UNIT

XI

IN-VITRO DRUG DISSOLUTION TESTING MODELS

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INTRODUCTION

An in-vitro dissolution model must be able to predict in-vivo behaviour to the point where an in-vivo bioavailability test is unnecessary. When creating a dissolution test model, keep the following considerations into account.

a) Factors relating to the dissolution apparatus, such as- The design, container volume and shape, agitation type, and so on.

b) Dissolution fluid-related factors- Such as composition, volume, temperature, and sink condition maintenance**.**

c) Process parameters such as dosage form introduction method, sampling techniques, and so on.

The ideal features of a dissolution apparatus are:

a) Simple in design and operation;

b) Sensitive enough to detect process and formulation differences;

c) Nearly perfect sink conditions should be maintained;

d) The apparatus should provide minimal mechanical abrasion to the dosage form; Evaporation of the solvent medium must be avoided;

e) Samples should be easily withdrawn;

f) The apparatus should be capable of evaluating disintegrating, non-disintegrating, dense, or floating tablets or capsules

There are two main types of dissolution apparatus, depending on whether or not sink conditions exist:

a) Closed-compartment apparatus: This is essentially a limited-volume apparatus that operates outside of a sink. For example, the rotating basket and rotating paddle apparatus.

b) Open-compartment (continuous flow-through) apparatus: It is the one in which the dosage form is brought in continuous contact with fresh, flowing dissolution medium (perfect sink condition).

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Available official or compendia dissolution models:

a) **The Rotating Basket Apparatus (Apparatus 1) -** is a closed-compartment, beaker-style apparatus with a cylindrical basket made of 22 mesh in the centre to hold the dosage form. **Application:** Conventional Tablets

b) **Rotating Paddle Apparatus (Apparatus 2) -** The rotating basket is replaced with a paddle that acts as a stirrer, just like in apparatus 1. Sinkers are recommended to keep capsules and other floatable forms from floating. **Application:** Tablets, capsules, controlled release products.

c) **Reciprocating Cylinder Apparatus (Apparatus 3) -** consists of a set of cylindrical glass vessels with flat bottoms and reciprocating cylinders. **Application:** controlled release bead-type (pellet) formulations.

d) **Flow-Through Cell Apparatus (Apparatus 4) -** consists of a dissolution medium reservoir and a pump that forces dissolution medium through the test sample cell. Fresh dissolution media is pumped on a regular basis (between 240 and 960 mL/h), ensuring sink conditions. **Application:** Formulations containing poorly soluble drugs.

e) **Paddle Over Disc Apparatus (Apparatus 5) -** consists of a product-holding sample holder or disc located at the bottom of the apparatus. 2. **Application:** evaluation of transdermal products.

f) **Cylinder Apparatus (Apparatus 6) -** A stainless steel cylinder is used to hold the sample instead of a basket, as in apparatus 1. **Application:** transdermal product evaluation.

g) **Reciprocating Disc Apparatus (Apparatus 7) -** The samples are placed on vertically reciprocating disc-shaped holders. Application: for testing transdermal products and non-dissolving controlled-release oral preparations.

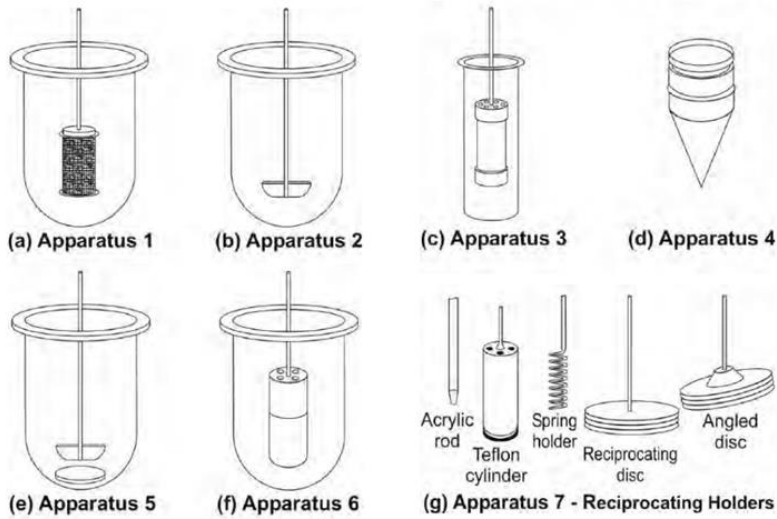

Figure 11.1: Diagram showing various compendia dissolution model.

Table 11.1: Dissolution methodology for immediate-release products based on BCS

BCS Class	Dissolution Methodology
I	Single point if NLT 85% Q in 15 minutes Multiple point if Q < 85% in 15 minutes
II	Multiple point
III	Same as class I
1V	Same as class II

IN VITRO—IN VIVO CORRELATION (IVIVC)

The predictive mathematical model that describes the relationship between an in-vitro property (such as the rate and extent of dissolution) of a dosage form and an in-vivo response is known as in vitro-in vivo correlation (such as the plasma drug concentration or amount of drug absorbed).

The main goal of developing and evaluating an IVIVC is to make the dissolution test a surrogate (alternative) for human in vivo bioavailability studies.

The applications of developing such an IVIVC are:

1. To ensure batch-to-batch consistency in the physiological performance of a dosage form.
2. To serve as a tool in the development of a new dosage form.
3. To assist in validating or setting dissolution specifications.

There are two basic approaches by which a correlation between dissolution testing and bioavailability can be developed:

1. By establishing a relationship between in vitro dissolution and in vivo bioavailability parameters, which is usually linear.
2. By modifying the dissolution methodology based on data from previous bioavailability studies, we were able to achieve a meaningful in vitro-in vivo correlation.

The following are some of the most commonly used quantitative linear in vitro-in vivo correlations:

1. Correlations based on plasma level data: This section develops linear relationships between dissolution parameters and plasma level data parameters. Plots of percent drug dissolved versus percent drug absorbed, for example.
2. Urine Excretion Data Correlation: Dissolution parameters are correlated with the amount of drug excreted unchanged in the urine, the cumulative amount of drug excreted as a function of time, and so on.
3. Pharmacological Response Correlation: Any of the dissolution parameters is related to an acute pharmacological effect such as LD_{50} in animals.

IN VITRO-IN VIVO CORRELATION LEVELS

Three IVIVC levels have been defined and categorised in descending order of usefulness.

Level A: It represents a point-to-point relationship between in-vitro dissolution and in-vivo rate of absorption, or a superimposable in-vitro and in-vivo profile, in the highest category of correlation.

The following are some of the benefits of level a correlation:

1. No additional human studies are required to justify any change in manufacturing procedure or formula modification.
2. In-vivo dissolution is used as a quality control procedure for predicting the performance of dosage forms.

Level B: The mean in vitro dissolution time is compared to either the mean in vivo dissolution time or the mean residence time. However, because there is no point-to-point correlation, level B correlation cannot be used to justify manufacturing or formula changes.

Level C: It is a single point correlation. It relates one dissolution time point (e.g. t_{50}%, etc.) to one pharmacokinetic parameter such as AUC, t_{max} or C_{max}. This level is generally useful only as a guide in formulation development.

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