DISSOLUTION TESTING MODELS

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The ideal features of a dissolution apparatus are …

- Fabrication dimensions and positioning of all components must be specified and reproducible.

- Apparatus must be simply designed i.e., easy to operate and usable under variety of conditions.

- The apparatus must be sensitive enough to reveal process changes and formulation differences yields repeatable results under identical conditions.

- Apparatus should permit controlled variable intensity of mild uniform non-turbulent liquid agitation.

- Nearly perfect sink conditions should be maintained.

- Apparatus should provide easy means of introducing the dosage form into dissolution medium and holding it.

- Should provide minimum mechanical abrasion to dosage form during the test period to avoid disruption of environmental surrounding the dissolving form.

- Evaporation of solvent medium must be maintained at a fixed temperature within a specified range.

- Sample should be easily withdrawn for automatic or manual analysis without interrupting the flow characteristic of liquid.

- Apparatus should be capable of allowing the evaluation of disintegrating, non-disintegrating and finely powdered drugs.

- Apparatus should allow good inter laboratory agreement.

The two principle types of apparatus design are

- Limited volume apparatus

- Continuous flow cells

LIMITED VOLUME APPARATUS

- The general principle of dissolution tests is that the powder or solid dosage form is tested under uniform agitation which is accomplished by using a stirrer inside the apparatus or rotating cylinder holding dosage form.

- Two general methods used are:-
  - Basket Apparatus
  - Paddle Apparatus

BASKET APPARATUS

Apparatus consists of ….

- Motor
- Metallic drive shaft
- Cylindrical basket
- Covered vessel made of glass
- Dimensions :-
    - 160-120mm high
    - Inner diameter 98-106mm
    - Basket -25±2mm
- Capacity :- 1000ml [other sizes of 2 and4 L also available]
- Shape of vessel:-
    - Hemispherical bottom(concave)
    - Slides are flanged at top
- Temperature maintained:- 37±0.5°c

Other necessaries:~

- **Fluid cover:~** Retard evaporation but provide sufficient opening to allow insertion of thermometer and withdrawal of samples.

- **Position of shaft** is NMT 2mm at any point from vertical axis of vessel.

- **Rotation speed of shaft** is ±4% of rate specified in monograph

- **Stainless steel mesh** of 40 or 425µm is used.

Problems:-

- The wire basket corrodes following exposure to acidic media.

- It gives poor reproducibility due to inhomogeneity of agitation produced by rotating basket.

- Clogging of basket occur due to adhering substances.

- Particles can fall from rotating basket and sink to the bottom of flask or vessel.

PADDLE APPARATUS

USP 24 (8) and BP 2000 (9)

Apparatus consists of

- Mortar

- Metallic drive shaft

- Container vessel

- Three-blade polyethylene stirrer placed centrally [paddle]

- Dimensions:-

  - Diameter of paddle ~5cm

  - Distance between blade and bottom of vessel – 25±2mm

- Capacity:- 400ml beaker with 250ml dissolution fluid.

- Temperature maintained:- 37±0.5ºc

- RPM :- 59 Rpm

- Other necessaries :-
  - Sinkers to prevent the floating of the dosage form
  - The dosage form is allowed to sink before the rotation o the paddle.
  - [remaining are similar to basket method]

Other Methods for Limited Volume Apparatus

□ The various other methods including the limited volume apparatus are…

- Flask Stirrer Method
- Rotating & Static Disc Method
- Rotating Filter~ Stationary Basket Apparatus
- Bio~ Disc Apparatus
- Reciprocating Cylinder Method

FLASK STIRRER METHOD

- Apparatus –
  - Round bottom flask
  - Polyethylene stirrer
- Dimensions –
  - Diameter of stirrer~ 50mm
  - Immersed to a depth of 27mm
- RPM – 60 RPM
- Capacity – 400cm³ vessel with 250cm³ dissolution fluid.
- The problem of formation of mounds of particles in different positions is minimized.

ROTATING & STATIC DISC METHOD

- Apparatus –
  - Container vessel
  - Non-disintegrating disc

- The disc is mounted in a holder so that only one face is exposed.

- The holder or disc is held in a fixed position [static] and rotated at a given speed [rotating]

- This measures the dissolution rate from a constant surface area i.e., intrinsic dissolution rates are determined.

ROTATING FILTER~ STATIONARY BASKET APPARATUS

- Apparatus ~
  - Glass flask container
  - Stationary sample basket

- Capacity – 1000ml or 2L & 4L [remaining similar to basket method]

BIO-DISC APPARATUS

- This is a commercial apparatus for Magnetic basket apparatus.

- It consists of vertically reciprocating tubes sealed with mesh discs at end to restrain the dosage forms.

RECIPROCATING CYLINDER METHOD

☐ This apparatus is official in USP 24(8) for the dosage form of drug release.

☐ It consists of tubes raised up and down 9.9~10.1cm in dissolution.

PROBLEMS OCCURING IN LIMITED VOLUME APPARATUS

- They operate under non sink conditions and hence limitations occur when poor soluble drugs are used.

- Lack of flexibility

- Lack of homogeneity

- Establishment of concentration gradients

- Variable shear

- Their semi quantitative agitation

- Obscuring the details of dissolution procedure

CONTINUOUS FLOW CELLS

☐ This is used in close mode when the fluid is recirculated when it is of fixed limited volume.

☐ In case of open mode there is a continuous replenishment of the fluids.

☐ Apparatus –

  ▫ Reservoir

  ▫ Pump

  ▫ Heat exchanger

  ▫ Column

  ▫ Tablet support

  ▫ Filter system

  ▫ Analytical method

- The system enables solvent to be taken from a suitable reservoir and passed straight through the apparatus containing the dosage form to be assayed and removed or recirculated.

- The design of the pump to remove the solvent from the reservoir is crucial to the results obtained from such systems.

- The pumps used are
  - Displacement [oscillating or peristaltic]
  - Momentum [centrifugal]

    Note: Peristaltic pumps create oscillations result in faster dissolution rates.

- Ascending fluid flow is used.

- Flow rate: ~ 240 – 960mL/h from bottom.
- Dimensions:~
  - 12 or 22.6mm
  - 1mm diameter (Glass beads)
- Maintenance of controlled flow is crucial and done by inlet system.
- The table support used is holder constructed with a folded wire cross above the inlet pipe.
- Factors affecting dissolution:~
  - Volumetric flow rate
  - Cross sectional area of cell
  - Initial drug quantity
  - Drug concentration
  - Liquid velocity

SAMPLE COLLECTION PROCEDURES

- The samples should be down from a zone midway between the surface of the dissolution medium and the top of the rotating basket or blade not less than 1cm from the vessel wall.

- A volume of media equal to the volume of sample withdrawn should be replaced or compensated for the calculation.

- The removed sample should be filtered. The filter pore size should not be greater than 1μm.

DATA PRESENTATION AND INTERPRETATION

- The data collected during dissolution tests especially at developmental stage should be presented as dissolution profiles.

- In these profiles the amount released is plotted as a function of time.

- The drug release is generally monitored at several intervals until 100% of dose is dissolved and dissolution profiles showing drug release against time can be produced.

- Values equivalent to times for 10, 50, 70, or 90% ($t_{10}\%$, $t_{50}\%$, $t_{70}\%$, $t_{90}\%$) is cited and the profiles are sigmoidal in shape for tablets and capsules.

- A pharmacopoeia does not suggest performing a dissolution profile but should specify certain amount of drug dissolve within a specified time.

- If 2 or more times specified then the samples are withdrawn with a tolerance of ±2% of the stated time.

ASSESSMENT

STAGE	No. of UNITS	SPECIFICATIONS
I	6	Each unit at specified time should have Q+5% in solution.
II	6+6	Average content dissolved from the combined two stages should be equal or greater than Q with no unit be less than Q-15%.
III	6+6+10	The average of the total of 24 units should be equal or greater than Q. No more than 2 units should be less than Q+15%, no unit should be less than Q-25%.

FACTORS AFFECTING DISSOLUTION MEDIUM

□ The dissolution medium is important and should be properly selected for the dissolution testing since to dissolve/solubilize the drug.

□ Various considerations for dissolution medium seen are:

  ◻ P^H of medium

  ◻ Surface Tension of medium

  ◻ Viscosity of Medium

1.p^H Of Medium

- In general the P^H should be acidic between the p^H of 1 to 3.

- The acidic solution tends to disintegrate the tablets slightly faster than water and thereby enhances the dissolution rate by increasing the effective surface area.

- p^H with acidic medium is corroding action of acid fumes on equipment.

- Examples:
    - 0.1N HCl
    - Buffered solution pH close to gastric juice like sodium acid phosphate etc.

2.Surface Tension of Medium

- It has significant effect on the dissolution rate of drugs and also the release rate from solid dosage forms.

- In general surfactant when used reduces the contact angle and thus improve the penetration process of matrix by dissolution medium.

- The dissolution rate of poorly soluble drugs increases at the lower surface tension of the medium obtained by using various surfactants even below their CMC.

- Examples of SAA used are:
  - 0.01% dioctyl sodium sulfosuccinate
  - Polysorbate 80 etc.

3.Viscosity of Medium

- Generally in diffusion controlled dissolution process, the dissolution rate decreases with an increase in viscosity.

- In case of interfacial controlled dissolution process viscosity have very little.

- Stokes-Einstein equation describes the diffusion coefficient D as a function viscosity.

EFFECT OF TEST PARAMETERS ON DISSOLUTION RATE

1. Agitation:

- The rate relationship between intensity of agitation and the rate of dissolution varies according to the type of agitation used.

- The effect of agitation on the rate of heterogeneous reactions led to empirical relationship between rate of dissolution and the intensity of agitation.

$$K=a(N)^b$$

N=speed of agitation

K=dissolution rate

a,b=constants

- In case of…

- Diffusion controlled dissolution-b should be 1 in accordance to Nernst – Brunner film theory, states that film thickness is inversely proportional to stirring speed.

- Interfacial reaction controlling dissolution-b should be 0.

- Both processes-b should fall between 0 to 1.

Temperature:

- As drug solubility depends on temperature, the dissolution process control is very important.

- It should be maintained within $+ 0.05^0$ along with 37^0.

- For a dissolved molecule the diffusion coefficient D, depends on the temperature T according to stokes equation.

$$D=K.T/(6\pi\eta r)$$

- Indication of terms in equation:
  - K=Boltzmann constant
  - $6\pi\eta r$=Stokes force for spherical molecule
  - T=temperature