

PHARMACEUTICS 3

سوتكس ٣

chapter : DRUG RELEASE &
DISSOLUTION

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(THE ROLE OF DISSOLUTION TESTS):

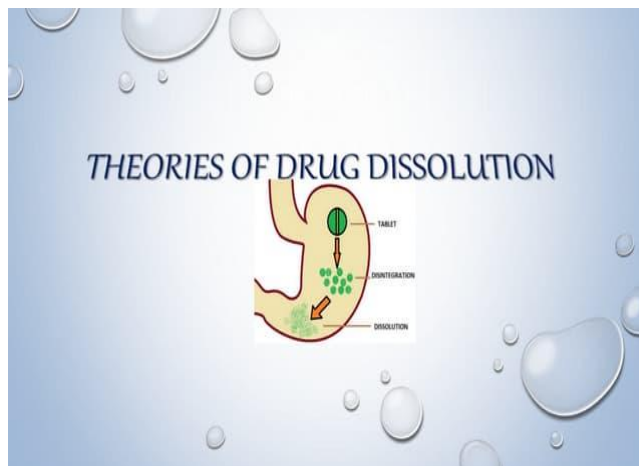
- In the development of new products, for **quality control** and, to **assist with the determination of bioequivalence**.
- The objective of most pharmacopeial dissolution monographs is to establish procedures for **evaluating batch-to-batch consistency** in the dissolution of drug products (similar dissolution characteristics for different batches of the drug product imply similar performance of the product in humans).
- BCS highlighted the importance of dissolution in the regulation of post-approval changes and introduced the possibility of substituting dissolution tests for clinical studies in some cases.

→Therefore, there is a need for dissolution tests that better predict the in vivo performance of drug products. This could be achieved if the conditions of the GIT were successfully reconstructed in vivo.

(physicochemical and physiologic factors that control the dissolution of drug products in humans):

- Composition, mixing patterns (hydrodynamics), and the volume and contents in the GIT.
- The effective **surface area** of the drug (reduction in particle size increases wettability).
- In the intestine, there are **natural surface tension reducing agents** found in the secretions of the stomach or bile that promote dissolution.

- The maximum solubility of the drug in the intestine is affected by many factors: such as buffer capacity, pH, the presence of food, and the natural surfactants such as bile salts and lecithin. Presence of a meal raised pH of the stomach from its normally acidic state (pH 1.5-3.0) to pH 5.5-7.0. This could dramatically affect the solubility which can affect the oral bioavailability.



- The diffusivity of the drug will be a function of the viscosity of the intestinal contents. It will depend on the level of natural secretions, which may vary in the fed and fasted states.
- The boundary layer thickness around the dissolving particles will depend on how **vigorous local mixing** is (higher motility or mixing smaller stagnant layer surrounding the particles).
- For dissolution to proceed, there must be a **driving force (dc/dx)** where $dc = C_s - X_d/V$). To maximize the dissolution, the concentration of the dissolved drug must be minimized. This happens when the drug is absorbed through the intestinal wall into the blood. The rate of absorption is related to permeability and the intestinal drug concentration.



- For passively absorbed drug, the greater the intestinal drug concentration, the faster is the rate of absorption. Therefore, dissolved drug concentration in the intestine, can be kept low, which enhances dissolution. This condition is met when X_d/V is no greater than 20% and is known as “sink conditions”

DESIGNING DISSOLUTION TEST

- **Dissolution apparatus**

- Design, shape and size of the container.
- Agitation method (nature and speed).

- **Dissolution fluid**

- Composition
- Viscosity
- Volume
- Temperature
- Sink condition

- **Process of dissolution**

- Method of introduction of dosage form (holding the dosage form in the medium without obstructing the release mechanism are relevant to drug testing).
- Sampling techniques
- Changing the dissolution fluid (to obtain a pH gradient or to simulate fed and fasting for a modified-release delivery system)

(Biorelevant Media):

- Media representative of the gastric and intestinal environments are commonly used. The major differences between these two media are the pH and the presence of bile.
- Another important consideration is the **absence** (less variability between patients) or **presence of food**.
- Because the stomach is acidic in most patients in the fasted state, the main variable are the type and volume of liquid administered with the dosage form. **If water is administered, the buffer capacity is low, and this would not be a factor in the dissolution testing.**
- The surface tension of gastric contents is reduced. Therefore **SLS is commonly used in the dissolution media to achieve this effect.**
- In the fed state, the conditions of the stomach are highly dependent on the type and quantity of meal ingested.
- Other considerations are the volume and the contents of the stomach or intestinal segment and the duration of the test as it is related to residence time in the stomach or intestinal segment.

TABLE 13–2

COMPOSITION OF DISSOLUTION MEDIA FOR IN VITRO DISSOLUTION TESTING

Medium	Composition	Amount
Simulated gastric fluid pH 1.2 (SGFsp), USP 26	NaCl	2.0 g
	Concentrated HCl	7.0 mL
	Deionized water to	1.0 L*
Simulated intestinal fluid pH 6.8 (SIFsp), USP 26	KH ₂ PO ₄	68.05 g
	NaOH	8.96 g
	Deionized water to	10.0 L†

* Add 3.2 g of pepsin for SGF.

† Add X g of pancreatin for SIF.

زي ما حكيتكم فوق احنا بنعمل اختبار وفحص للدسليوشن بالمختبر وبهاي الحاله لازم اختار وسط مشابه لجسمي يعني مثلا الدوا رح ينزل عالمعدة وانا بعرف انو المعدة هي وسط حامضي لذلك بدي استخدم مواد حامضيه زيها عشان هاذ الفحص يطلع دقيق وكأني بعمله على جسم الانسان الطبيعي ونفس الاشئ للامعاء بدي اختار مواد قاعديه مشابهه للامعاء وزى ما بنعرف سواء بالامعاء او المعدة عندي انزيمات هاضمه بدي اخذهم بعين الاعتبار واضيفهم عالوسط الي بشتغل عليه بالمختبر وكمان مش دايمًا بقدر استخدم المي خلال هالاختبار لانو المي ما عندها بفر وتقدر تقاوم التغير في درجة الحموضه خلال رحلة حبة الدواء على طول الجهاز الهضمي وزى ما بنعرف كل مكان اله درجة حموضه معينه

- Other commonly used media include **(a) water, (b) 0.1N HCl, (c) buffer solutions, (d) water or buffers with surfactants, and (e) low-content alcoholic aqueous solutions**
- Although water is one of the most listed dissolution media found in USP monographs, **it may not be physiologically relevant due to the lack of buffering capacity.**

DISSOLUTION MEDIUM	EXAMPLE
Water	Ampicillin caps, Na butabarbital tabs
Buffers	Azithromycin caps., paracetamol tabs.
HCL solution	Cimetidine tabs.
Simulated gastric fluid	Astemizole tabs., piroxicam caps.
Simulated intestinal fluid	Valproic caps., Glipizide tabs.
Surfactant solution	Clofibrate caps, danazol caps

شو الدوا الي بدنا نعمل عليه هالاختبار؟ وشو الوسط المناسب لهاد الدوا؟
الجدول رح يجاوب ع هذول السؤالين وبرضو مازن بحكيك انهم حفظ

(General categories of dissolution apparatus):

- **General classification:**

1-*Official methods*: (The most commonly used methods appeared in the 13th edition of the U. S. Pharmacopeia in early 1970).

2-*Non-official methods*

→Regulatory guidances recommend 4 dissolution apparatuses for modified release dosage forms. Although the existing apparatuses are adequate for the intended purposes, equipments may require either modifications or completely new design

- **Classification according to technique:**

1-Beaker methods

2-Open flow-through compartment system

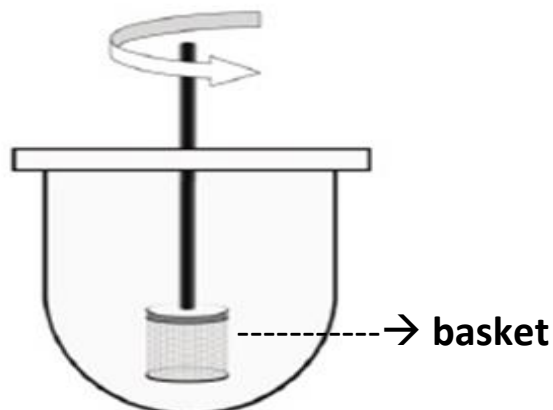
3-Dialysis concept

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- The USP **has 7 different apparatus** that can be used for dissolution testing.
 - USP **basket (method I) and paddle (method II) are referred to as 'closed-system' methods because a fixed volume of the dissolution medium is used.**
 - They provide a steady state stirring motion in a large vessel with 500-1000 ml of fluid that is immersed in a temperature (usually body temperature) controlled water bath.
 - The devices are very simple, robust, and easily standardized.

- These two methods are methods of choice for dissolution testing of immediate-release oral solid dosage forms (tablets and capsules). The use of alternative dissolution methods should only be considered after USP methods I and II are found to be unsatisfactory.
- USP Apparatuses III and IV are used for MR dosage forms.

✚ (Rotating Basket Apparatus “Apparatus I”):

- This apparatus is useful for solids (mostly floating), monodisperse (tablets) and polydisperse (encapsulated beads) drug products.
- It is basically a closed-compartment, beaker type apparatus.
- It is comprising of a cylindrical glass vessel with hemispherical bottom of one liter capacity partially immersed in a water bath.
- A cylindrical basket made of **#22 mesh** is located centrally in the vessel at a distance of 2 cm from the bottom and rotated by a variable speed motor through a shaft.
- All metal parts (basket and shaft) are made of stainless steel 316.



✚ (Rotating Paddle Apparatus “Apparatus II”):

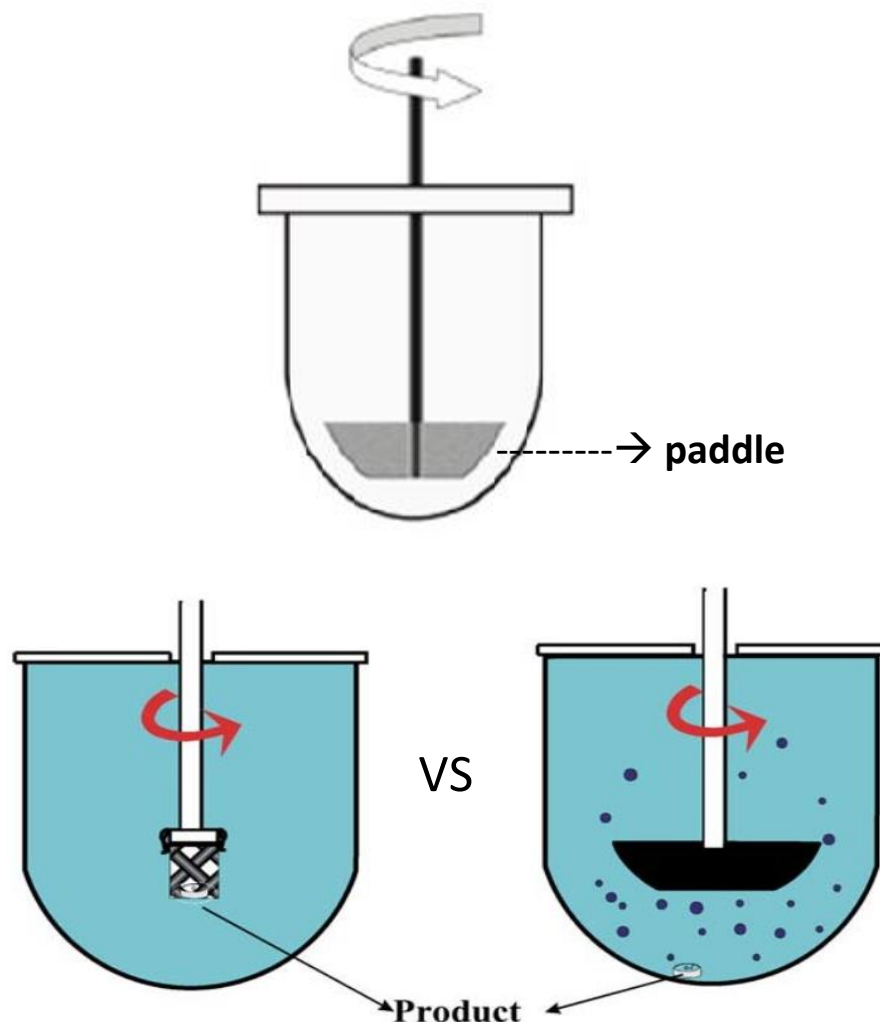
Like USP Apparatus I, apparatus II is useful for solids (mostly floating), monodisperse (tablets) and polydisperse (encapsulated beads) drug products.

In the Apparatus II, a **paddle** replaces the basket as the source of agitation.

Floating dosage forms require sinker that is a small, loose, wire helix attached to the dosage form that would otherwise float. This could be considered as a disadvantage of the apparatus.

Moreover cone formation and positioning of tablet during the test is sometimes hard to maintain.

The position and alignment of the paddle are specified in the official books.



(advantages and disadvantages of USP apparatus I and II):

(advantages):

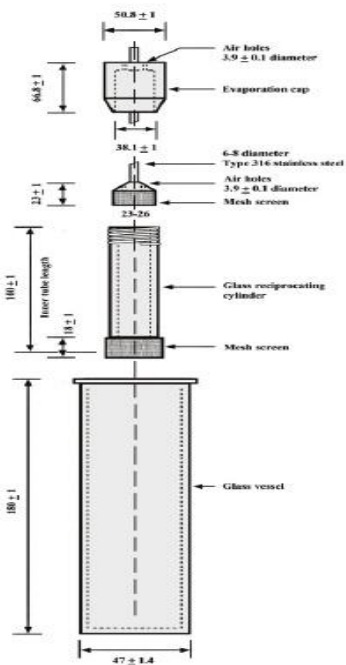
1. Widely accepted apparatus for dissolution test
2. Apparatus of first choice for solid oral dosage forms
3. Standardized
4. Easy to operate
5. Robust
6. Broad experience.

(Disadvantages):

1. Limited volume of the dissolution media
2. Simulation of the gastrointestinal transit is not possible
3. Hydrodynamic conditions are not known.

“Dissolution results obtained with USP Apparatuses 1 and 2 may be significantly affected by **shaft wobble, location, centering, and coning.**”





(The Reciprocating Cylinder Method “Apparatus III”):

- The design of USP apparatus III is based on the **disintegration tester**.
- The assembly of USP apparatus III consists of a set of cylindrical, flat-bottomed glass outer vessels; a set of glass reciprocating inner cylinders; and stainless steel fittings and screens made of suitable material and that are designed to fit the tops and bottoms of the reciprocating cylinders.
- Operation involves programming the agitation rate, in dpm, of the up and down for the inner tube inside the outer tube.
- On the up stroke, the bottom mesh in the inner tube moves upward to contact the product and on the down stroke the product leaves the mesh and floats freely within the inner tube. Thus the action produced, carries the product being tested through a moving medium.

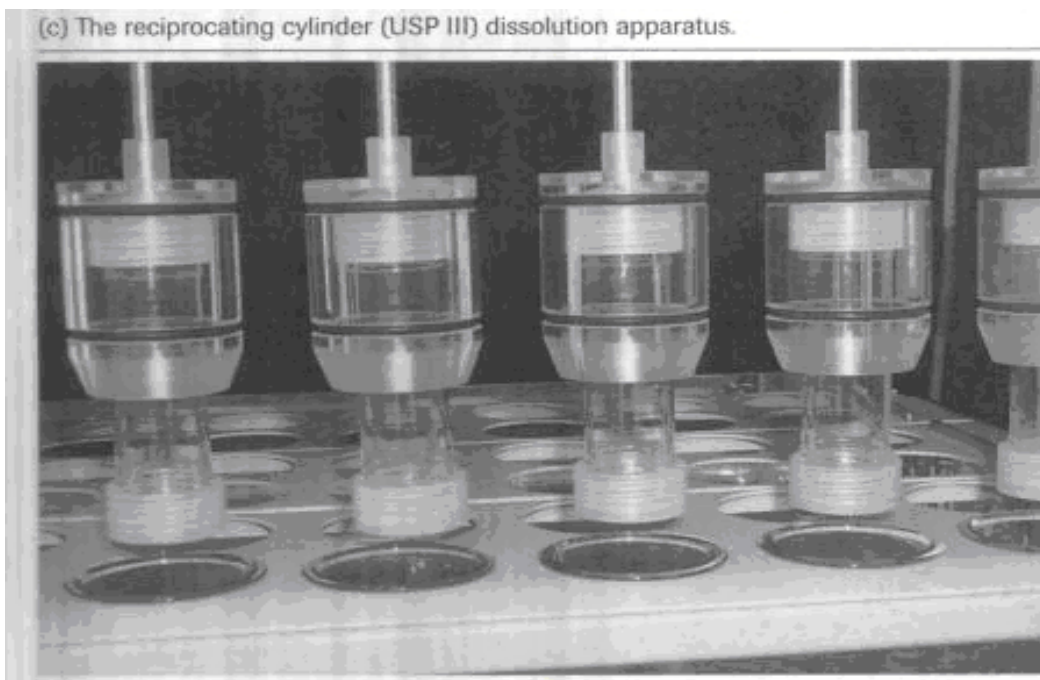
- This apparatus is originally used for extended release products, bead type modified release dosage form, particularly beads in capsules. It is also useful for solids which are mostly non-disintegrating.

Advantages of apparatus III:

1. Programmed for dissolution in various media for various time
2. The media can be changed easily
3. May start at pH 1 and then pH 4.5 and then at pH 6.8
4. Attempts to mirror GIT pH changes and transit times.

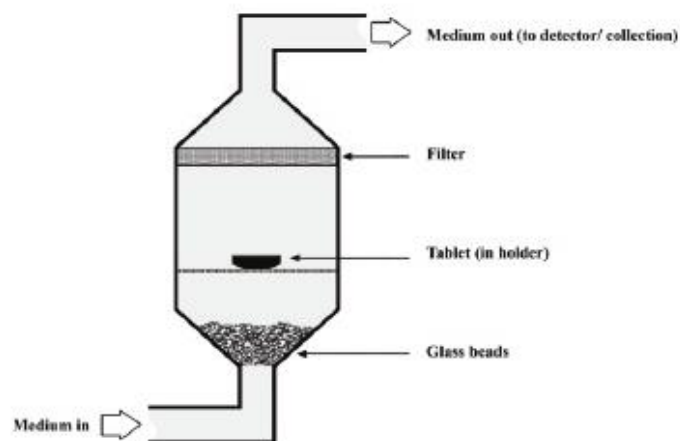
Disadvantages apparatus III:

1. Disintegrating dosage forms show too low results
2. Surfactants cause foaming
3. Volume of dissolution media is too small.
4. This method is less suitable for precise dissolution testing due to the amount of agitation and vibration involved.



(Paddle over Disk method “Apparatus V”):

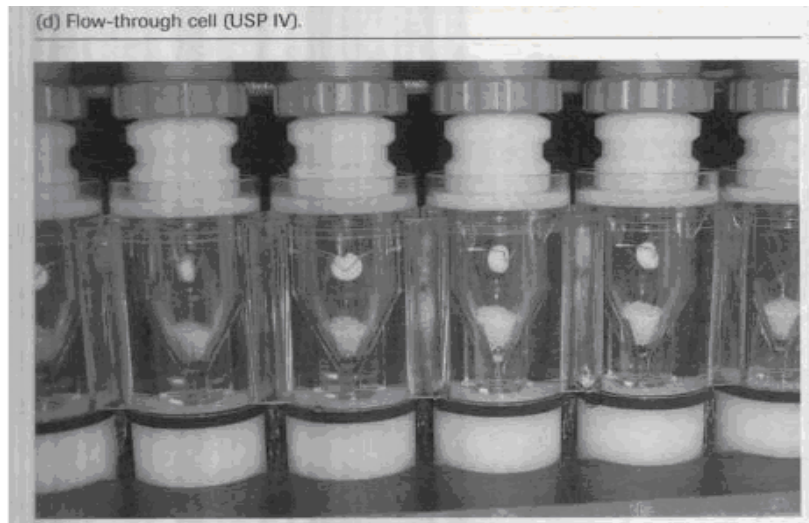
- In Paddle-over-**Disk** method, the paddle and vessel assembly from Apparatus II with the addition of a stainless steel disk assembly designed for holding the transdermal system at the bottom of the vessel.
- The disk/device should not sorb, react with, or interfere with the specimen being tested.
- The temperature is **maintained at $32^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$** .
- The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade.
- The apparatus is **used to test transdermal patches**.



(Open Flow-through Compartment System IV):

- The dosage form is contained in a small vertical glass column with built in filter (a porous glass plate or a bed of beads) through which a continuous flow of the dissolution medium is circulated upward at a specific rate from an outside reservoir using a peristaltic or centrifugal pump.

- **Turbulent or laminar flow can be achieved by changing the bottom barrier.**
- The medium can be changed to provide a pH gradient, surfactants, and other medium components.
- Dissolution fluid is collected in a separate reservoir.
- **Apparatus can be used for dissolution testing of lipid filled soft gelatin capsule.**



USP Apparatus VI (Cylinder Apparatus):

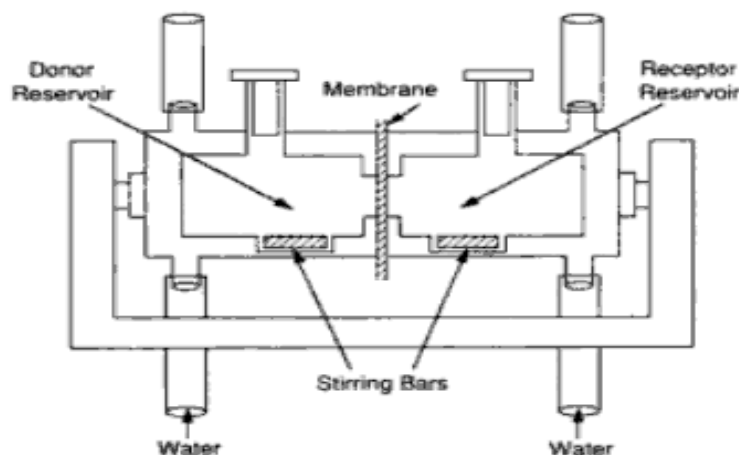
- This is a modification of the USP Apparatus I (basket).
- It uses the vessel assembly from Apparatus I except to replace the basket and shaft with a stainless steel cylinder stirring element.
- The apparatus is **used to test transdermal patches.**

USP Apparatus VII (Reciprocating Holder Apparatus):

Originally introduced in the USP as a small-volume option for **small transdermal patches**, the reciprocating disk apparatus was later renamed the reciprocating holder apparatus with the adoption of four additional holders for **transdermal systems, osmotic pumps, and other low-dose delivery systems.**

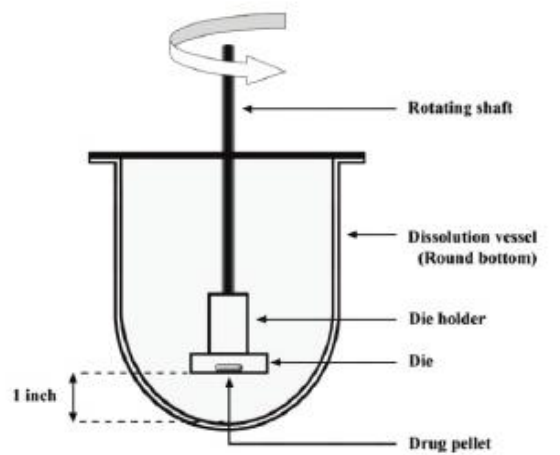
DIALYSIS SYSTEM

- Here, dialysis membrane is used as a selective barrier between fresh solvent compartment and the cell compartment containing dosage form.
- It can be used in case of very poorly soluble drugs and dosage form such as ointments, creams and suspensions.

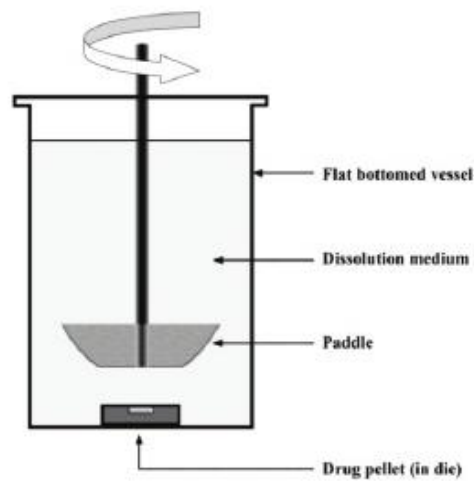


ROTATING AND STATIC DISK METHODS

- The intrinsic dissolution rate is defined as the rate of dissolution of a pure pharmaceutical active ingredient when conditions such as surface area, temperature, agitation or stirring speed, pH, and ionic strength of the dissolution medium are kept constant.
- Determining this parameter allows the screening of drug candidates and aids in understanding their solution behavior under various biophysiological conditions.
- The compound is compressed into non disintegrating disc and mounted so that one surface is exposed to medium.



(A)



(B)

Schematic diagram of (A) the rotating disk apparatus (Wood Apparatus) and (B) the stationary disk apparatus

CHAPTER TWO "DRUG RELEASE& DISSOLUTION" CHAPTER TWO

☑ DONE!

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