In vivo in vitro correlation

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INTRODUCTION

An **in-vitro in-vivo correlation** (**IVIVC**) has been defined by the U.S. Food and Drug Administration (FDA) as "a predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response".

Generally, the in-vitro property is the rate or extent of drug dissolution or release while the in-vivo response is the plasma drug concentration or amount of drug absorbed. The United States Pharmacopoeia (USP) also defines IVIVC as "the establishment of a relationship between a biological property, or a parameter derived from a biological property produced from a dosage form, and a physicochemical property of the same dosage form".

Typically, the parameter derived from the biological property is AUC or Cmax, while the physicochemical property is the in vitro dissolution profile.

The main roles of IVIVC are:

- To use dissolution test as a surrogate for human studies.
- To supports and/or validate the use of dissolution methods and specifications.
- To assist in quality control during manufacturing and selecting appropriate formulations

BENEFITS OF IVIVC

IVIVC can benefit programs in many different ways. For example, IVIVC analyses can be used to support New Drug Applications (NDA) for oral drugs with extended release characteristics, Abbreviated New Drug Applications (ANDA), or Abbreviated Antibiotic Drug Applications (AADA) as a surrogate for *in vivo* BE determinations. Between 2009-2012, 89% of regulatory submissions containing IVIVC models were NDAs.

IVIVC can also be used to support a biowaiver, which allows sponsors to waive an *in vivo* BA and/or BE study requirement. When requesting biowaivers for drug manufacturing changes, IVIVC can be used in lieu of certain otherwise required *in vivo* studies if sufficient safety and efficacy have been established.

IVIVC also can be used in setting dissolution specifications. Examples include supporting strength change justification, small changes in the formulation, changes to the site of manufacture, and batch-to-batch quality control. Most recently, IVIVC has been used in the Quality by Design (QbD) framework to establish clinically meaningful drug product specifications using dissolution as the endpoint.

Regulatory Importance

An IVIVC model is recommended by regulatory authorities for most modified release dosage forms. The main advantage of IVIVC is that it provides a mechanism for evaluating the change in *in vivo* absorption based on *in vitro* dissolution changes when there are small changes in a formulation. Once a validated IVIVC model has been established, it can be used to predict bioavailability/bioequivalence (BA/BE) based on *in vitro* data that are already available. In such cases, dissolution test results can be used to provide the desired information without the need for any human BE studies.

Another advantage of IVIVC is that it conveys a better understanding of the drug product itself. This may allow for setting wider drug product acceptance criteria, formulation stability, and can be especially useful for predicting the *in vivo* effects of changes to the manufacturing process, site of manufacture, or formulation components.

As important as this is during initial product development, the value of IVIVC does not end there. Establishing an IVIVC model can be even more helpful after the product has been approved by determining the impact of post-approval manufacturing changes, changes in the site of manufacture, and issues with individual lots of manufactured products all without having to repeat costly *in vivo* BE studies.

IN VITRO / IN VIVO DISSOLUTION

Therapeutic efficacy of a formulation can be explained by-

In vitro dissolution pattern and in vivo bioavailability

This inherent interdependency of drug –patient biosystem is the major factor which decides importance of in vivo/ in vitro correlation studies.

In vitro dissolution is the dissolution or release of drug from dosage form and can be measured by an in vitro dissolution apparatus.

While in vivo dissolution is the process of dissolution/ absorption of drug in GIT.

IVIVC is the relationship between the two as used in bioequivalence studies through carefully designed correlation models.

Need of such comparisons were recognized in early 1960's and regulations on bioavailability and bioequivalence were issued by FDA in 1977.

Quantitative measurement

Some of the mostly used quantitative linear IVIV correlations are-

1. Correlation based on plasma level data: here linear relationship is established between dissolution parameters and plasma data.

2. Correlation based on urinary excretion data: Here dissolution parameters are correlated to the amount of unchanged drug excreted in the urine, cumulative amount of drug excreted with respect to time, etc.

3. Correlations based on pharmacological response: Here dissolution parameters are correlated to acute pharmacological response like LD50 in animals.

4. Statistical moment theory such as mean dissolution time in vitro verses mean residence time in vivo can also be used.

Positive correlation is not always possible.

Some factors which may limit such correlation include dissolution methodology, physicochemical properties of drug, physiological barriers, etc.

IVIVC MODELS

It is generally assumed that dissolution and absorption have a linear relationship hence these two are generally shown interchangeably. One should be able to establish drug profiles with dissolution profiles along with pharmacokinetic characteristics of the drug.

This process of obtaining a drug profile from dissolution results is known as convolution. Opposite of this i.e. obtaining a dissolution from a blood profile, is known as deconvolution.

DETERMINATION OF DISSOLUTION

Dissolution is a powerful and useful method for determining

- The product quality
- Clinical performance of dosage form
- Batch to batch consistency
- Bioequivalence data
- Provide an idea about insight to in vivo behavior

Factors affecting dissolution

- ❖ Surface area of drug
- ❖ Diffusivity of drug
- ❖ Thickness of layer
- ❖ Solubility
- ❖ Amount of drug already dissolved
- ❖ Volume of solvent available

DISSOLUTION APPARATUS

1, Apparatus 1 – Rotating basket- USP & BP

2. Apparatus 2 – Paddle type – USP & BP

3. Apparatus 3 - Reciprocating cylinder – USP &
Flow through cell – BP

4. Apparatus 4 – Flow through cell – USP

5. Apparatus 5 – Paddle over disc - USP

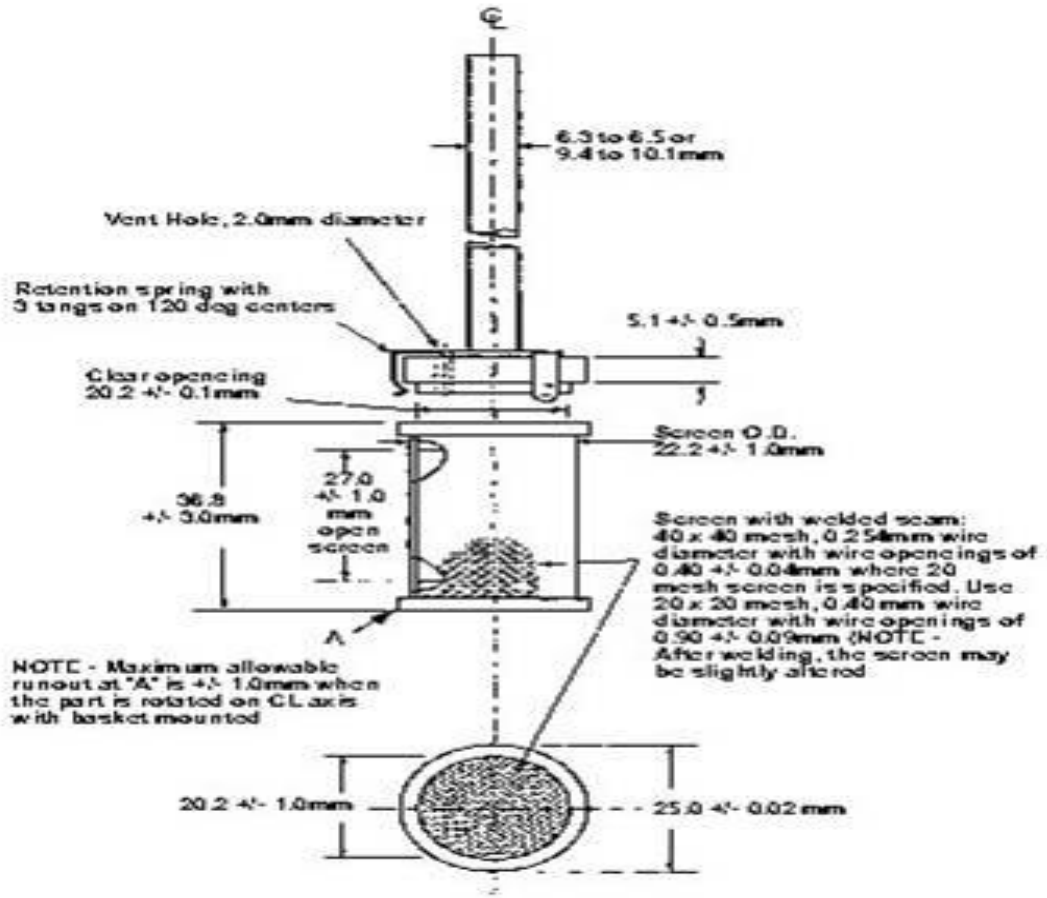
6. Apparatus 6 – Cylinder - USP

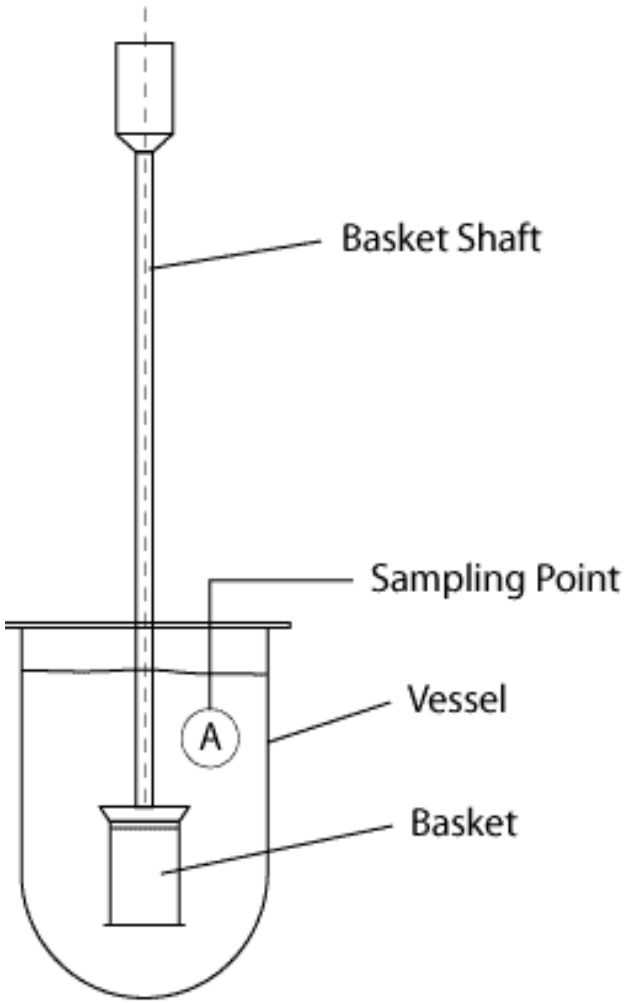
7. Apparatus 7 – Reciprocating disc - USP

Apparatus 1- Basket

Standard volume – 900/1000ml,(1,2,4 L vessel)

Useful for – capsules, beads, delayed release, enteric coated, floating dosage forms



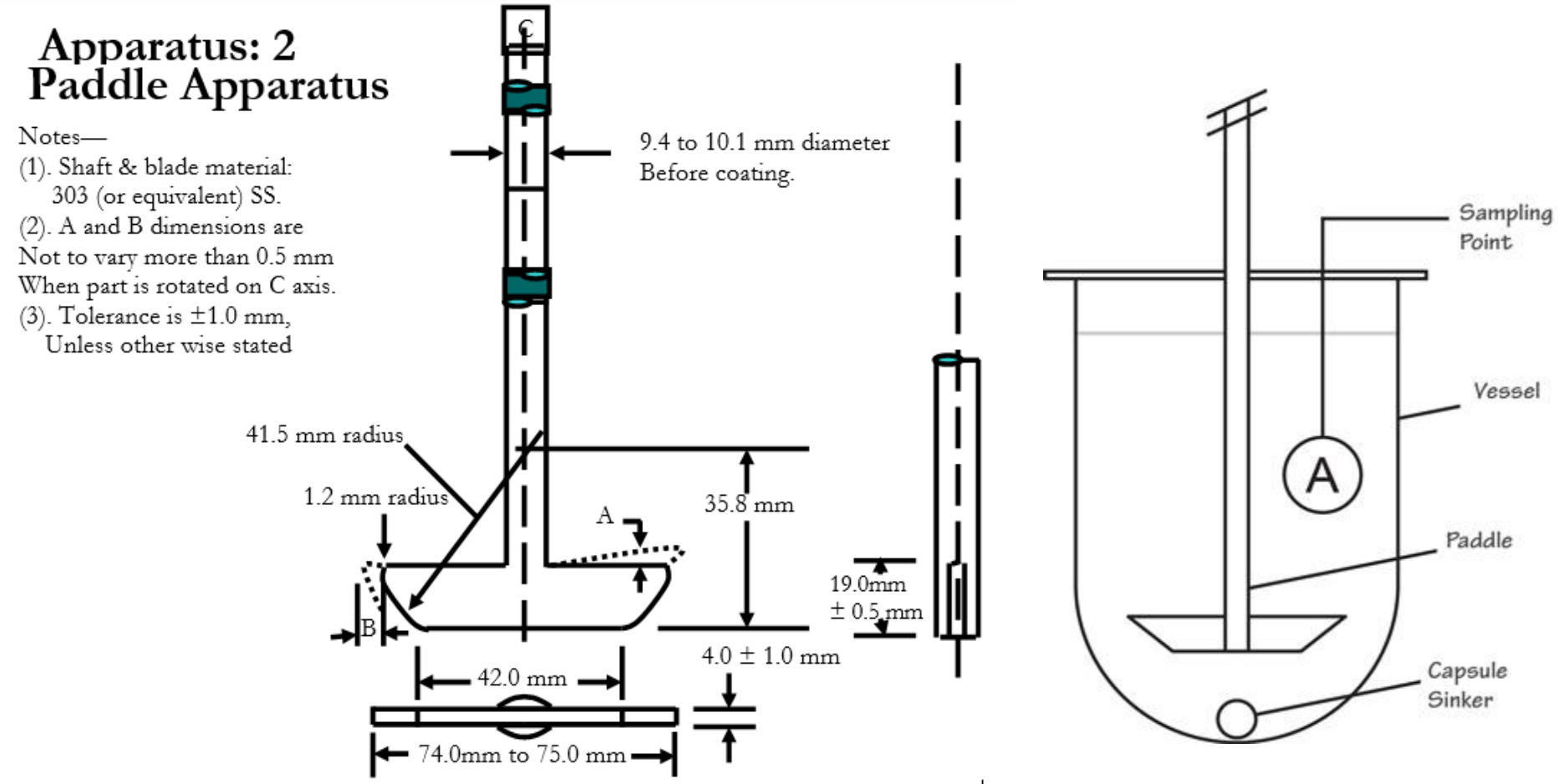


Apparatus 2 – Paddle

Method of first choice

Standard volume – 900/1000 ml

Useful for – tablets, capsules, beads, delayed release, enteric coated dosage forms



Apparatus 3- Reciprocating cylinder

Useful for tablets, beads, controlled release

Design:

Vessel:- Cylindrical flat bottom glass vessel.

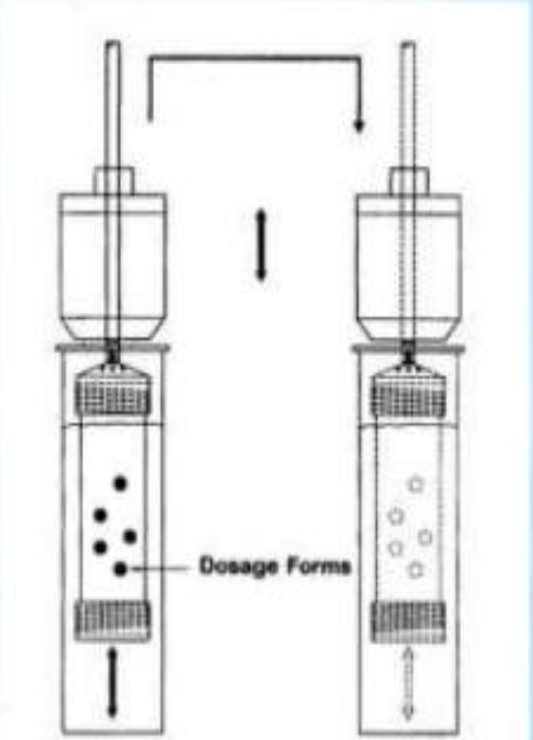
Agitation:- Reciprocating

Generally 6-35 cycles/min

Volume of dissolution fluids:- 200-250 ml

Water bath:- Maintain at 37 ± 0.5˚C

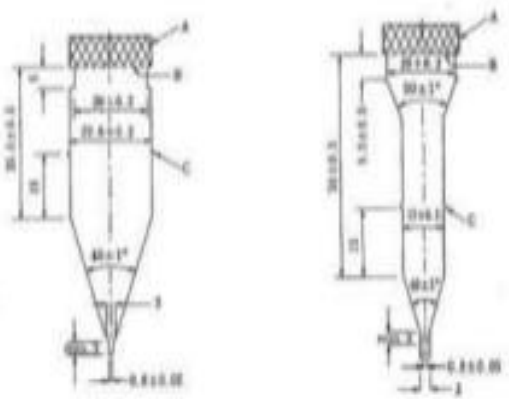
Use:- Extended release



Apparatus 4 – Flow through cell

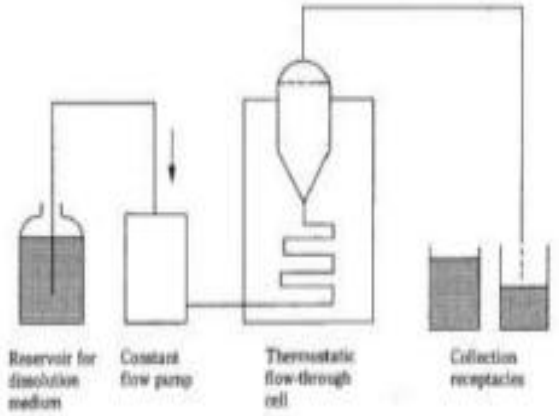
Useful for

- low solubility drugs
- microparticulates
- implants
- suppositories
- controlled release formulations



Variations

- open system
- closed system



Apparatus 5 – Paddle over disc

Useful for – transdermal patches

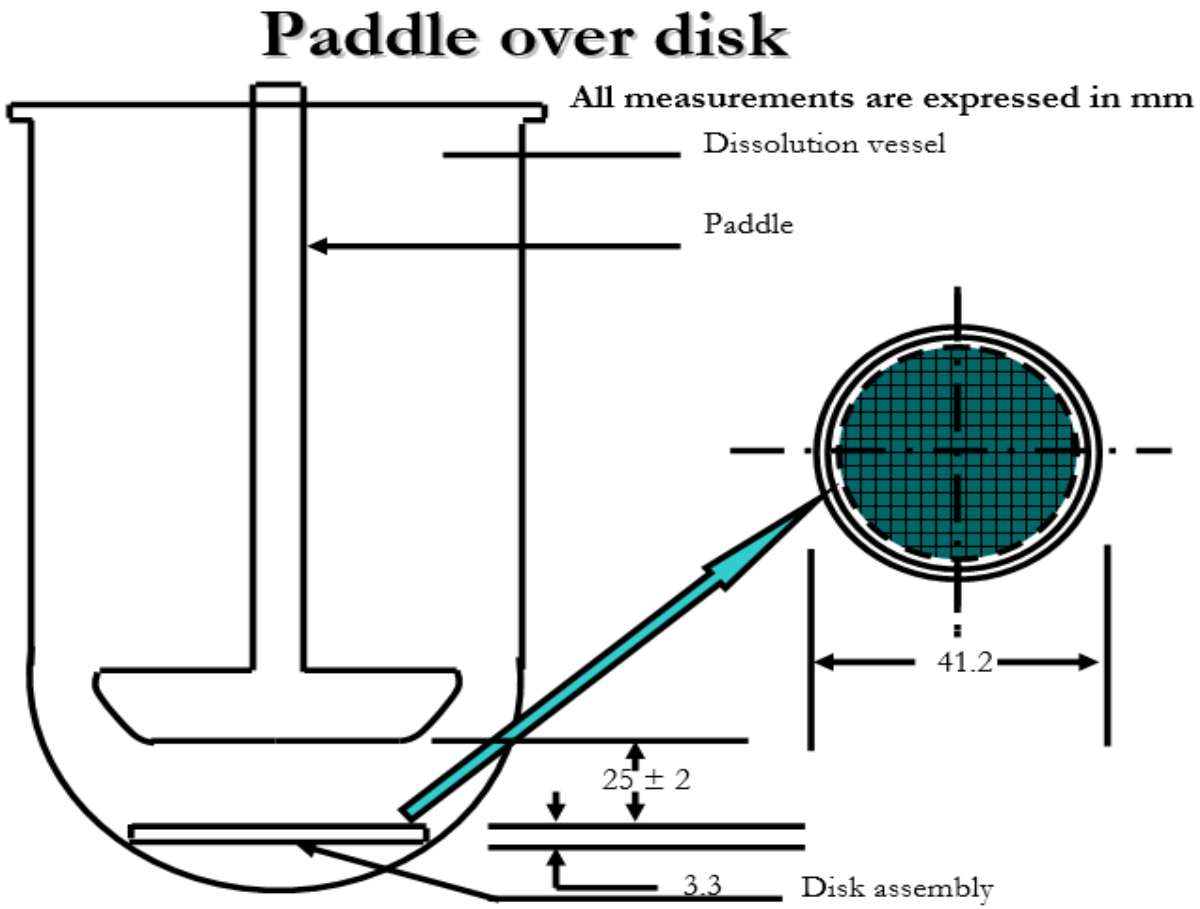
Standard volume – 900 ml

Advantages – standard equipment (paddle type) can be used, only add a stainless steel disc assembly

Disadvantages –

Disc assembly

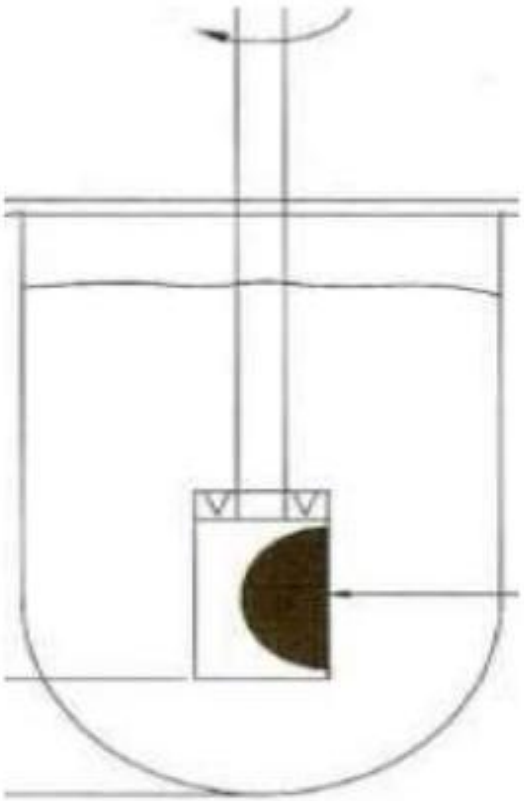
restricts patch size



Apparatus 6 – Rotating cylinder

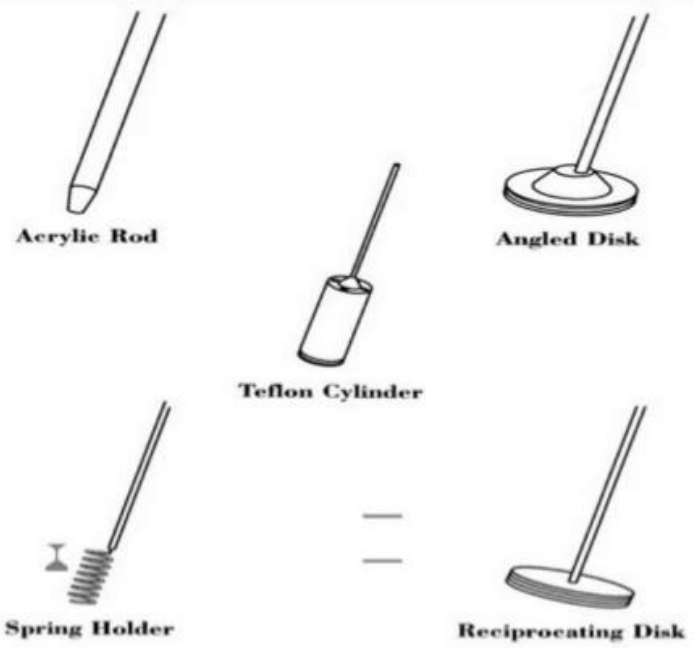
Useful for – transdermal patches

Design is similar to apparatus 1. In place of basket, a stain steel cylinder holds the sample.



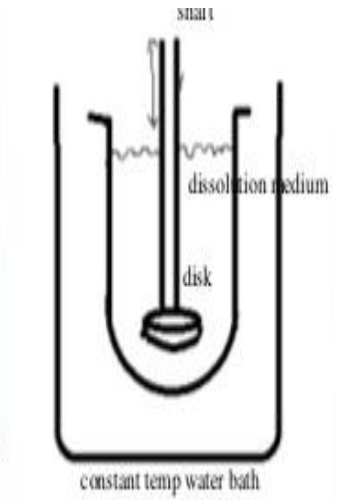
- The vessel assembly from apparatus 1 except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.05°C
- The dosage unit is placed on the cylinder at the beginning of each test.
- The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

Apparatus 7 – Reciprocating disc



Reciprocating disc sample holder

- **DESIGN:**
  - Vessel:-Flat bottomed cylindrical vessel
    -Volume of dissolution medium 900 mL.
  - Sample : -Placed on disk shaped holders
  - Agitation :-Reciprocation
    -Reciprocating frequency 30 cycle/min
  - Water-bath:-Maintain at 32 ± 0.5°C



- **USE:**
  - Transdermal patches
  - The assembly consists of a set of volumetrically calibrated solution containers made of glass or suitable inert material, a motor , a drive assembly used to reciprocate the system vertically.
  - The samples are placed on the disk shaped holders using cuprophan supports
  - The test is carried out at 32°C.
  - The reciprocating frequency is 30cycles/min.

Types of Dissolution medium

1. COMPENDIAL DISSOLUTION MEDIA:
   a) Simulated Gastric Fluid:
   b) Water:
   c) Simulated Intestinal Fluid:
2. BIORELEVENT MEDIA:
   a) Fasted State Gastric Conditions: FaSSGF:
   b) Fasted State Small Intestinal Conditions: FaSSIF:
   c) Fed State Gastric Conditions:
3. 0.1 N HCl - to simulate gastric media
4. Phosphate buffers of various Ph
5. TRIS buffered saline (TBS)

Selection of dissolution media

Selection of dissolution medium depends upon following parameters.

- Type of formulation (Immediate or modified release).
- Solubility characteristics of active component.
- Type formulation design, e. g. Soft gel capsule, Hard gel capsule, Tablets, Suspension, powder etc.

Selection of other parameters -

- The volume of dissolution media is ideally 900ml, however if label claim is less than 5mg and if active substances has less absorbance at selected wavelength, then in that case dissolution volume can be reduced to 500ml.
- The dissolution media temperature is fixed i. e. 37.0 (±0.5)°C
- Clean the dissolution apparatus and jars with suitable detergent, but do not wash with organic solvent.

APPLICATIONS OF IVIVC

1. **Applications in drug delivery system:**

   Various rate controlling technologies are used as the basis for modified release dosage forms to control and prolong the release of drugs, for administration by oral or parenteral route. The objective of novel drug delivery systems like liposomes, neosomes, microspheres, nanoparticles, parenteral depots, implants etc. is to achieve zero order, long term, pulsatile delivery.

2. **In early stages of drug delivery technology development:**

   Drug candidate selection is the most crucial stage of drug development which primarily based on physicochemical properties of the drug, results of preformulation studies, efficacy and toxicity studies, etc. during this stage, IVIVC of the drug in animal model provide an idea about the feasibility of the drug delivery system for the given drug.

3. **Formulation Assessment:**

   A suitable dissolution method, capable of distinguishing the performance of formulations with different release rates in vitro andin vivo is an important tool in drug development.

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4. Dissolution specifications:

Modified release dosage forms require dissolution testing at multiple time points and IVIVC plays an important role in setting these specifications.

5. Future biowaivers:

Frequently, drug development requires changes in formulations due to a variety of reasons such as unexpected problems in stability, development, availability of better materials, better processing results, etc. an established IVIVC can help avoid bioequivalence studies by using the dissolution profile from the changed formulation and subsequently predicting the in vivo concentration- time profile.

6. IVIVC parenteral drug delivery:

IVIVC can be developed and applied to parenteral dosage forms, depot system, implants, etc. but, success rate is low because of many reasons. Sophisticated modeling techniques are required to correlate the in vivo in vitro data , in case of burst release which is unpredictable and unavoidable.

7.

Dissolution as surrogate for BA Studies

▪The purpose of in vitro dissolution studies in the early stages of drug development is to :

- select the optimum formulation
- evaluate the active ingredient and excipients
- assess any minor changes in the drug products

▪ By IVIVC, in vitro dissolution is proposed to be a surrogate of drug bioavailability studies

▪This is possible only by an accurately validated IVIVC

▪ No single dissolution test conditions can be applied to all drugs

▪Dissolution test results depend upon various dissolution test conditions such as Ph, volume, ionic strength, deaeration, dissolution medium, surfactants, agitation and temperature

Dissolution and BA studies

If a valid correlation of in vitro dissolution is established with in vivo performance of the formulation then it can be used to :

- ✓ Assess batch to batch consistency
- ✓ Distinguish acceptable and unacceptable i.e. bioequivalent and bioinequivalent drug products
- ✓ Ensure product quality i.e. ability to manufacture the product reproducibly and maintain its release properties throughout shelf life
- ✓ Provide insight to in vivo behavior of product
- ✓ Guide development of new formulations

Biopharmaceutical Classification System

The biopharmaceutical classification system (BCS) is a way to categorize drug compounds based on their solubility and permeability properties. Under the BCS, drug substances can be grouped into four classes: Class 1 compounds are highly soluble and highly permeable; Class 2 substances have high permeability but relatively low solubility; Class 3 compounds are highly soluble but not very permeable; and Class 4 drug substances have both low solubility and low permeability. In general, it is recognized that the successful development and application of an IVIVC require dissolution to be the rate-limiting step in the process of drug administration and absorption. For Class 1 compounds, there are no rate-limiting steps for drug absorption, with the possible exception of immediate release dosage forms, for which gastric emptying could potentially become the rate-limiting step. For Class 2 compounds dissolution is the rate-limiting step in absorption, therefore the establishment of IVIVC is expected. For Class 3 compounds, IVIVC is generally regarded as unlikely but may be possible depending on the relative rates of dissolution and intestinal transit. For Class 4 compounds IVIVC is highly unlikely. Classification according to the BCS will enable early determination of whether IVIVC can be developed for a certain drug candidate.

Limitations of BCS

❖Effects of food, absorptive transporters, efflux transporters, and routes of elimination (renal/biliary) are important determinants of Bioavailability for immediate release oral dosage forms, which are not considered in BCS.

❖BCS based biowaivers are not applicable for the following:

- Narrow therapeutic range drug products
- Limited applications for class II drugs and not applicable for class III
- Dosage form meant for absorption in the oral cavity e.g. sublingual or buccal tablets

Limitations of IVIVC

- **Complexity of drug absorption:**

  Biological factors which affect drug absorption can not be mimicked in vitro.

- **Weakness of the dissolution design:**

  Being in vitro model, it has certain limitations. Some forces that act during dissolution cannot be understood and explained by in vitro designs.

CONCLUSION

- IVIVC is a tool applied in various stages of drug development to find a place in regulatory bodies .
- IVIVC can substitute in vivo bioavailability and can support biowaivers.
- IVIVC is also a very useful substitute of expensive clinical trials.
- From the regulatory point of view, IVIVC can help certain scale-up and post approval changes.
- IVIVC is a tool which can save precious resources and can decrease the cost of drug development.
- IVIVC principles are mostly applied to oral products but now there is a need to develop more meaningful dissolution and permeation methods for non-oral delivery systems.