Dissolution kinetics

Dr. OUAHAB Ammar

Learning Objectives:

By the end of this lesson, students will be able to:

1. Define dissolution kinetics and its role in the pharmaceutical industry.
2. Understand the factors affecting dissolution of a drug product.
3. Identify different dissolution test methods and their applications.

Table of Content:

1. Definitions

- *Dissolution* According to the IUPAC, it is defined as "The mixing of two phases with the formation of one new homogeneous phase (i.e. the solution)." (IUPAC, 1997).
- *Dissolution kinetics/rate* is the study of the rate at which a drug dissolves in a liquid medium. It is the change in the concentration of dissolved drug (individualized drug molecules/ions/atoms), dc, in the time interval dt:
- *The dissolution test* is a *pharmaceutical technical procedure* (Chapter 2.9 in Ph.Eur 11.5) intended to determine the greater or lesser ability of dosage forms to allow the API they contain to pass into solution in a specific medium. The passage into solution is assessed by the presence of API in samples taken from the dissolution medium at different time points.

2. Objectives

In the pharmaceutical industry, drug dissolution tests are commonly used to provide critical information on in vitro drug release for the purposes of

✓ quality control, i.e. to assess batch-to-batch consistency of solid oral dosage forms such as tablets

✓ drug development, i.e.: to predict drug release profiles in vivo.

Typical situations where dissolution testing plays a vital role: There are three:

- (i) **formulation and optimization decisions**:
- (ii) **Bioequivalence decisions**:
- (iii) **Product conformity and release decisions**:

3. **Factors involved in dissolution**

3.1. Factors linked to the physicochemical properties of the molecule:

3.1.1. Factors that influence solubility:

a. Chemical nature of the molecule:

b. pH of the dissolution medium:

c. Temperature

d. Polymorphism

3.1.2. Factors that influence the speed of dissolution:

a. Particle size and contact surface:

b. Steering speed :

c. Viscosity of the dissolution medium:

d. Surface tension:

e. Sink Condition: SINK conditions normally occur in a volume of dissolution medium that is at least 3 to 10 times the saturation volume.

3.2. Formulation factors:

Excipients have a galenic role because they facilitate the manufacture of tablets. In addition, they must guarantee the release of the active ingredient.

a. Diluents
b. Binders and adhesives
c. Disintegrants
d. Lubricants, antiadherents, and glidants
e. Colors and dyes
f. Flavoring agents
g. Artificial sweeteners
h. Adsorbents

3.3. Factors related to manufacturing processes:

a. The granulation method

b. The compression

3.4. Factors depending on the dissolution method (Operating conditions):

- The apparatus to use;
- the composition,
- the volume
- the temperature of the dissolution medium;
- rotation speed;
- the time interval,
- the method and volume of sampling of the dissolution medium or the conditions of continuous recording;
- the method of analysis of the dissolution medium taken;
- the acceptance criteria.

4. **The ideal characteristics of a dissolution apparatus**

- ✓ Simple, easy to handle and usable in different conditions.
- ✓ Specific and reproducible components.
- ✓ Sensitive to detect process changes and formulation differences.
- ✓ SINK conditions maintained.
- ✓ Allows the study of different solid oral forms.

It is not possible to design a single apparatus that can be used for all forms: 200 apparatuses in the literature.

5. Dissolution tests

5.1. Dissolution test for solid dosage forms

The choice of equipment is determined by the physicochemical characteristics of the pharmaceutical form considered.

The paddle apparatus is often best suited for solid oral forms.

The registration authorities have gradually standardized four apparatuses:

- ***Apparatus*** 1: basket apparatus.
- ***Apparatus*** 2: Paddle Apparatus
- ***Apparatus*** 3: Reciprocating Cylinder
- ***Apparatus*** 4: Flow-Through Cell

Apparatus 1: Basket Apparatus.

Components

- Vessel made of inert, transparent material, possibly covered
- Motor and drive shaft
- Cylindrical basket (stirring element)

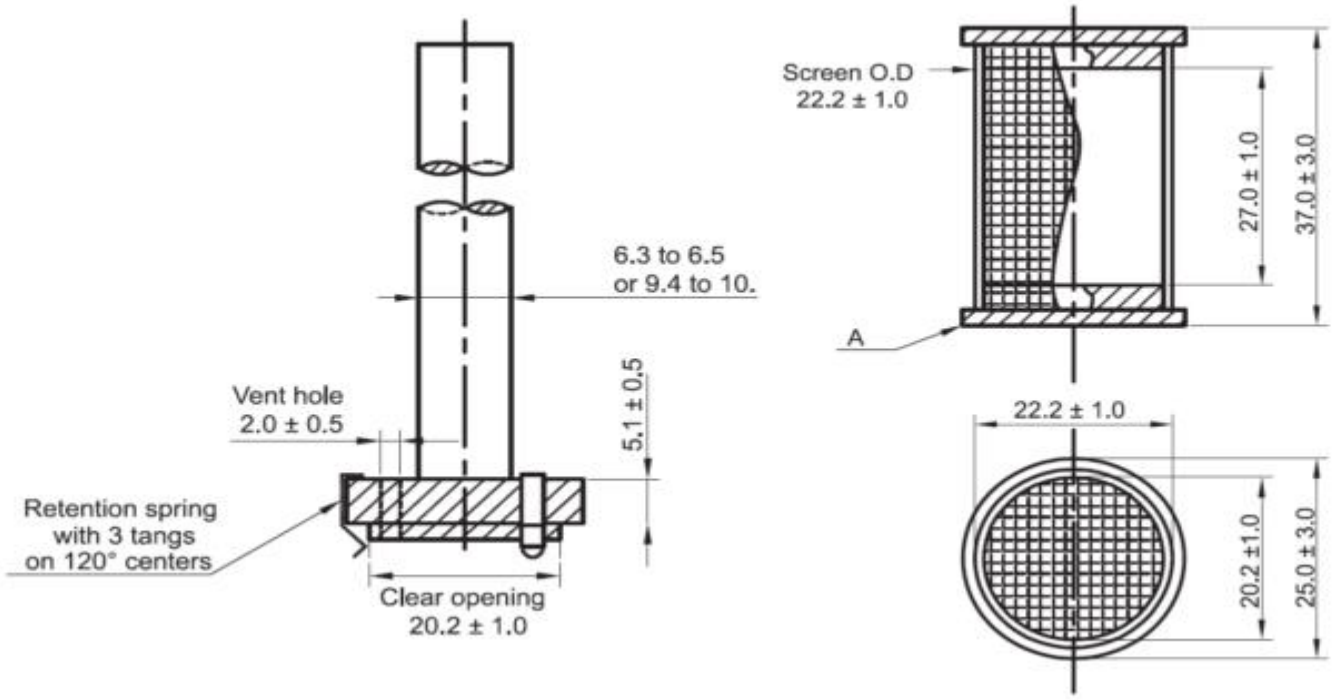


Fig. Basket apparatus

Procedure

Conventional release solid dosage forms.

1. Place specified volume of dissolution medium in the vessel (± 1 per cent).
2. Equilibrate medium to 37 ± 0.5 °C and remove thermometer.
3. Conduct test with or without thermometer, ensuring equivalent results.
4. Insert 1 dosage unit, excluding air bubbles.
5. Operate apparatus at specified rate.
6. Withdraw samples at specified intervals from mid-zone of medium, away from vessel wall.
7. Replace withdrawn samples with fresh medium or correct for volume change.
8. Keep vessel covered and monitor medium temperature.
9. Analyze using suitable assay method and repeat with additional units if needed.

Dissolution Medium

- Use suitable medium, measure volume at 20-25°C, adjust pH if buffered, remove gases to avoid bubbles.

Time

- Shorten test if minimum dissolution is met, withdraw samples only at specified times within ±2% tolerance.

Prolonged-release solid dosage forms

- *Procedure.* Proceed as described for conventional release dosage forms.
- *Dissolution medium* .Proceed as described for conventional release dosage forms.
- *Time.* Test time points, usually 3, are expressed in hours. (1is point at 20% to 30% dissolved. The second point is therefore set at around 50% release. The last point at more than 80%)

Delayed-release solid dosage forms

Procedure. Use method A or method B

Method A

- **Acid Stage:**
  - Use 750 mL of 0.1 M hydrochloric acid in the vessel at 37 ± 0.5 °C.
  - Place 1 dosage unit, cover, and operate at specified rate for 2 hours.
  - Withdraw aliquot for analysis, then proceed to Buffer stage.
- **Buffer Stage:**
  - Add 250 mL of 0.20 M trisodium phosphate dodecahydrate at pH 6.8 ± 0.05.
  - Continue operation for 45 min and withdraw aliquot for analysis.

Method B

- **Acid Stage:**
  - Use 1000 mL of 0.1 M hydrochloric acid in the vessel at 37 ± 0.5 °C.
  - Place 1 dosage unit, cover, and operate at specified rate for 2 hours.
  - Withdraw aliquot for analysis, then proceed to Buffer stage.
- **Buffer Stage:**
  - Replace acid with pH 6.8 phosphate buffer, prepared from 0.1 M hydrochloric acid and 0.20 M trisodium phosphate dodecahydrate.
  - Continue operation for 45 min and withdraw aliquot for analysis.

Time. All stated test times shall be observed within a tolerance of ±2% unless otherwise specified.

Apparatus 2: Paddle Apparatus

Components:

Use the assembly from Apparatus 1, except that a paddle formed from a blade and a shaft is used as the stirring element.

Conditions:

- The distance of 25 ± 2 mm between the bottom of the blade and the inside bottom of the vessel is maintained during the test.
- The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started

Procedure: Same as ***Apparatus*** 1

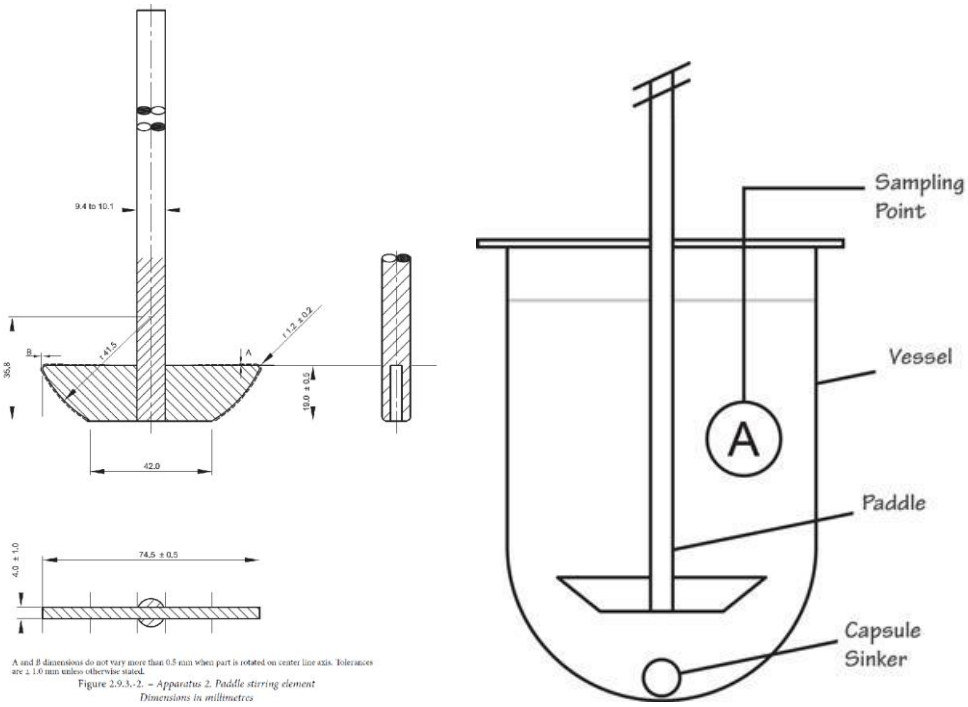


Fig. Paddle apparatus

Sinker

- A small, loose piece of non-reactive material, such as not more than a few turns of wire helix, may be attached to dosage units that would otherwise float.

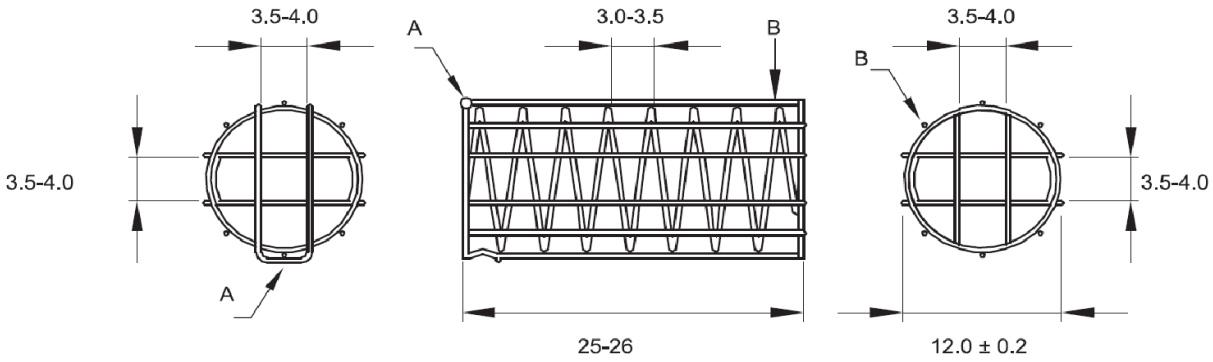


Figure 2.9.3.-3. – *Alternative sinker*
Dimensions in millimetres

Fig. Sinker

- Using the paddle or basket apparatus, the volume of dissolution medium is normally 500 to 1000 ml. A stirring speed between 50 rpm and 100 rpm is normally chosen; it should not exceed 150 rpm.

Apparatus 3: Reciprocating Cylinder

Components:

- Cylindrical, flat-bottomed glass vessels
- Glass reciprocating cylinders
- Inert fittings made of stainless steel type 316 or other suitable material
- Screens made of nonsorbing and nonreactive material, designed to fit the tops and bottoms of the reciprocating cylinders
- Motor and drive assembly for vertical reciprocation of the cylinders inside the vessels
- The vessels are provided with an evaporation cap

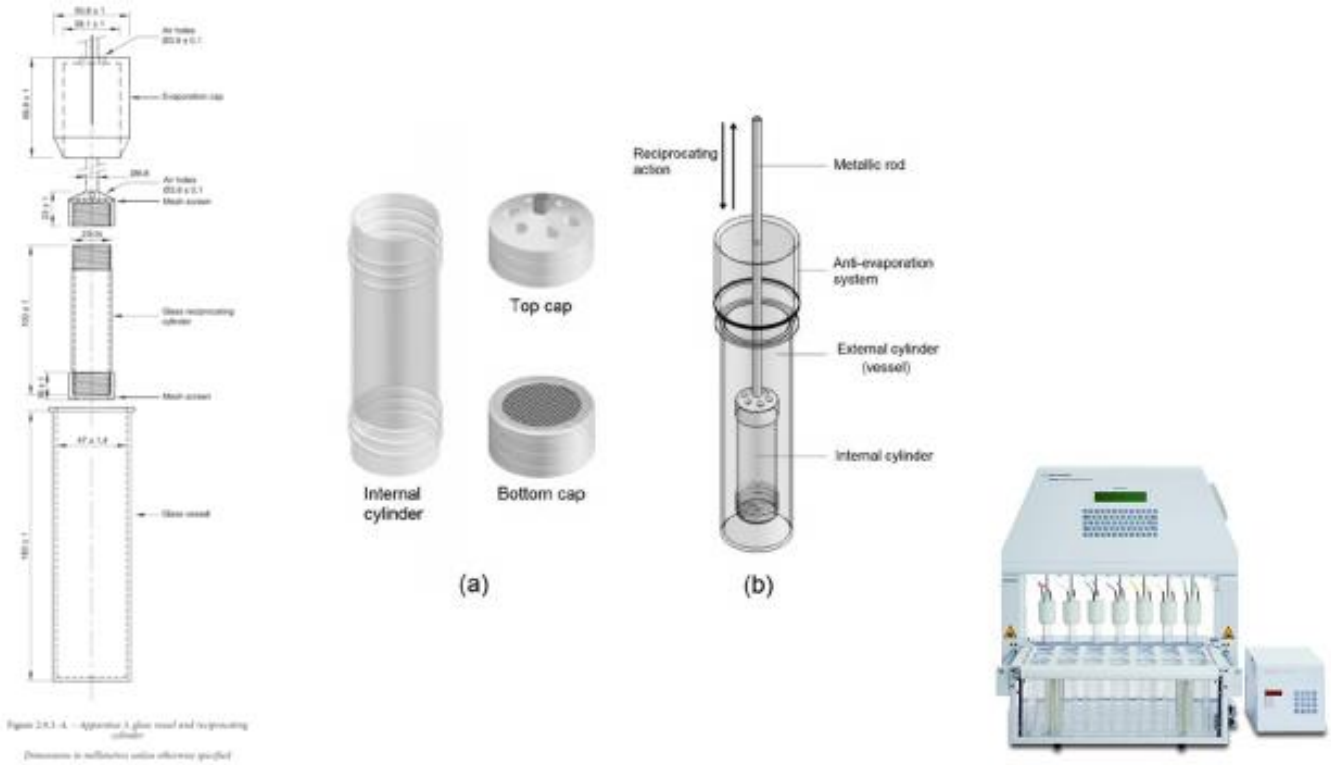


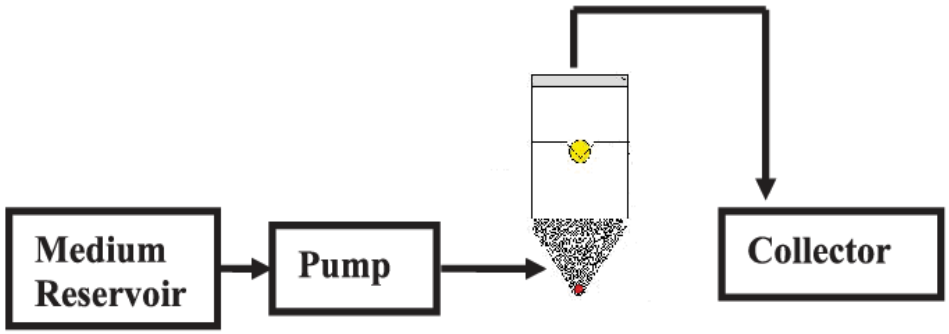
Fig. Reciprocating Cylinder

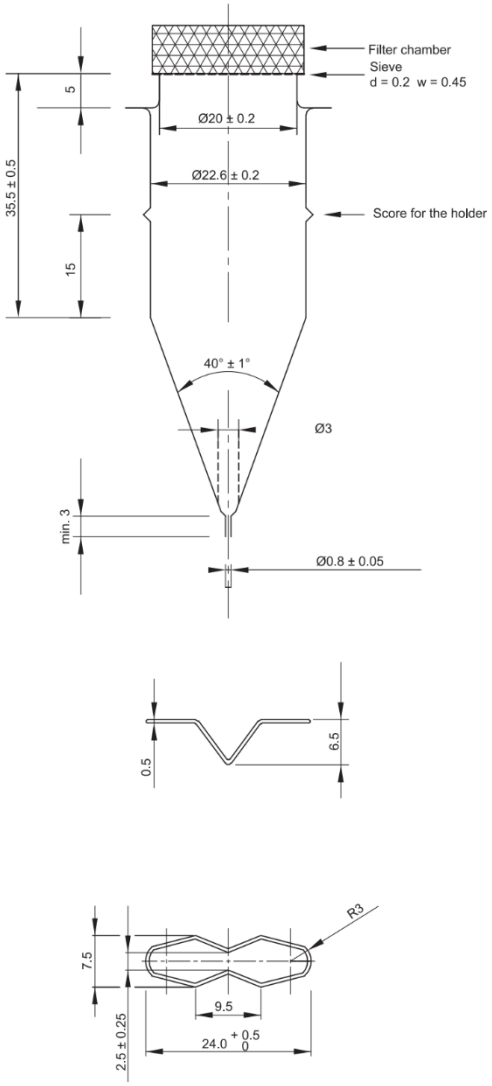
- This apparatus corresponds to an improvement of the disintegration apparatus.
- It was more particularly developed to study the dissolution of sustained release forms and to simulate the pH variations encountered in the gastrointestinal tract.

Apparatus 4: Flow-Through Cell

Components:

- A reservoir
- A pump for the dissolution medium
- A flow-through cell;
- A water-bath that maintains the dissolution medium at 37 ± 0.5 °C
- A collector





- Dissolution is ensured by the passage of the dissolution medium through the permanent renewal of the solid-liquid interface.
- The medium loaded with API is recovered in the collector.
- The system operates in an open or closed circuit, new solvent is constantly supplied.

5.2. Dissolution testing of transdermal patches

5.2.1. Disk Assembly Method

- Apparatus 2 - 32 ± 0.5 °C
- Stainless Steel Disk Assembly (SSDA)= Stainless Steel Disk Assembly

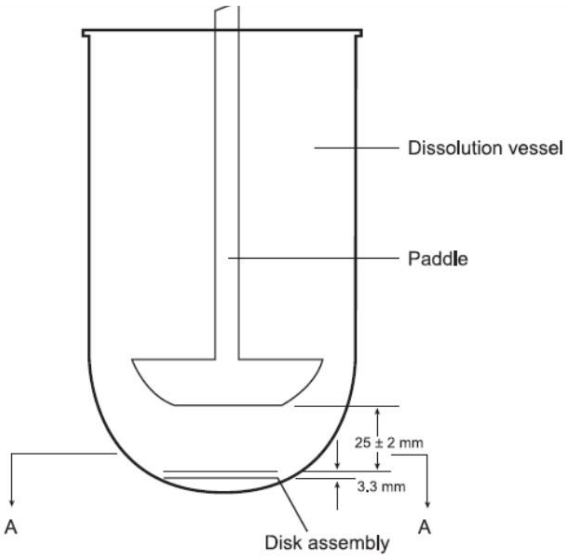


Figure 2.9.4.-2. – *Paddle and disk*

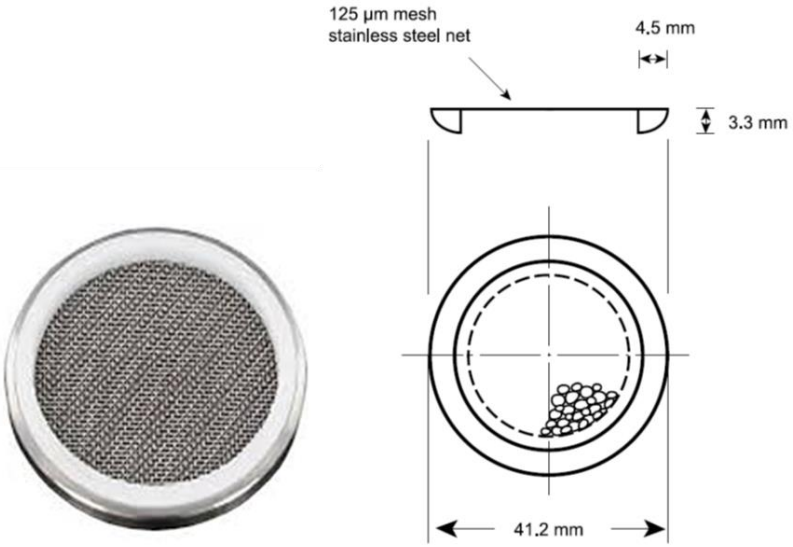
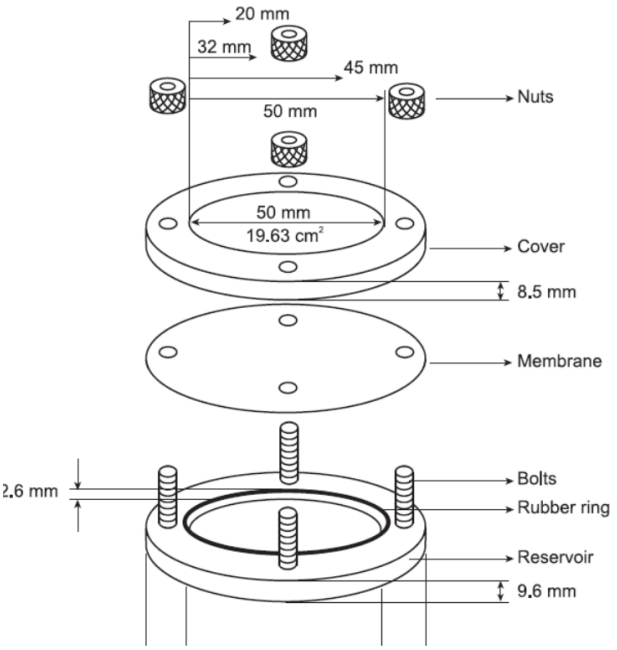


Figure 2.9.4.-1. – *Disk assembly*

Fig. disk assembly

5.2.2. Cell Method



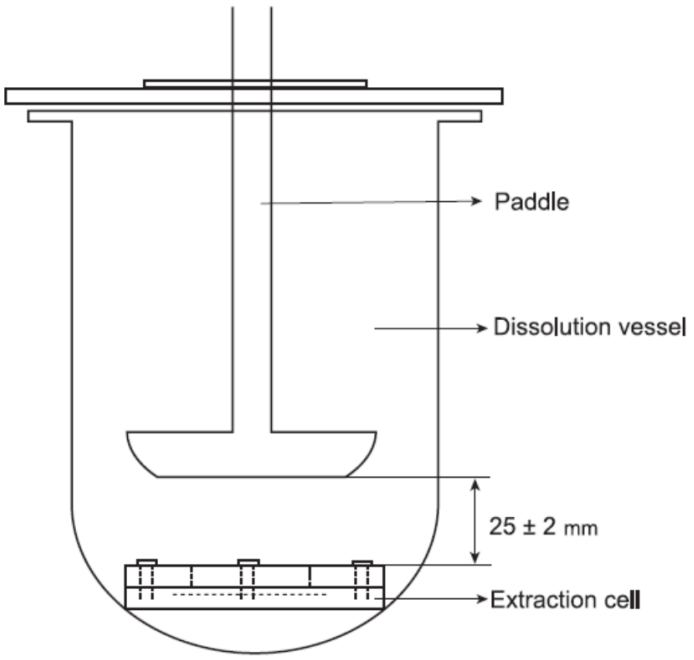
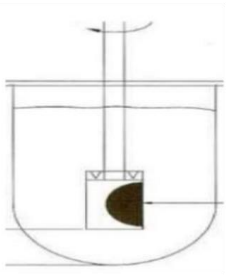


Figure 2.9.4.-4. – *Paddle over extraction cell*

5.2.3. Rotating Cylinder Method



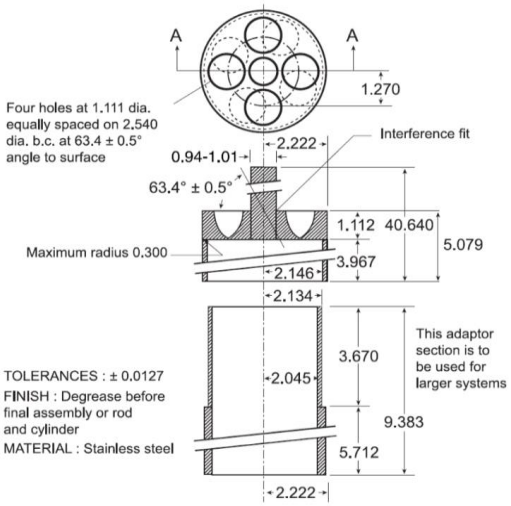
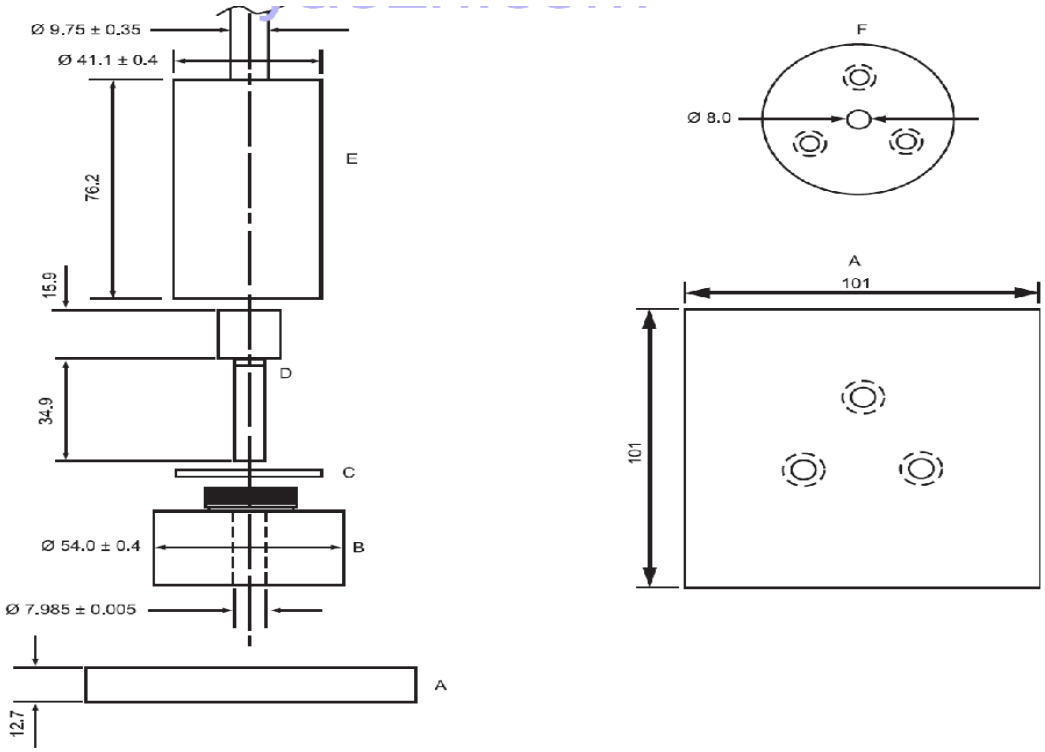


Figure 2.9.4.-5. – *Cylinder stirring element*
Dimensions in centimetres

5.3. Intrinsic dissolution

Intrinsic dissolution is defined as the rate of dissolution of pure substances after compaction under constant surface conditions. Its evaluation is useful for the characterization of active substances and excipients. Measurements are in milligrams per minute per square centimeter (mg/min/cm2).



A. Surface plate B. Die C. Neoprene gasket D. Punch E. Holder and shaft assembly F. Die underside

Figure 2.9.29.-1. – *Typical apparatus used to obtain the compact for the determination of the intrinsic dissolution*
Dimensions in millimetres

6. Interpretation of Dissolution Kinetics

- Dissolution kinetics: results obtained are expressed in cumulative % as a function of time and tend towards 100%.
- In the case of immediate release forms a single point is used, usually 30 or 60 minutes.
- For Prolonged release: three points: start, middle, end.

6.1. Conventional-release solid dosage forms

Meet requirements based on the following Table unless specified. Continue testing through 3 levels unless S1 or S2 criteria met.

Q is the specified percentage of dissolved active substance, Q values are provided in individual product monographs, representing the expected percent release (dissolution) of the drug at certain times, such as 30, 45, 60 minutes, etc.)

Values in the table (5%, 15%, 25%) are percentages of labelled content, aligning with Q.

Level	Number tested	Acceptance criteria
S_1	6	Each unit is not less than $Q + 5$ per cent.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15$ per cent.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15$ per cent, and no is less than $Q - 25$ per cent.

6.2. Sustained release dosage forms

Level	Number tested	Acceptance criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10 per cent of labelled content outside each of the stated ranges; and none is more than 10 per cent of labelled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10 per cent of labelled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10 per cent of labelled content below the stated amount at the final test time; and none of the units is more than 20 per cent of labelled content outside each of the stated ranges or more than 20 per cent of labelled content below the stated amount at the final test time.

6.3. Delayed release dosage forms

Acid stage:

Level	Number tested	Acceptance criteria
A_1	6	No individual value exceeds 10 per cent dissolved.
A_2	6	The average value of the 12 units ($A_1 + A_2$) is not more than 10 per cent dissolved, and no individual unit is greater than 25 per cent dissolved.
A_3	12	The average value of the 24 units ($A_1 + A_2 + A_3$) is not more than 10 per cent dissolved, and no individual unit is greater than 25 per cent dissolved.

Buffer stage: Unless otherwise stated, the Q value is 75% dissolved.

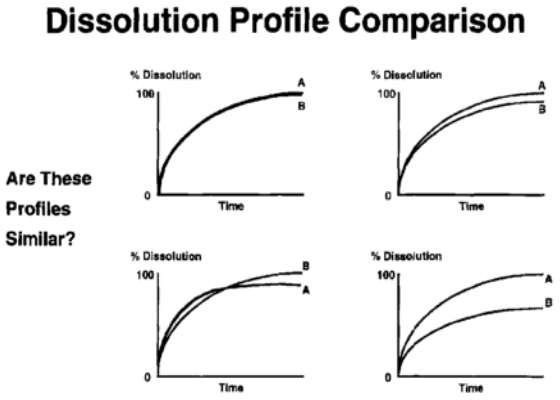
Level	Number tested	Acceptance criteria
B_1	6	No unit is less than $Q + 5$ per cent.
B_2	6	The average value of the 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than $Q - 15$ per cent.
B_3	12	The average value of the 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15$ per cent, and no unit is less than $Q - 25$ per cent.

7. Comparison of dissolution profiles

7.1. Graphical Method

In this method, we plot the concentration versus time graph of solute (drug) in the dissolution medium or biological fluid.

- The shape of two curves is compared for comparison of dissolution pattern and drug concentration at each point
- If two or more curves overlap, the dissolution is comparable.
- If the difference is small, it is acceptable but when
- the differences are greater, this indicates that the dissolution profile is not comparable.



7.2. Statistical approaches,

7.2.1. The Student's test, or the t-test can be used, for example, to determine whether the means of two sets of data are significantly different from each other.

7.2.2. Analysis of Variance (ANOVA)provides a statistical test for whether two or more population means are equal, and therefore generalizes the t-test beyond two means.

7.3. Dependent model method,

7.3.1. Zero order kinetics (osmotic system, transdermal system)

The pharmaceutical dosage forms following this profiles release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$Qt = Q0 + K0t$

Where, Qt is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution and K0 is the zero order release constant.

Application

transdermal systems, as well as matrix tablets containing drugs with low solubility in coated form, osmotic systems, etc …

7.3.2. First-order kinetics (water-soluble drugs in porous matrix)

Using the Noyes Whitney equation,

$\log Q_t = \log Q_0 + (K_1/2.303)$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303

Applications

Dosage forms containing water-soluble drugs in porous matrices.

7.3.3. Hixson and Crowell model (1931)

Drug powder having uniformed size particles, Hixson and Crowell derived the equation that expresses rate of dissolution based on cube root of weight of particles, while the radius of particle is assumed not constant:

This is expressed by the equation, $\mathbf{M_0^{1/3} - M_t^{1/3} = \kappa_t}$

Where, M_0 is the initial amount of drug in the pharmaceutical dosage form, M_t is remaining amount of drug in the pharmaceutical dosage form at time 't' and κ is proportionality constant.

Applications

Tablets, where the dissolution occurs in planes which are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a way that the initial geometrical form keeps constant all the time

7.3.4. Higuchi model (diffusion matrix formulation) (1961)

Higuchi in 1961 developed models to study the release of water-soluble and poorly soluble drugs incorporated into semi-solid and solid matrices. To study dissolution from a homogeneous matrix system, the relationship obtained was

$$\mathbf{Q = A\,[D(2C\text{-}Cs)\,Cs\,t]^{1/2}}$$

Where, Q is the amount of drug release in time t per unit area A, D is the diffusion coefficient of drug molecules, C is initial concentration of drug and Cs is solubility of drug in matrix media.

Applications

Modified release dosage forms, transdermal systems and matrix tablets with water-soluble drugs

7.3.5. Baker-lonsdale model (microspheres, microcapsules) (1974)

Baker-Lonsdale developed the model from the Higuchi model and described the controlled release of drug from a spherical matrix which can be represented as follows:

$$\mathbf{3/2\,[1-(1-A_t/A_\infty)^{2/3}]-A_t/A_\infty = (3D_mC_{ms}) / (r_0^2C_0) - t}$$

Where At is the quantity of drug released at time t

A_∞ is the quantity of drug released at infinite time,

D_m is the diffusion coefficient,

C_{ms} is the solubility of the drug in the matrix,

R_0 is the radius of the spherical matrix

C_0 is the initial concentration of the drug in the matrix.

Applications

This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres

Guidance for the industry

To enable the application of these models to the comparison of dissolution profiles, the following procedures are suggested:

1. Select the most suitable model for dissolution profiles
2. Using the data from the profile generated for each unit, fit the data to the most appropriate model.
3. **Calculate the MSD** (Multivariate Statistical Distance) in model parameters between test and reference batches.
4. Estimate the 90% confidence zone of the true difference between the two lots.

5. Compare the boundaries of the trust region with the similarity region. If the confidence region falls within the region of similarity, the test batch is considered to have a similar dissolution profile to the reference batch.

7.4. Independent model method

7.4.1. The difference factor (f1)

The difference factor (f1) as defined by the FDA calculates the % difference between 2 curves at each time point and is a measure of the relative error between 2 curves.

$$f_1 = \left\{ \frac{\left\{ \sum_{t=1}^{n} |Rt - Tt| \right\}}{\sum_{t=1}^{n} Rt} \right\} \times 100$$

n = Number of time points

Rt = % dissolved at a temperature t of reference product

Tt = % dissolved at a time t of product tested

7.4.2. The similarity factor (f2)

The similarity factor (f2) as defined by the FDA is the logarithmic transformation of the reciprocal square root of the sum of squared errors and is a measure of the similarity of the percentage (%) of dissolution between the two curves.

$$f2 = 50 \times \log\left[\left\{ 1 + \frac{1}{n} \sum_{r=1}^{n} wt(Rt - Tt) \right\}^{-0.5} \times 100 \right]$$

Procedure: The test for similarity between dissolution profiles is based on the following conditions

- ✓ At least three dissolution time points are measured
- ✓ The ideal number of drug products tested for dissolution is 12 for the test and 12 for the reference (6 minimum)
- ✓ No more than an average value > 85% dissolved for each product
- ✓ The standard deviation of the mean of any product must not be greater than 10% from the 2nd to the last dissolution point
- ✓ **Use DDSolver (Microsoft Excel Add-on)**

Interpretation: In case of high variability, the F 2 test is not applicable, and the MSD test is frequently proposed as an alternative by the FDA and EMA

Conclusion

This lesson has covered essential topics related to dissolution kinetics in the pharmaceutical industry. We have defined dissolution kinetics and its role, discussed factors affecting drug dissolution, and explored different dissolution test methods along with their applications. These insights are fundamental in pharmaceutical research, development, and quality assessment processes, providing a strong foundation for further study and professional application in the field.

References

- European Pharmacopoeia 11.5
- Presentation : Akash gujarathi. Comparison of dissolution profile by different methods & ivivc. dept. of pharmaceutics. poona college of pharmacy, centre of advanced research in pharmaceutical sciences. 2019
- Ramteke KH, Dighe PA, Kharat AR, Patil SV. Mathematical models of drug dissolution: a review. Sch. Acad. J. Pharm. 2014 Jan;3(5):388-96.
- Siepmann J, Siepmann FJ. Mathematical modeling of drug dissolution. International journal of pharmaceutics. 2013 Aug 30;453(1):12-24.
- Elmas A, Akyüz G, Bergal A, Andaç M, Andaç Ö. Mathematical modelling of drug release. Research on Engineering Structures and Materials. 2020;6(4).