Module 05

USP dissolution apparatus

Apparatus	Name	Drug formulation tested
Apparatus 1	Rotating Basket	Conventional tablets, chewable tablets, controlled release formulations
Apparatus 2	Rotating paddle	Tablets, orally disintegrating tablets, capsules, controlled release products, suspensions
Apparatus 3	Reciprocating cylinder	Controlled release formulation, chewable tablets
Apparatus 4	Flow-through cell	Formulation containing poorly soluble drugs, powders and granules, microparticles, implants
Apparatus 5	Paddle over disc	Transdermal formulations
Apparatus 6	Cylinder	Transdermal formulations
Apparatus 7	Reciprocating disc	Controlled release formulations (non disintegrating oral formulations and Transdermal formulations)

Dissolution Determination- Dissolution testing should be carried out in

- USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 rpm.
- Dissolution media (900 ml): 0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid.
- Compare dissolution profiles of test and reference products using a similarity factor (f_2).

Stage	Number units	Acceptance Criteria
S1	6	Each unit is not less than Q* +5%
S2	6	Average of the 12 (S1+S2) units is ≥ Q and no unit is less than Q-15%
S3	12	Average of 24 (S1+S2+S3) units is ≥ Q and not more than 2 units are less than Q-15% and no unit is less than Q-25%

*Q is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Biopharmaceutics classification system

Class	Parameters	Example of drugs
Class 1	High Solubility, High Permeability	Metoprolol, diltiazem, verapamil
Class 2	Low Solubility, High Permeability	Glibenclamide, phenytoin, ketoprofen
Class 3	High Solubility, Low Permeability	Cimetidine, ranitidine, acyclovir
Class 4	Low Solubility, Low Permeability	Hydrochlorothiazide, furosemide

Important terms

- A drug substance is considered **highly soluble** when the highest dose strength is soluble in <250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered **highly permeable** when the extent of absorption in humans is determined to be > 90% of an administered dose, in comparison to an intravenous reference dose.
- A drug product is considered to be **rapidly dissolving** when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Biowaiver- Biowaiver is an exemption of clinical bioequivalence studies given to a drug product. When we get Biowaiver it means we do not have to show bioequivalence with innovator product.

Examples of dosage form that are exempted from bioequivalence study

- Intravenous preparation
- Topically applied preparation like cream, ointment or gel,
- The drug product in an oral dosage form that is not intended to be absorbed e.g. antacids,
- Solution, elixir and syrups
- Immediate release solid dosage form of Class 1 drug, that exhibit rapid dissolution

IVIVC (*Invitro-invivo* correlation)

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".

Level	**In vitro**	**In vivo**
Level A	Dissolution curve	Absorption curve
Level B	MDT	MRT, MAT
Level C	One dissolution time point (t50%, t90%, etc.)	One mean pharmacokinetic parameter such as AUC, tmax or Cmax.
Multiple Level C	Amount of drug dissolved at several time point of dissolution profile. Time to have 10, 50, 90% dissolved (t10%, t50%, T90%)	Cmax, Tmax, AUC, time to have 10, 50, 90 % absorbed, Ka (Absorption rate constant)
Level D	It is not a formal correlation but it is a semi quantitative (qualitative analysis) and is not considered useful for regulatory purpose but can be serves as an aid in the development of a formulation or processing procedure.	