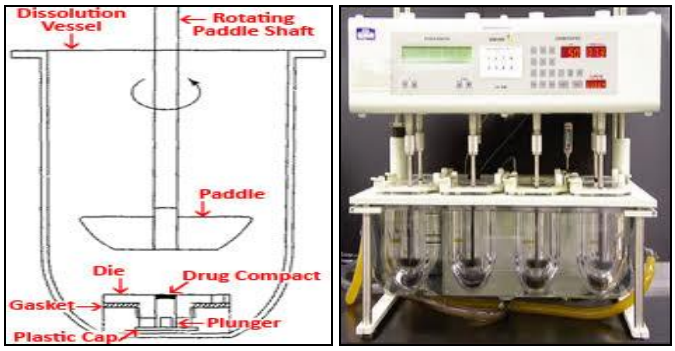

Fig 2: Drug dissolution apparatus-II USP (Paddle)

The paddle apparatus (Apparatus II) [11] consists of a special, coated paddle that minimizes turbulence due to stirring. The paddle is attached vertically to a variable-speed motor that rotates at a controlled40 speed. The tablet or capsule is placed into the round-bottom dissolution flask, which minimizes turbulence of the dissolution medium. The apparatus is housed in a constant-temperature water hall maintained at 37^0C, similar to the rotating-basket method. The position and alignment of the paddle are specified in the USP. The paddle method is very sensitive to tilting. Improper alignment may drastically affect the dissolution results with some drug products. The same set of dissolution calibration standards is used to check the equipment before tests are run. The most common operating speed for Apparatus II are 50 rpm for solid oral dosage forms and 25 rpm for suspensions. Apparatus II is generally preferred for tablets. A sinker, such as a few turns of platinum wire. May be use to prevent a capsule or tablet from floating. A sinker may also be used for film coated tablets that stick to the vessel walls or help position the tablet or capsule under the paddle (Gray *et al*, 2001). The sinker should not alter the dissolution characteristics of the dosage form.

- Apparatus 2, commonly known as the paddle method, was originally developed by Poole (1969) and was refined by scientists at the FDA for Drug Analysis in St Louis. The specifications for Apparatus 2 are identical with those for Apparatus 1 except that the paddle is substituted for the rotating basket.
- The USP specifies that the paddle must rotate smoothly without significant wobble. The arc of the paddle blade creates considerable flow and wobble has the effect of increasing the angular velocity at the paddle tips in a manner that couples with the fluid much more significantly than would a comparable wobble in the basket.
- The contours of the paddle blade must not include any sharp edges — at the tips for instance — that could produce turbulent instead of laminar flow patterns. The USP constrains wobble and vertical alignment with the axis of the vessel to within ±2.0mm.
- The USP suggests that paddles 'may' be coated with polyfluorocarbon and most commercial paddles are accordingly coated.
- Such coating serves two purposes: it prevents corrosion and the introduction of unwanted ions into the media and it seals the joint where the blade is attached to the shaft, thus preventing the accumulation of traces of contaminants.
- Because of the precise geometry required for the repeatability of the paddle method, the stirring paddle has been specified as a stainless steel device rather than a glass one with a detachable blade, largely because glass cannot be manufactured to such close cost specifications without incurring excessive cost.
- Rotation speed for solid dosage forms is 50 RPM, while for Liquid dosage forms (suspension) it is 25RPM.
- It cannot be used for testing of powder dosage forms.
- This apparatus is used mainly for testing of uncoated tablets, Enteric coated tablets, Sublingual tablets, hard gelatin capsules and Soft gelatin capsules, Gels, Ointments.

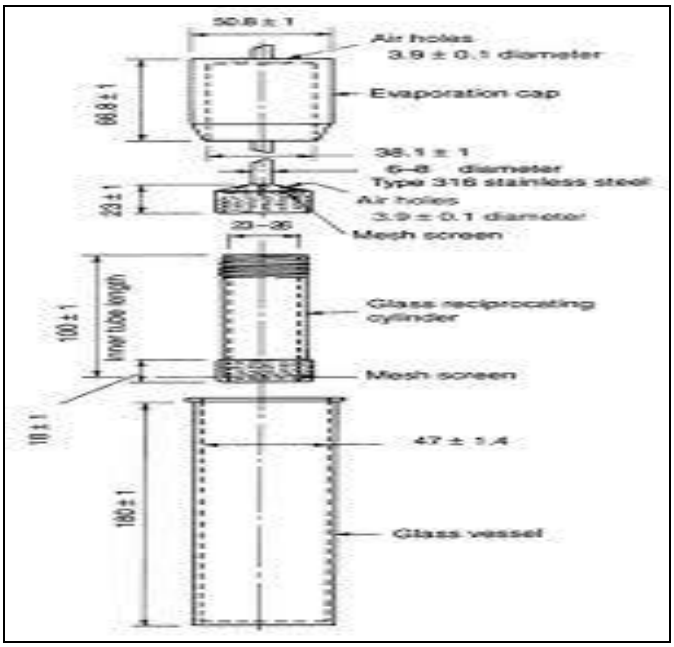

Fig 3: Drug dissolution apparatus-III USP (Reciprocating cylinder)

The reciprocating cylinder was proposed by Beckett and coworkers and its incorporation into the USP followed in1991. The idea to generate a new test method [11, 12] came from a presentation at the International Pharmaceutical Federation (FIP) Conference in 1980 (U.S. Pharmacopoeial Convention). A team of scientists working under Beckett's direction in

London, UK, subsequently developed the reciprocating cylinder, which is often referred to as the ''Bio-Dis.'' Although primarily designed for the release testing of extended-release products, USP apparatus 3 may be additionally be used for the dissolution testing of IR products of poorly soluble drugs44. In terms of design, the apparatus is essentially a modification of the USP/NF disintegration tester.

The assembly consists of

- A set of cylindrical, flat-bottomed glass vessels;
- A set of glass reciprocating cylinders.
- Inert fittings (stainless steel type 316 or other suitable material) and
- Screens that are made of suitable nonsorbing and nonreactive material, and that are designed to fit the tops and bottoms of the reciprocating cylinders;
- A motor and drive assembly to reciprocate the cylinders vertically inside the vessels.
- The vessels are partially immersed in a suitable water-bath of any convenient size that permits holding the temperature at 37 ± 0.5 °C during the test.
- A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate, within ± 5 per cent.
- This apparatus resembles the Disintegration apparatus.
- Upward and downward strokes of cylinder are observed.
- It's quite useful for beaded products like pellets, granules etc.
- Also useful for controlled and immediate release products.

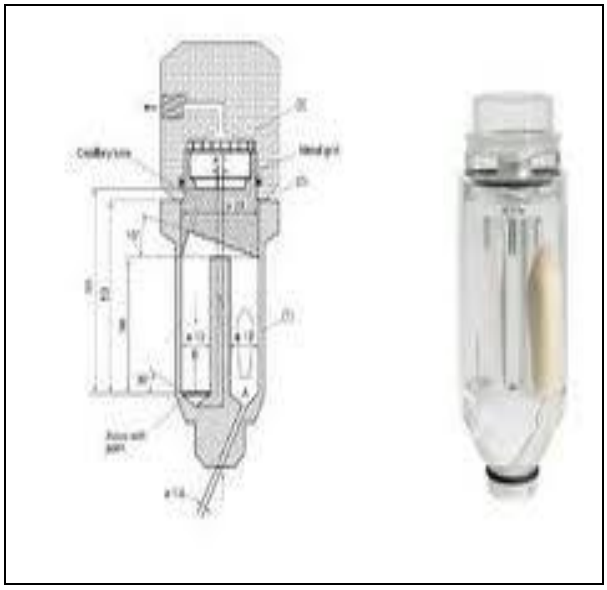

Fig 4: Drug dissolution apparatus-IV USP (Flow-through cell)

The flow-through-cell apparatus (Apparatus IV consists of a reservoir for the dissolution medium and a pump that force dissolution medium through the cell holding the test sample. Flow rate ranges from 4 to 16 ml/min. six samples are tested during the dissolution testing. And the medium is maintained at 37^0C. Apparatus IV may be used for modified-release dosage forms that contain active ingredients having very limited solubility. There are many variations of this method. Essentially, the sample is held in a fixed position while the dissolution medium is pumped through the sample holder. Thus dissolving the drug, Laminar flow of the medium is achieved by using a pulse less pump. Peristaltic or centrifugal pumps are not recommended. The flow rate is usually maintained between 10 and 100 ml/min. The dissolution medium may be fresh or recalculated. In the case of fresh medium, the dissolution rate at any moment may be obtained, whereas in the official paddle or basket method, cumulative dissolution rates are monitored. A major advantage of the flow-through method is the easy maintenance of a sink condition for dissolution. A large volume of dissolution medium may also be used, and the mode of operation is easily adapted to automated equipment. The use of flow through cells for the dissolution testing of tablets and capsules is not a new idea. The flow through cell used today is based on subsequent development work by Dr. F. Langenbucher and Prof. H Moeller and was incorporated as Apparatus IV in the USP, the European Pharmacopoeia and the Japanese Pharmacopoeia during the 90s. The flow through method uses an unlimited amount of solvent. There are a number of advantages compared to the apparatus I and II. Sink conditions can easily be reached with Apparatus IV. Also pH changes during the test are easily performed. The media change is performed by switching a valve from one medium to another medium. As the cell volume is only about 10 ml and a typical flow rate is 16 ml/min it only requires about one minute for a complete pH change. Sampling in stirrer methods often leads to problems. The introduction of the sampling probe can change the hydrodynamics and therefore the dissolution conditions. In addition, the sampling position must always be at the same point to guarantee reproducibility. In the flow through method there are no problems related to sampling. Neither manual nor automated manipulations are necessary. The sample solution is automatically filtered upon leaving the cell and can be analyzed directly or after fractioning without interference of the dissolution process.

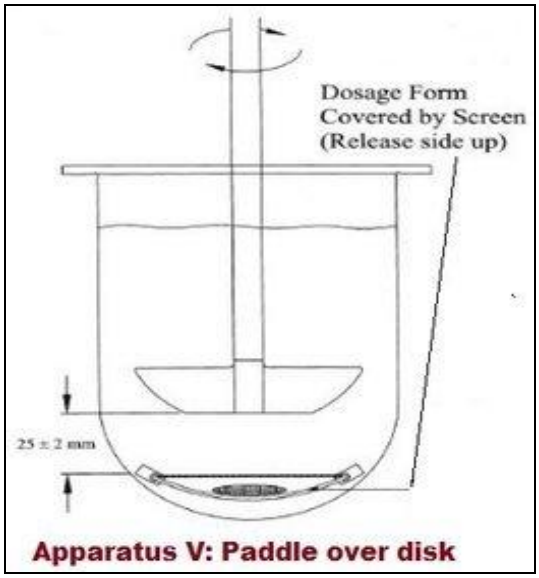

Fig 5: Drug dissolution apparatus-V USP (Paddle over disc)

- Transdermal patch testing is carried out using USP method 5 (paddle over disc).
- With paddle over disc, the transdermal patch is placed between a glass disc and an inert PTFE (Poly Teflon) mesh.
- This is placed at the bottom of the vessel, with the mesh facing upwards, under a rotating paddle.
- Unlike dissolution testing, transdermal testing is carried out at 32°C to reflect the lower temperature of the skin. Other variables such as the height setting and sampling requirements are the same as dissolution testing.
- USP 5 apparatus is made-up of borosilicate glass with a PTFE 17 mesh, held together by PTFE clips. Patches up to 90mm in diameter can be tested.

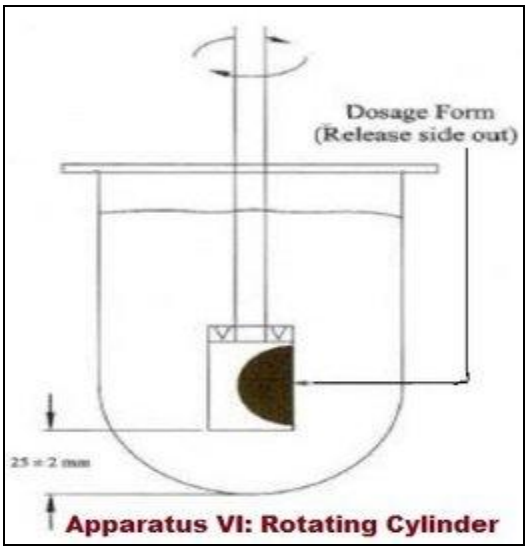

Fig 6: Drug dissolution apparatus-VI USP (Rotating cylinder)

- Transdermal or patch testing is carried out using USP method 5 (paddle over disc) or USP method 6, the rotating cylinder.[11, 13, 14]
- The rotating cylinder is very similar to USP method 1 (the rotating basket).
- With USP method 6 however, the basket assembly is replaced by a solid stainless steel cylinder.

Different media [15-18]

- The cylinder consists of two parts that fit together: the main shaft/cylinder assembly plus an extension. The extension is used when the transdermal patch requires a larger area.
- The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.
- The temperature is maintained at 32 ± 0.5 °C. The vessel is covered during the test to minimize evaporation.

Fig 7: Drug dissolution apparatus-VII USP (Reciprocating holder)

- The vessels are partially immersed in a suitable water-bath of any convenient size that permits holding the temperature at 37 ± 0.5 °C during the test.
- A device is used that allows the reciprocation rate to be selected and maintained at the specified dip rate, within ± 5 per cent.
- Useful for testing of extended release dosage forms, Osmotic pumps, Tablets, Ointments, Gels etc.
- Cuprophan (Cellophane paper) is used for holding of semisolid dosage forms.

Table 1

Medium	Proposed composition
0.1 N hydrochloric acid	3.636 g HCL, corresponding to 8.3 ml hydrochloric acid 37 % (m/m) per 1000 ml of aqueous solution
Buffer solution pH 4.5	Acetate buffer solution Ph 4.5: 2.99 G of sodium acetate trihydrate and 1.66 g of glacial acetic acid are dissolved in water to 1000 ml Phosphate buffer solution pH 4.5: 13.61 g monobasic potassium phosphate is dissolved in 750 ml of water. After adjusting the pH to 4.5 with 0.1 N hydrochloric acid or 0.1 N sodium hydroxide, water is added to make 1000 ml
Simulated intestinal fluid without pancreatin pH 7.5	250 ml of a solution containing 6.8 g monobasic potassium phosphate + 190 ml of 0.2 N sodium hydroxide +water to make 1000 ml
0.05 M phosphate buffer solution of pH 5.8 to 8.0	50 volumes of 0.2 M monobasic potassium phosphate solution + specified volume of 0.1 N sodium hydroxide +water to 200 volumes
Simulated gastric fluid(SGF)	HCL 0.01-0.05 N Sodium lauryl sulfate 2.5 g

	Sodium chloride 2.0 g Distilled water q.s. 1000 ml
Fasted simulated intestinal fluid (FaSSIF)	KH2 PO4 0.029 M NaOH q.s Ph 6.8 Na taurocholate 5 Nm Lecithin 1.5 mM KCL 0.22 M Distilled water q.s 1000 ml
Fed simulated intestinal fluid (FeSSIF)	Acetic acid 0.1444 M NaOH q.s Ph 5 Na taurocholate 15 Mm Lecithin 4 Mm KCL 0.19 M Distilled water q.s 1000 ml

Changes in media [19-23]

Table 2

Drug	Medium used	Medium changed
Warfarin sodium-aspirin tablets	Water and acetate buffer (pH 4.5;0.05)	900 ml phosphate buffer (Ph 6.8;0.05 M)
Rabeprazole sodium	Phosphate buffer (pH 6.8), Phosphate buffer (pH 7.5)	Borate buffer pH 9.0 (paddle)
Danol	Buffer Ph 6.8 and 0.035% Tween 80	FaSSIF, 0.07% Tween 80
Spiridon	0.07% tween 80, 0.14% tween 80	Buffer (6.8), FaSSIF
Nimodine	Ph 4.5 acetate buffer containing 0.3% SDS, 15 % (v/v) of alcohol	pH 4.5 acetate buffer containing 0.05% sodium dodecyl sulphate (SDS) (900ml)
Cox-2 inhibitor BCS-class II (Rofecoxib)	-	900 ml of 2 % sodium lauryl sulphate (SLS)
Fosamprenavir tablets	0.1 ml HCL 900 ml acetate buffer pH 4.5	Apparatus I 900 ml HCL 0.01 M, 75 rpm acetate buffer Ph 4.5
Cetrizine HCL	Ph 4.5 buffer 0.1 M HCL	Water Ph 6.1, Ph 6.8 buffer
Diacerhein capsules	Phosphate buffer Ph 7.0,75 and 100 rpm	Phosphate buffer pH 7.0,100 rpm, 0.75% sodium lauryl sulphate
Glyburide	0.25% cetyl trimethyl ammonium bromide (w/v) in DD water, Ph 1.2 HCL buffer, Ph 4.5 acetate buffer	0.05 M borate buffer pH 9.6, 0.05 M phosphate buffer pH 6.5 containing 0.1-2% (w/v) cetyl trimethyl ammonium bromide and 0.05 M phosphate buffer pH 7.4 containing 0.1-2% cetyl trimethyl ammonium bromide
Simvastatin	Ph 7.0 phosphate buffer with 0.5% SLS as medium, SLS containing fasted fluid(FaSSGF) having 0.25% (8.67mM) SLS	pH 4.5 acetate/phosphate buffer, Ph 6.8 phosphate buffer, pH 7.2/7.4 phosphate buffer, water or 0.1 N HCL
Citalopram	0.01 M HCL, acetate buffer pH 4.1	900 ml of deaerated 0.1 M HCL, phosphate buffer pH 6.8
Glibenclamide	0.01 M HCL, acetate buffer pH 4.1	Borate buffer pH 9.5 containing 8.5% alcohol and 0.24% tween 80
Phenytoin	water	pH 6.8 phosphate buffer containing 12 % alcohol and 0.4 % tween 80
Prednisolone	pH 6.8 phosphate buffer	pH 6.8 bicarbonate buffer

Discriminatory dissolution [24-35]

Often in literature and discussion, terminology of a discriminatory test is used to describe that a dissolution test is capable of differentiating or discriminating between products based on formulation and/or manufacturing differences. However, implied understanding of this terminology is that these differences may reflect products *in vivo* differences, thus their quality in humans. The underlying implied assumption of *in vivo* relevance is emphasized by suggestions that dissolution testing be conducted using *in vivo* relevant experimental conditions, e.g., dissolution medium be aqueous having pH in the range of 1 to 7. Interestingly, it is also very well documented in the literature that dissolution results with formulation/manufacturing differences seldom reflect corresponding *in vivo* behavior.

It is, therefore, safe to consider that the use of terminology of "discriminatory test" as commonly used does not appear to be correct. To be correct, the discriminatory test terminology should clearly identify a test as "*in vitro* discriminatory test" or "*in vivo* discriminatory test" also known as bio-relevant test.

An *in vitro* discriminatory test would be the test to reflect differences in physical characteristics of the test products (formulation/manufacturing) with no direct or definite consequences *in vivo*. Such tests may be conducted using any of the experimental conditions necessary concerning apparatuses (paddle/basket, Erlenmeyer flask with magnetic stir etc.) and media (organic or aqueous solvents having any pH), etc. In this respect, disintegration test may be considered as a discriminating test, if formulation/manufacturing differences be linked to disintegrating time.

An *in vivo* discriminatory test or a bio-relevant test, on the other hand, would be a test which would relate differences in formulation/manufacturing of products to corresponding differences *in vivo* such as bioavailability/bioequivalence characteristics. For an in vivo discriminatory test, an essential requirement is that the test must be conducted using physiologically relevant experimental conditions. For

example, an apparatus must provide gentle but efficient stirring and mixing environment, medium must be aqueous with pH in the range of 5-7 and maintained at 37^0C, and the medium must not be de-aerated but equilibrated with dissolved gasses. In addition, as the testing environment is linked to the GI tract physiology, which does not change from product to product (e.g. IR to ER), the experimental conditions should not be changed from product to product as well. [36-39] Therefore, it is prudent that one should clearly indicate the nature of the test described whether it is an *in vitro* or *in vivo* discriminatory type so that proper evaluation and use of the test be considered.

In vitro discriminatory dissolution testing in Generics [40-45]

Generics are drug products which are considered identical in dose, strength, route of administration, safety, efficacy, and intended use as an innovators product. However, generics are different from innovators' products with regard to formulation and manufacturing attributes. Because of these differences in formulation and manufacturing, it is expected from the generics that they demonstrate that the drug release from their product is similar to those of the corresponding innovators' product.

This similarity or equivalence in drug release between generic and innovator products is established by conducting bioavailability/bio-equivalence studies. Such bioequivalence studies, in fact, establish that drug release (dissolution) *in vivo* from both products is the same. A very important point in understanding this principle is that generics strive to achieve similarity of drug release from innovators products *in vivo* having vastly different formulation and manufacturing attributes. Otherwise, generics and innovator products would have different bio-availabilities and would not be bioequivalent, Therefore, a difference in formulations or manufacturing attributes, or finding these differences by *in vitro* dissolution tests, are of no real consequences. Thus, the practice of finding such differences or developing dissolution tests under the terminology of "discriminatory test", is an erroneous and misguided exercise.

The dissolution procedure requires an apparatus, a dissolution medium, and test conditions that provide a method that is discriminating yet sufficiently rugged and reproducible for day-to-day operation and capable of being transferred between laboratories.

The acceptance criteria should be representative of multiple batches with the same nominal composition and manufacturing process, typically including key batches used in pivotal studies, and representative of performance in stability studies.

The procedure should be appropriately discriminating, capable of distinguishing significant changes in a composition or manufacturing process that might be expected to affect in vivo performance. It is also possible for the procedure to show differences between batches when no significant difference is observed in vivo. This situation requires careful evaluation of whether the procedure is too sensitive or appropriately discriminating. Assessing the results from multiple batches that represent typical variability in composition and manufacturing parameters may assist in this evaluation. It is sometimes valuable to intentionally vary manufacturing parameters, such as lubrication, blend time, compression force, or drying parameters, to further characterize the discriminatory power of the procedure.

With regard to stability, the dissolution test should appropriately reflect relevant changes in the drug product over time that is caused by temperature, humidity, photosensitivity, and other stresses. The drug products are bioequivalent (BE) when their active ingredients in pharmaceutical equivalents or pharmaceutical alternatives are available at the site of action with similar rate and extent when administered at the same molar dose under similar conditions. A discriminatory in vitro dissolution test should be able to demonstrate the similarity between BE products as well as the dissimilarity between bioinequivalent products.

Discriminatory Power [46-48]

The discriminatory power of the dissolution method is the method's ability to detect changes in the drug product. Demonstrating the discriminatory power of the dissolution method is both challenging and important, particularly in monitoring API or formulation parameters critical for optimal product performance of the poorly soluble compound. Ideally, the dissolution test conditions should discriminate product changes that may affect biopharmaceutical product performance. However, unless an IVIVR or IVIVC exists for the product, variations in

dissolution behavior may or may not reflect variations in the product's *in vivo* performance.

Challenging the discriminating power

To determine if a dissolution method can discriminate product changes, the method must be challenged. The most common way to challenge the discriminatory power of the method is to test formulations with differences resulting from changes in the characteristics of the API (*e.g.*, particle size, crystal form, bulk density), drug product composition (*e.g.*, drug loading, and identity, type, and levels of excipients), the drug product manufacturing process (*e.g.*, dosage form, equipment variables), and stability conditions (*e.g.*, temperature, humidity). In conducting the challenge, the change in the drug product is evaluated versus the change in the dissolution data. If the data show a measurable difference for the key variables, then the method may be considered a discriminating test for critical manufacturing variables. The choice of experimental design to evaluate the critical variables will depend on the design of the dosage form, the manufacturing process, and intrinsic properties of the API. These experiments should be designed on a case-by case basis in consultation with the formulation and manufacturing scientists. It is important to remember, however, that differences in the dissolution rates as a result of changing selected variables may or may not reflect *in vivo* product performance. As mentioned previously, the purpose of the dissolution test method evolves through the various stages in drug development. Therefore, the test method should be re-evaluated and optimized (if needed) after human bioavailability data become available from the clinical trials. During further method development, optimization, and before selection of the final method, formulations used in the late-phase clinical trials are tested using various test medium compositions (*e.g.*, pH, ionic strength, surfactant

composition). The effect of hydrodynamics on the rate of dissolution of the formulations also should be evaluated by varying the apparatus agitation speed of the dissolution apparatus. If a non-bioequivalent batch is discovered during a bioequivalency study, the dissolution methodology should be further optimized to allow for the differentiation of non-bioequivalent batches from the bioequivalent batches by dissolution specification limits, if possible. This will ensure batch to-batch consistency within a range that guarantees comparable biopharmaceutical performance *in vivo*. The biorelevant method may not always be feasible, and may or may not be the same as the QC method. Once a discriminating method is developed, the same method should be used to release product batches for future clinical trials, if possible.

References

1. Saeed A. Qureshi, Developing Discriminatory Drug Dissolution Tests and Profiles: Some Thoughts for Consideration on the Concept and Its Interpretation, Dissolution Technologies, 2006, 18-23.
2. Raju V, Murthy KVR. Development and Validation of New Discriminative Dissolution Method for Carvedilol Tablets, Indian J Pharm Sci. 2011; 73(5):527-536.
3. Eduardo Costa Pinto, Lucio Mendes Cabral, and Valéria Pereira de Sousa, Development of a Discriminative Intrinsic Dissolution Method for Efavirenz, Dissolution Technologies, 2014, 31-40.
4. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennerna H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. Molecular Properties of WHO Essential Drugs and Provisional Biopharmaceutical Classification. Mol. Pharm. 2004; 1(1):85-96.
5. Lindenberg M, Kopp S, Dressman JB. Classification of orally administered drugs on the World Health Organization list of Essential Medicines according to the biopharmaceutics classification system. Eur. J. Pharm. Biopharm. 2004; 58(2):265-278.
6. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution Testing as a Prognostic Tool for Oral Drug Absorption: Immediate Release Dosage Forms. Pharm. Res. 1998; 15(1):11-22.
7. Dokoumetzidis A, Macheras P. A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. Int. J. Pharm. 2006; 321(1-2):1-11.
8. Dickinson PA, Lee WW, Stott PW, Townsend AI, Smart JP, Ghahramani P, Hammett T, Billett L, Behn S, Gibb RC, Abrahamsson B. Clinical Relevance of Dissolution Testing in Quality by Design. AAPS J. 2008; 10(2):380-390.
9. Kesisoglou F, Wu Y. Understanding the Effect of API Properties on Bioavailability through Absorption Modeling. AAPS J. 2008; 10(4):516-525.
10. Ayres C, Burke W, Dickinson P, Kirk G, Pugh R, Sharma–Singh G, Kittlety R. Intrinsic dissolution rate determinations in early development and relevance to in vivo performance. Am. Pharm. Rev. 2007; 10(1):74-78.
11. The United States Pharmacopeia and National Formulary USP 34–NF 29; the United States Pharmacopeial Convention, Inc.: Rockville, MD, 2011.
12. Yu LX, Carlin AS, Amidon GL, Hussain AS. Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs. Int. J. Pharm. 2004; 270(1-2):221-227.
13. Zakeri-Milani P, Barzegar-Jalali M, Azimi M, Valizadeh H. Biopharmaceutical classification of drugs using intrinsic dissolution rate (IDR) and rat intestinal permeability. Eur. J. Pharm. Biopharm. 2009; 73(1):102-106.
14. Issa MG, Ferraz HG. Intrinsic Dissolution as a Tool for Evaluating Drug Solubility in Accordance with the Biopharmaceutics Classification System. Dissolution Technol. 2011; 18(3):6-13.
15. Šehic´ S, Betz G, Hadžidedic S, El-Arini SK, Leuenberguer H. Investigation of intrinsic dissolution behavior of different carbamazepine samples. Int. J. Pharm. 2010; 386(1-2):77-90.
16. Flicker F, Eberle VA, Betz G. Variability in commercial carbamazepine samples—Impact on drug release. Int. J. Pharm. 2011; 410(1-2):99-106.
17. Dissolution Methods Database. U.S. Food and Drug Administration Web site. http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_ Dissolutions. cfm? Print All =1 (accessed April 15, 2016).
18. Brazilian Pharmacopoeia, 5th ed.; Brazilian Health Surveillance Agency: Brasília, 2010. 32. The International Pharmacopoeia, 4th ed.; Dept. of Essential Medicines and Pharmaceutical Policies, World Health Organization: Geneva, 2011.
19. Wood JH, Syarto JE, Letterman H. Improved holder for intrinsic dissolution rate studies. J. Pharm. Sci. 1965; 54(7):1068.
20. Chadha R, Arora P, Saini A, Jain DS. An insight into thermodynamic relationship between polymorphic forms of efavirenz. J. Pharm. Pharm. Sci. 2012; 15(2):234-251.
21. da Fonseca LB, Labastie M, de Sousa VP, Volpato NM. Development and Validation of a Discriminative Test for Nimesulide Suspensions. AAPS PharmSciTech. 2009; 10(4):1145-1152.
22. Bergström CAS, Wassvik CM, Johansson K, Hubatsch I. Poorly Soluble Marketed Drugs Display Solvation Limited Solubility. J. Med. Chem. 2007; 50(23):5858-5862.
23. Chan HK, Grant DJW. Influence of compaction on the intrinsic dissolution rate of modified acetaminophen and adipic acid crystals. Int. J. Pharm. 1989; 57(2):117-124.
24. Bartolomei M, Bertocchi P, Antoniella E, Rodomonte A. Physico-chemical characterisation and intrinsic dissolution studies of a new hydrate form of diclofenac sodium: comparison with anhydrous form. J. Pharm. Biomed. Anal. 2006; 40(5):1105-1113.
25. Brown CK, Chokshi HP, Nickerson B, Reed RA, Rohrs BR, Shah PS. Acceptable analytical practices for dissolution testing of poorly soluble compounds. Pharm. Technol. 2004; 28(12):56-65.
26. Qureshi S. Developing Discriminatory Drug Dissolution Tests and Profiles: Some Thoughts for Consideration on the Concept and Its Interpretation. Dissolution Technol. 2006; 13(4):18-23.

27. Rossi RC, Dias CL, Bajerski L, Bergold AM, Fröehlich PE. Development and validation of discriminating method of dissolution for fosamprenavir tablets based on in vivo data. J. Pharm. Biomed. Anal. 2011; 54(3):439-444.
28. Wagner JG. Biopharmaceutics and Relevant Pharmacokinetics; Drug Intelligence Publications: Hamilton, IL, 1971, Chapter 10.
29. Abdou HM. Dissolution, Bioavailability, and Bioequivalence; Mack Publishing Company: Easton, PA, 1989, p 6. 5.
30. Dissolution Testing of Immediate Release Solid Oral Dosage Forms; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
31. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations; Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), U.S. Government Printing Office: Washington, DC, 1997.
32. USP General Chapter the Dissolution Procedure: Development and Validation. Pharm. Forum. 2004; 30:351-363.
33. Meyer MC, Straughn AB, Mhatre RM, Shah VP, Williams RL, Lesko LJ. Lack of in vivo/in vitro correlations for 50 mg and 250 mg primidone tablets. Pharm Res. 1998; 15:1085-1089.
34. Leeson LJ. In vitro/in vivo correlations. Drug Inf. J. 1995; 29:903-915.
35. Cox DC, Wells CE, Furman WB, Savage TS, King AC. Systematic Error Associated with Apparatus 2 of the USP Dissolution Test II: Effects of Deviations in Vessel Curvature From That of a Sphere. J. Pharm. Sciences. 1982; 71:395-399.
36. Kukura J, Baxter JL, Muzzio FJ. Shear Distribution and Variability in the USP Apparatus 2 under Turbulent Conditions. Int. J. Pharm. 2004; 26:9-17.
37. McCarthy LG, Kosiol C, Healy AM, Bradley G, Sexton JC, Corrigan OI. Simulating the Hydrodynamic Conditions in the United States Pharmacopeia Paddle Dissolution Apparatus. AAPS PharmSciTech. 2003; 4:172-187.
38. Morihara M, Aoyagi N, Kaniwa N, Katori N, Kojim S. Hydrodynamic Flows Around Tablets in Different Pharmacopeial Dissolution Tests. Drug Develop. Ind. Pharm. 2002; 28:655-662.
39. Qureshi SA, Shabnam J. Cause of high variability in drug dissolution testing and its impact on setting tolerance. Eur. J. Pharm. Sci. 2001; 12:271-276.
40. Qureshi SA, Shabnam J. Application of a new device (spindle) for improved characterization of drug release (dissolution) of pharmaceutical products. Eur. J. Pharm. Sci. 2003; 19:291-297.
41. Qureshi SA. A new crescent-shaped spindle for drug dissolution testing–but why a new spindle? Dissolution Technol. 2004; 11(4):13-18.
42. Qureshi SA. Choice of rotation speed (rpm) for biorelevant drug dissolution testing using a Crescentshape spindle. Eur. J. Pharm. Sci. 2004; 23:271-275.
43. Leeson LJ, Mayersohn M. Letter to the Editor. Dissolution Technol. 2005; 12:24-33.
44. Michael Hawley, Stage Appropriate Dissolution Methods in Formulation Development, American Pharmaceutical Review, 2013, http://www.americanpharmaceuticalreview.com/Featured-Articles/131183-Stage-Appropriate-Dissolution-Methods-in-Formulation-Development/ (accessed on 30-06-2017).
45. McAllister M. Dynamic Dissolution: A Step Closer to Predictive Dissolution Testing? Mol. Pharm. 2011; 7(5):1374-87.
46. Lee HG, Zhang GG, Flanagan DR. Cocrystal Intrinsic Dissolution Behavior Using a Rotating Disk. J. Pharm Sci. 2011; 100:1736-44.
47. Yu LX, Carlin AS, Amidon GL, Hussain AS. Feasibility studies of utilizing disk intrinsic dissolution rate to classify drugs. Int. J. Pharm. 2004; 270(1-2):221-7.
48. Rohrs BR, Thamann TJ, Gao P, Stelzer DJ, Bergren MS, Chao RS. Tablet dissolution affected by a moisture mediated solid-state interaction between drug and disintegrant. Pharm Res. 1999; 16(12):1850-6.