DISSOLUTION TECHNIQUES FOR EVALUATION OF NOVEL DRUG DELIVERY SYSTEM

- **WHY WE REQUIRED UNCONVENTIONAL METHODS FOR DISSOLUTION?**

OR

- **DISADVANTAGES OF CONVENTIONAL METHODS**

OR

- **WHY WE HAVE TO GO FOR UNCONVENTIONAL METHODS.**

1. Irregularities in round bottom flask.
2. Volume filled in that is normally 900 ml that will not mimic the GI track fluid volume that is around 70 ml.
3. Due irregularities positioning of the tablets and accumulation of the disintegrating material at the bottom is seen. That will retard the dissolution and will lead to wrong interpretation of the results.
   So, due to that fast dissolving material appears to be slow dissolving.
4. Laminar flow of the dissolution medium in case of the paddle and basket apparatus doesn't mimic the turbulence flow in the GIT.
5. Conventional method does not mimic the rate of release of the gastric fluid in the GIT which is 2 ml/min.
6. Stagnation of the material in case of sticking kind of tablets or where high grades of polymers are used.
7. Coning effect seen in the paddle apparatus.
8. Method of calculation is also very complex and includes various mathematical equations which are very complex and having very limited application.
9. Incomplete exposure to dissolution medium.
10. Occasional clogging of the basket screen by gummy particle.

- **EXPECTED REQUIREMENTS FROM UNCONVENTIONAL METHODS**

a. Reproducible and sensitive.
b. Easy to operate.
c. Gives good in vivo & in vitro correlation.
d. Simplicity of design.
e. Convenient means for introducing the dosage form.
f. Cost effectiveness.
g. It should provide:
   1:- complete bio relevant condition.
   2:- profile should be deconvoluted:- means your method should increase the absorption of the drug which was retarded by the conventional method.
h. It should be always justified that why official equipments are not suitable.

But it is not so easy to run non compendial methods there are also many hurdles in running the unconventional methods.

Difficulties in running the non-conventional methods:

- Look for adjustments and moving parts.
- Obtain vendor specifications and tolerances.
- Historical data base is not available because you are going to establishing new method.
- Develop a per run quality check.
- No guideline for how to use apparatus.
- Set limits
- Regulatory aspects.

Novel Dissolution test Apparatus for Buccal and Sublingual tablets:-

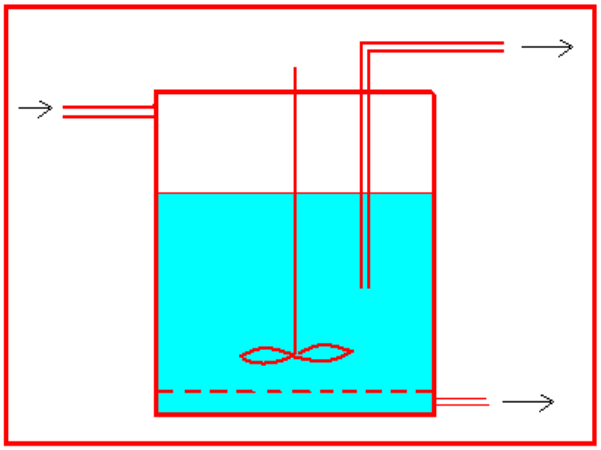
Buccal dissolution differs from G.I.dissolution in following ways…

- Smaller volume (of saliva)
- Short residence time (in mouth)
- Solids transfer
- Composition of fluid (saliva composition)
- Incomplete dissolution

So, our dissolution apparatus must provide above conditions for performing dissolution test of Buccal and sublingual tablets.

MODEL:-I

- It is given by Rohm & Haas Laboratories-spring house.



- This novel system comprises a single stirred continuous flow-through cell that includes a dip tube, a central shaft with propeller & a filter along with one inlet for saliva & one outlet for sample.

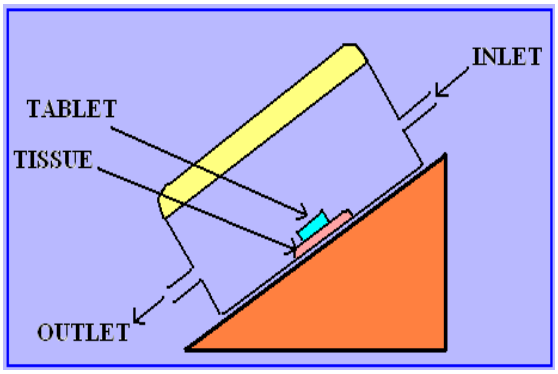
ADVANTAGE:

- ✓ It is a rapid, taking only about 20 minutes per test & repeatable.
- ✓ This method could be used as a QC test to ensure dosage uniformity.

MODEL:-II

- ✓ A new & simple dissolution apparatus which is **capable of evaluating the release of drug & bioadhesive properties of buccal tablets** has been developed by mumtaz & ch'ng in 1999.

- ✓ Apparatus consists of a **dissolution cell & an outer assembly**, the cell has been designed to **hold the chicken pouch membrane & bioadhesive tablet together** & also to **allow the dissolution medium to flow over them**, the outer assembly is to provide adjustment of the angle of the flow of the medium over the cell.
  - The device introduced by them is based on the circulation of pre-warmed dissolution medium through a cell.
- They stated "the results obtained by this using this apparatus for the release of drug from bio adhesive tablets concurred with the predicted patterns."



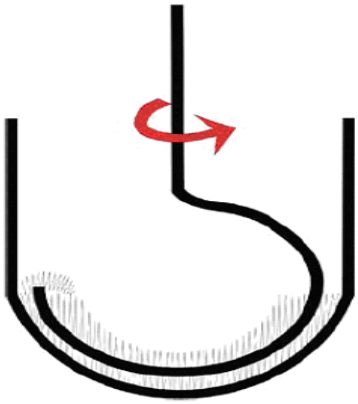
Novel Dissolution test Apparatus for Floating and Muco- adhesive delivery systems:-

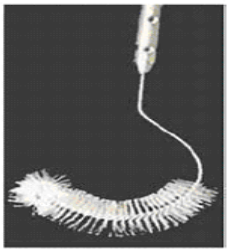
Ideal qualities for dissolution apparatus for Floating tablets.:-

1. Dosage form should not stick on the agitating device. Therefore, under driven arrangement is more suitable.
2. The test must try to mimic the gastric juice release rate (2-4ml/min).
3. The sample collection must be easy.
4. The volume of cell having dosage form in it must have nearly same volume as compared to in-vivo gastric volume.

■ MODIFICATION IN PADDLE DESIGN:

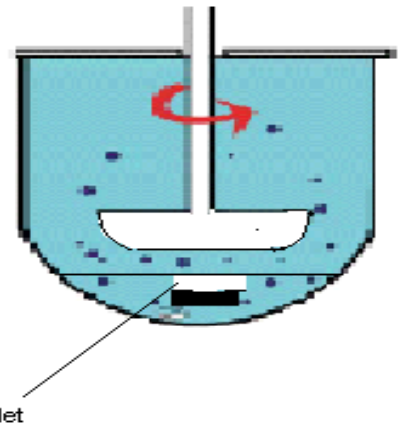
- Here, paddle is replaced by crescent shaped spindle.
- Sometimes due to accumulation of disintegrated products at the center, paddle apparatus shows inaccurate dissolution profile.
- The spindle has a curved shape corresponding to the bottom of the vessel.The gap between the metal part and bottom of the vessel is filled with filaments. Unlike the gap between the vessel and the spindle for the USP Paddle Apparatus, the crescent- shaped spindle does not have such a gap. The filament ends touch the surface of the vessel and rake through the material, or move the product if not disintegrated, at the bottom of the vessel.
- Dissolution profile shows that crescent shaped spindle gives better dissolution profile at low speed (25 RPM) than paddle.





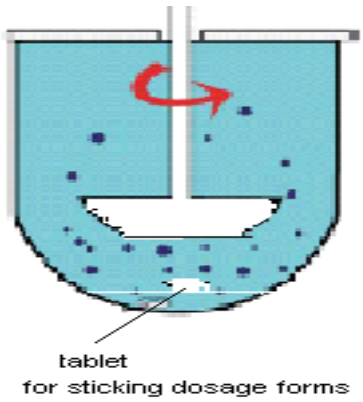
■ PILLAY & FSSIHI MODEL FOR FLOATING & STICKING TABLET:

- **FOR FLOATING TABLETS:** Here, Wire mesh is put above the floating dosage form so floating tablet doesn't interfere with paddle.



pillay and fisshi model for floating drug delivary

- **<u>FOR STICKING TABLETS</u>:** here, sticking tablet is put above the wire mesh so there is complete exposure of dissolution medium is occurs.

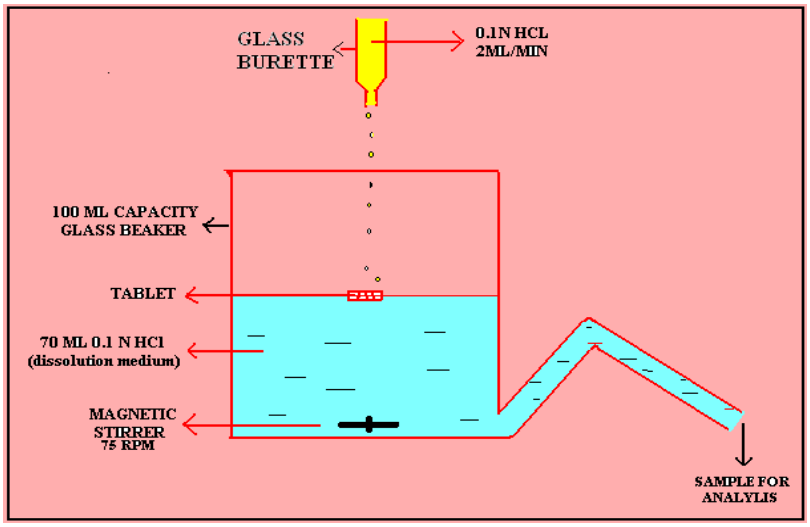


ROSSET-RICE TEST :

- ✓ This apparatus is used specifically for the study of the dissolution profile of Antacids and Anti-reflux preparations.
- ✓ This apparatus is modified for floating tablets.

■ <u>MODIFIED ROSSET –RICE TEST</u> (PROPOSED METHOD FOR FLOATING TABLET)

- Above apparatus is modified for easily sample collection (under driven) for floating tablet.



<u>Conclusion</u>:-

- ■ Better in-vivo-in-vitro correlation shown by this method.
- ■ It mimics three points.
  - i) Gastric volume
  - ii) Gastric acid secretion

iii) Gastric emptying.

Which USP-II apparatus fails to mimic. & Here, tablet does not stick to agitating device because it is under-driven.

Novel Dissolution test Apparatus for dosage form containing poorly soluble drugs:-

- Problems associated with conventional apparatus regarding the dissolution test for poorly soluble drugs:-
- Pharmaceuticals that exhibit pH dependent solubility may undergo..
  Dissolution (in stomach)
  Precipitation (in intestine) &
  Re dissolution (at site of absorption)

Through the g.i.t.because of the dramatically change in solubility as the pH of the g.i.t. changes.

- If we consider a weak base with poor intrinsic solubility, it may rapidly dissolves *in stomach* but get precipitates *in intestine.*
- Our conventional dissolution apparatus fails to correlate pH changes with the dissolution profile of the poorly soluble drugs.

  Therefore, to more accurately predict the "in-vivo" dissolution behavior of these pharmaceuticals, it is necessary to conduct a dissolution test that mimics the pH changes in the g.i.t.

Novel multi-compartment dissolution apparatus for poorly soluble drugs :-

Description of apparatus*:-*

1: **Gastric reservoir :** 5 liter : 2ml/min : 0.1N HCl : to mimic secretion of acid from gastric lining.

2: **Intestinal reservoir :** 5 liter : 2ml/min : 1.2M alkaline borate buffer

A: **Gastric compartment :** 70 ml : to mimic in-vivo conditions : removal of content by side arm mimics the pylorus opening.

B: **Intestinal compartment :** 400 ml : to mimic in-vivo conditions

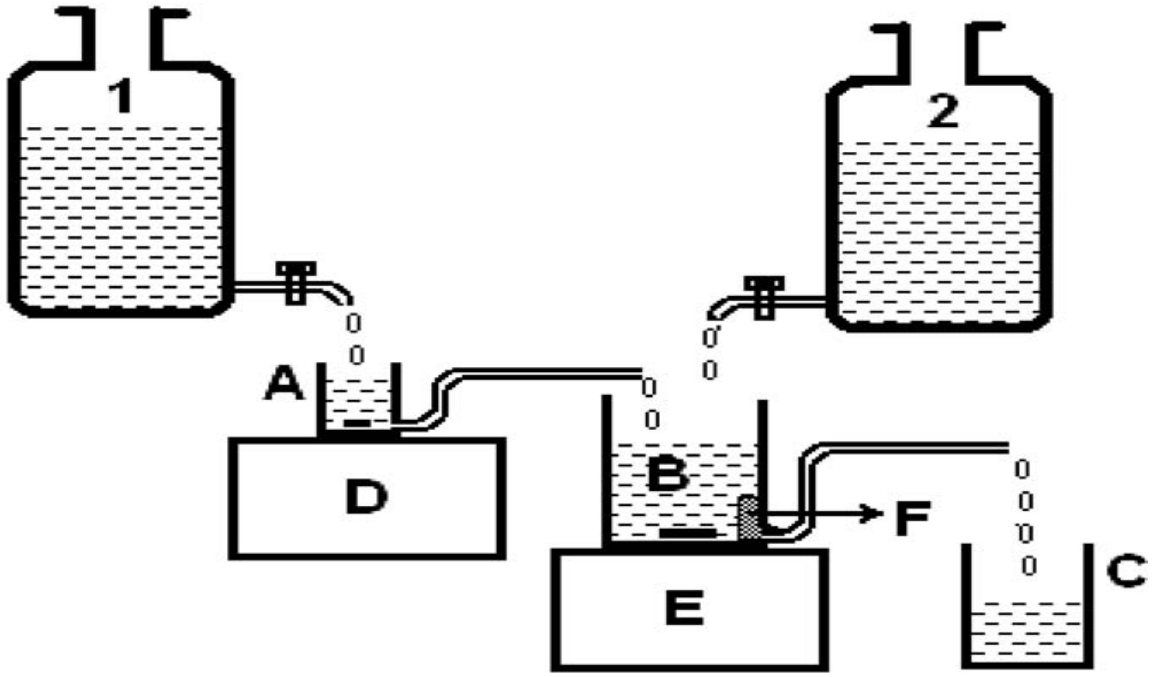
C: **Absorption compartment :** it gets fluid at the rate 4ml/min : 5 ml sample collected at various intervals.

D: & E: **Magnetic stirrer with heating capacity :** 75 rpm

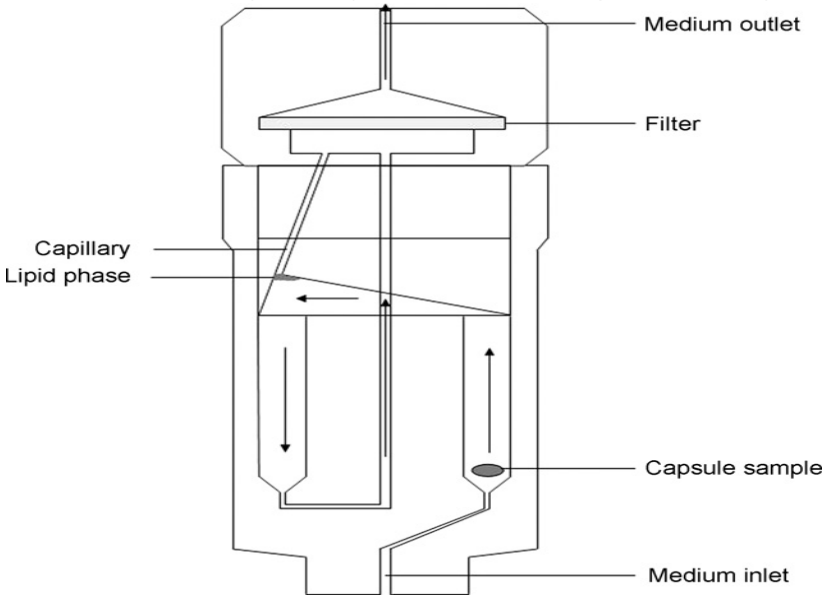
F: **filter :** To prevent entry of the un-dissolved particles.

Results:-

- The proposed apparatus shows good in-vitro in-vivo correlation as compared to other apparatuses proposed before because it mimics the most of the conditions which a dosage form of poorly soluble drug may suffer in the g.i.tract.
- Proposed apparatus used for cinnarizine which is a poorly soluble drug.
- It is simple apparatus for the researchers to use & provide better predictive characteristics.



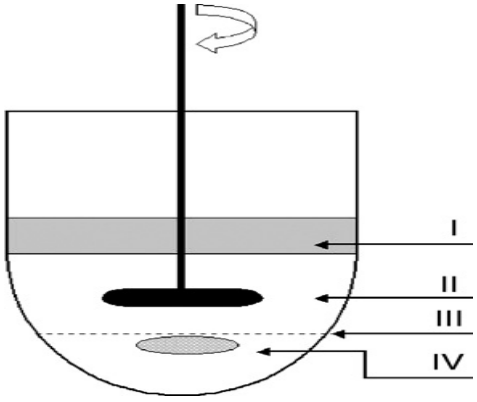
Dissolution study of Lipid filled soft gelatin capsules.:-



Working mechanism:-

- It is one type of flow through cell.
- Lipid content due to its lower density rises up in the cell after rupturing of the capsule.
- When lipid phase reaches the triangular area top of the left side cell, it stays there. thus ,dissolution medium continuously extracts the drug from the lipid layer as it flows through the cell.
- The dissolved drug can now be determined using a fractional collector and be analyzed in the medium.

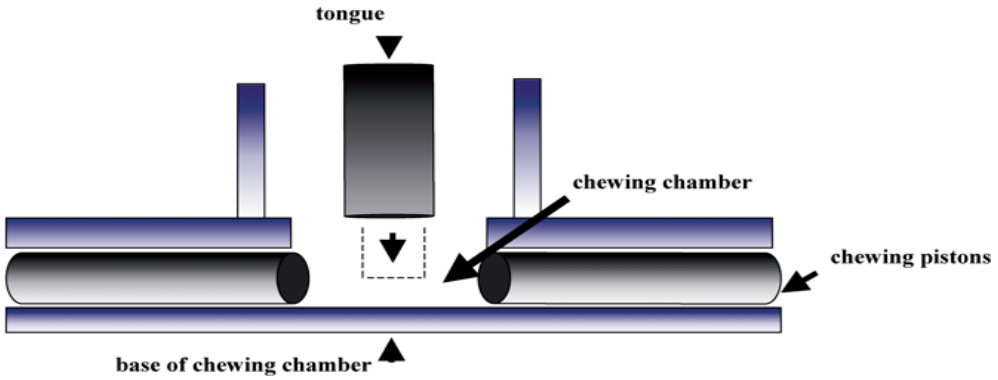
Pillay & Fassihi model for Lipid –filled soft gelatin capsules.:-



I = organic phase, i.e., 100 ml
II = aqueous phase
III = ring/mesh
IV = position of capsule

- This model is having organic phase in it to extract the lipid content of the soft gelatin capsules.
- Ring or mesh is used to prevent the sticking of the soft gelatin capsule to the rotating paddle.

Dissolution study of chewing gum as a dosage form:-



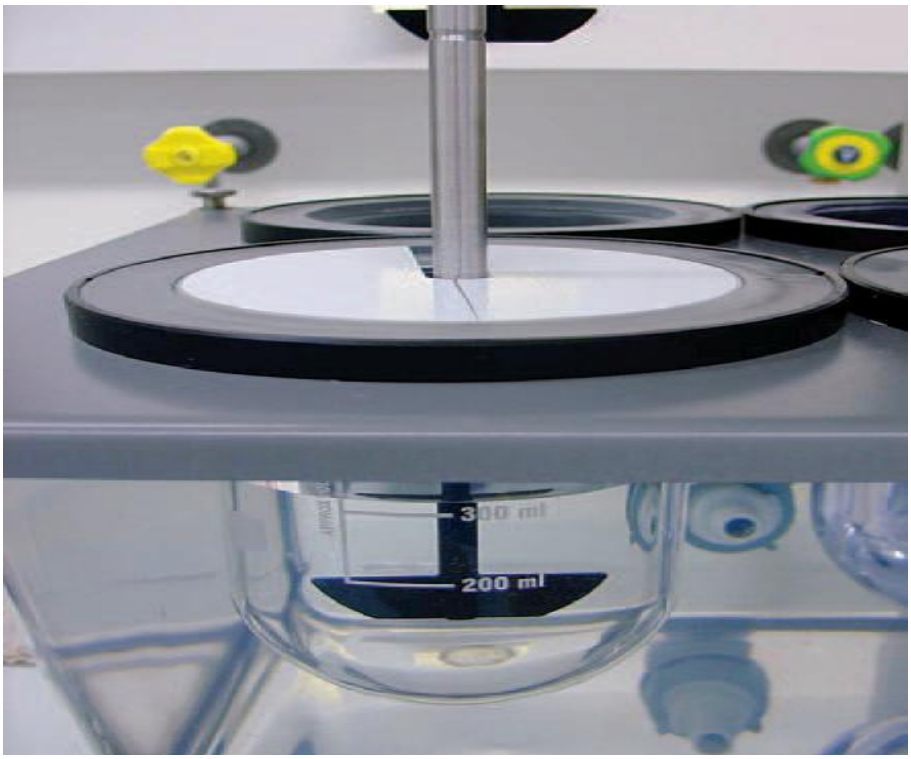
- European Pharmacopoeia published a monograph describing a suitable apparatus for studying the in vitro release of drug substances from chewing gums.

- The chewing machine consists of a temperature-controlled chewing chamber in which the gum piece is chewed by two electronically-controlled horizontal pistons driven by compressed air (Figure). The two pistons transmit twisting and pressing forces to the gum, while a third vertical piston, ("tongue") operates alternately to the two horizontal pistons to ensure that the gum stays in the appropriate position. The temperature of the chamber can be maintained at 37±0.5°C and the chew rate can be varied.Other adjustable settings include the volume of the medium, the distance between the jaws and the twisting movement. The European Pharmacopoeia recommends using 20 ml of unspecified buffer (with a pH close to 6) in a chewing chamber of 40 ml and a chew rate of 60 strokes per minute.

- A study was carried out to explore differences in the release of nicotine from the directly compressible gum base compared with a conventional nicotine gum using the European Pharmacopoeia chewing apparatus described in European pharmacopoeia.

  - **The temperature of the chewing chamber :37±1°C**
    chew rate : 60 chews/minute
    unspecified buffer (with a pH close to 6) : 20 ml

Mini Paddle Apparatus- for dissolution study of Immediate-Release Dosage Forms:-



- The mini paddle is based on the USP paddle setup but scaled down exactly 1/3 with respect to the dimensions.
- 250 ml volume used in the mini paddle apparatus.

- A stirring rate of 100 rpm in the mini paddle apparatus appears to be the most favorable.
- Run with a half of dose of drug than used for paddle apparatus.

Features of the mini- paddle apparatus:-

- Mini paddle apparatus might be a useful tool in characterizing drug release profiles under "standard test conditions."
- Here, smaller sample sizes and smaller volumes of media is used so, it offers various advantages in terms of substance, analytical, and material cost savings.
- The mini paddle set-up is also a promising alternative in the case of highly potent drugs.
- Useful for early development stage.
- The mini paddle should preferably be used for powders, multiparticulate dosage forms, small tablets or capsules(i.e., where the paddle apparatus would be the usual method of choice)

Novel dissolution method for Evaluation of In Situ Gel:

- The dissolution medium used in this study are either phosphate buffer (pH 7.4) or 0.15% Tween80 solution.
- Two different dissolution media are used to identify the one that is capable of distinguishing the formulation differences.
- The dialysis bag containing the gel is immersed in a 50-mL polypropylene tube containing 40 ml of the dissolution medium. This volume was selected to maintain a sink condition throughout the dissolution study.
- The entire dissolution medium was removed at preset time intervals (0.5 hours, 1.5 hours, 4 hours, 7.5 hours, 1 day, 2 days, 4 days, 7 days, 11 days, and 15 days).
- The dissolution medium was replaced with fresh medium to maintain a sink condition. The amount of buprenorphine released during a sampling period was measured using high-performance liquid chromatography (HPLC).

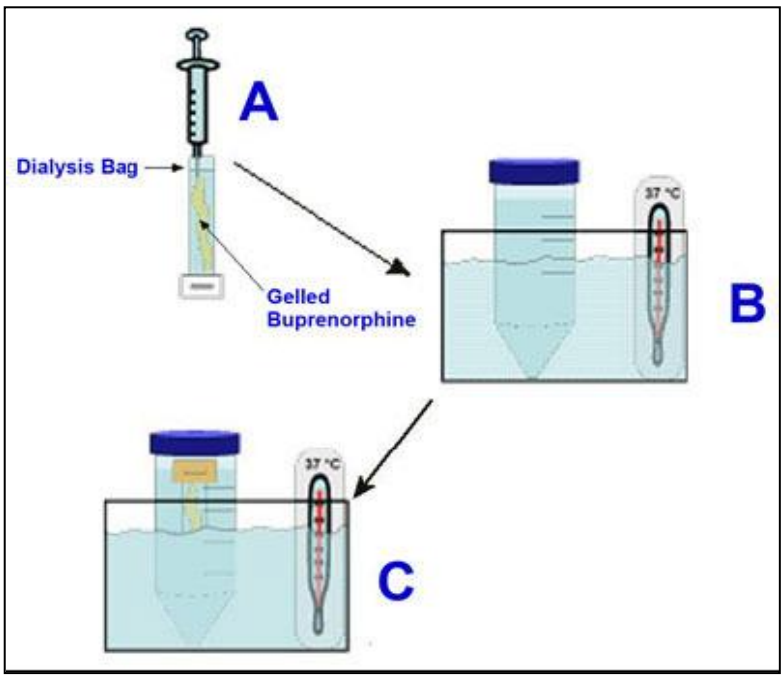


Figure : Schematic of the in vitro dissolution method for In situ gel formulation.
(A) Copolymer solution containing buprenorphine was injected into a dialysis tube containing the dissolution medium.
(B) Polypropylene tube containing the dissolution medium was immersed in a water bath.
(C) Dialysis tube containing in situ gel was immersed in the polypropylene tube.

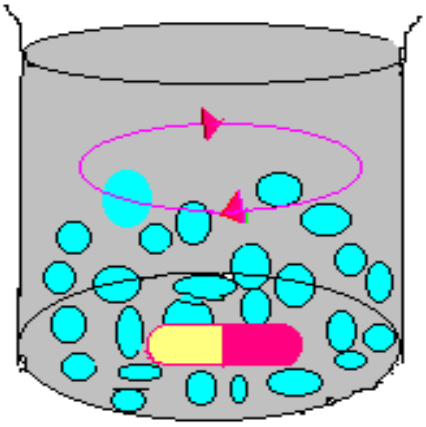
IN VITRO DISSOLUTION METHODS FOR COLON SPECIFIC DDS

Sequential dissolution testing
(paddle type, 37± 0.5 ˚ C)
Used for 5 ASA (5-amino salicylic acid)

TIME	SIMULATE	MEDIUM
Initial 2 hrs	Gastric emptying time	0.1 N HCl
1 hr	Duodenum transit time	Phosphate buffer (pH 6.0)
2 hrs	Ileum transit time	Phosphate buffer (pH 7.2)
2 hrs	Ascending colon transit time	Phosphate buffer (pH 6.4)

PRESSURE CONTROLLED COLON DELIVERY CAPSULE

- *ROTATING BEAD METHOD:*



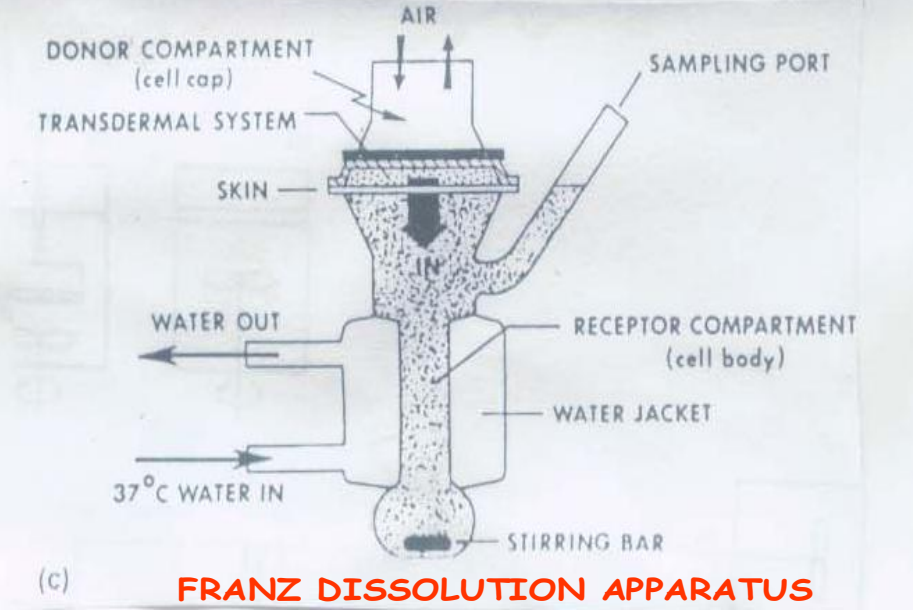
- **Volume: 500ml**
- **Glass beads (5000-10000):**
  impart frictional force
- **Dissolution medium:**
  0.067 M phosphate
  buffer + PVA
- **pH: 07**
- **Rotation speed of vessel: 5/10/25 rpm**
- **Temp: 37 ˚C**

TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS)

- **Aim of in vitro test for TDDS**
  To understand & predict the delivery of drug molecule from Transdermal patch & penetration from skin surface into the body via the skin of a living animal

Dissolution apparatus used

- Franz diffusion apparatus
- Paddle over disk
- Rotating cylinder method
- Flow through diffusion cell



❖ Factors to be considered in mimicking

- Animal skin – hairless mouse, guinea pig, rabbit.
  But no animal skin mimic human skin so human skin is preferred.
- Temp: 32 ±1 ˚C
- pH: 5-6
- Stirring rate: 100 rpm.
- Damaged skin: mimic injury / pathogenic condition.
- Enzymes for oxidation, reduction, hydrolysis, conjugation.
- Skin lipids
- Microbial flora (difficult to reproduce)

Examples of formulated as TDDS

CARVEDILOL
ONDANSETRON
NIMESULIDE
METOPROLOL

SEMISOLIDS

- Methods for in vitro study of semisolids

1) Classical permeation studies.
   Uses excised animal / human skin.
2) Finite dose technique.
   Applied to skin simulating actual use by patient.
3) Drug release studies using synthetic membrane.
   Membrane is used to separate donor & receptor compartment (or where no membrane is used the topical solution is kept in direct contact with a solvent acting as a sink).

❖ Commonly used membranes

- Polysulphone (Tuffryn, 0.45 µm size): **Most suitable** syn. membrane for ointments.
- Cellulosic acetate plus.
- Nylon
- Teflon
- Polycarbonate

❖ Factors to be monitored

- The membrane must be an inert material that does not interact chemically or physically with the drug.
- Receiving medium should simulate PHYSIOLOGICAL CONDITION OF SKIN.
- pH: 5.5 using phosphate buffer with 35% ethanol.
- Deaeration to avoid bubble formation at interface.
- Surface of applied formulation should be kept opened to room air.
- Viscosity.

❖ Dissolution apparatus used

- USP paddle over disk
- Franz diffusion apparatus
- Flow through apparatus
- Unconventional apparatus
  a) Designed by Chowhan b) Designed by Zuber

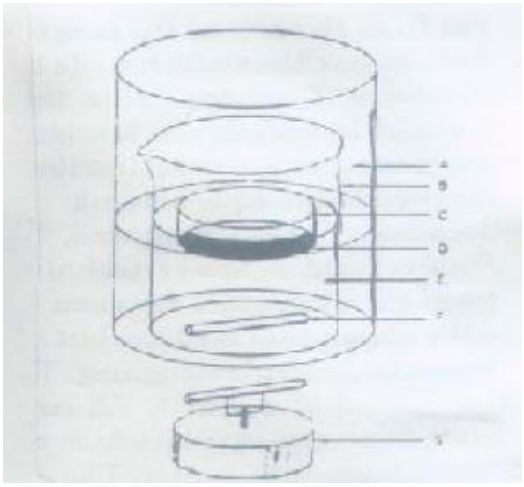


DIAGRAM:
A = Constant temp. water bath
B = 250 ml beaker
C = Teflon disk
D = Layer of ointment
E = sink
F = Magnetic stirring bar
G = Motor

Apparatus used in studying the release of drugs from an ointment layer containing suspended drug. [Reproduced from Z.T. Chowhan & R. Pritchard J. Pharm. Sci. 1975; 64(5): 754]

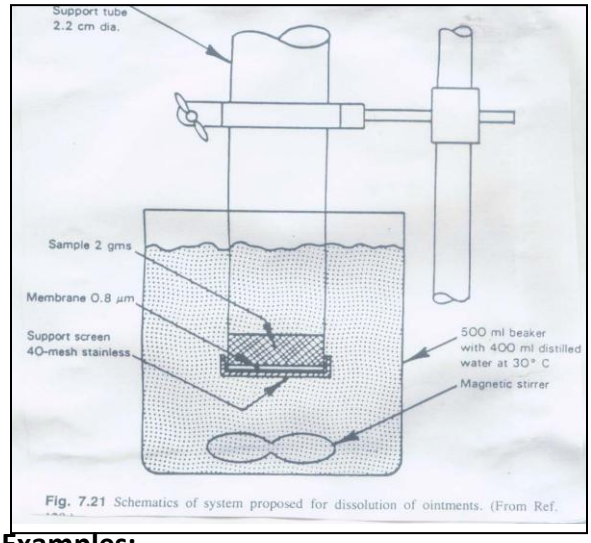


Fig. 7.21 Schematics of system proposed for dissolution of ointments. (From Ref.

Examples:

- **CORTICOSTEROID OINTMENTS**

1. BETAMETHASONE VALERATE (0.1%)
2. HYDROCORTISONE (0.5%)
3. TRIAMCINOLONE ACETONIDE (0.1%)

- The determination of rates of corticosteroid release from ointment bases had been problematical & challenging.
- However the procedure which seems reliable is the use of open chamber static diffusion FRANZ cell, with CELLULOSE ACETATE-NITRATE MEMBRANE & an appropriate mostly aq. receptor medium.
- ISOPROPYL MYRISTATE imparts lipophilicity to cellulose acetate-nitrate membrane soaked in it for 30 min. before use.
- Thus it facilitates diffusion of drug hydrocortisone released from ointments.

PARENTERAL DDS

Includes
[1] IMPLANTS
[2] DEPOT INJECTIONS

What is an IMPLANT?

- Sterile solid dosage forms involving dispersion of drug through the matrix (coated or laminated) to get CR.

❖ IN VITRO TEST FOR IMPLANTS

A) **SHAKING FLASK METHOD**

DISADV. – For poorly soluble drugs frequent replenishing of medium necessary to maintain sink condition.

Modification: Ethanol addition to enhance solubility.

B) **FLOW THROUGH CELL**.

❖ MIMICKING OF IN VIVO CONDITION

- Flow rate of dissolution medium: VERY SLOW.(Use of HPLC Pumps)
- Test is run for weeks. Thus precaution is to be taken to compensate against EVAPORATION & MICROBIAL GROWTH. (Add appropriate conc. of preservative)
- Osmolarity.
- pH
- Buffer capacity.

What is a DEPOT injection?

- Poorly soluble salt of active drug is suspended in oily type base releasing the drug slowly for absorption.

❖ IN VITRO TESTING FOR DEPOTS

DEPOT ⟶ DRUG IN SOLUTION ⟶ DRUG IN TISSUE FLUID

ROTATING DIALYSIS CELL

- USED FOR OILY PARENTERAL DEPOTS
- Eg. NAPROXEN IN COCONUT OIL
- Dialysis membrane provides well defined surface area & mixing is accomplished by rotating the dialysis cell which mimic the desired physiological condition in vivo.
- The apparatus consists of a rotating dialysis cell, mounted on a standard tablet dissolution apparatus. (The distance from the bottom of the vessel to the rotating cell is 5.6 cm).
- Ten samples of 2.0 ml (for HPLC detection) or 5.0 ml (for UV detection) were withdrawn during 96 hr study.
- Dissolution medium contg. the buffer solution resembles the pH of absorption site with respect to the nature of drug.
- Volume: 1000ml, maintained at 37 ± 0.5˚C.
- Stirring rate: 50 rpm.
- Dissolution medium used
  pH 3 ± 0.01 (0.05 M phosphate buffer)
  pH 5 ± 0.01 (0.05 M Acetate buffer)
  pH 7 ± 0.01 (0.05 M phosphate buffer)

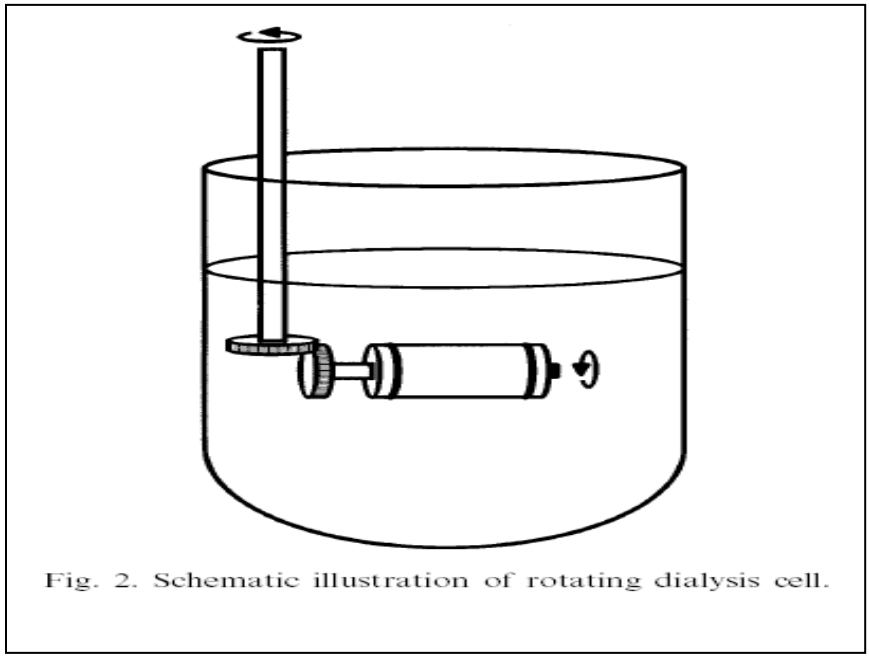


Fig. 2. Schematic illustration of rotating dialysis cell.

DISSOLUTION STUDY OF BUDESONIDE NANOPARTICLES :

- **Powder + 10ml Phosphate Buffer Saline was placed in a floatable dialysis membrane unit & this unit was allowed to float in a beaker containing 300ml of PBS at a speed 100rpm.**

IN-VITRO EVALUATION OF DRUG RELEASE FROM NICOTINE GELISPHERES (Alginate+HEC)

- Nicotine – 200mg
- Formulation immersed in 100ml of simulated CSF in a sealed 150ml glass jar placed in a shaker bath agitated at 50 rpm
- Sample is removed at an interval of 5 min for a period of 3hrs & analysed using UV-SPECTROSCOPY
- (JPS,Vol-98(6),2062 JUNE-2009)

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Study questions:-

- **Write short notes on…**
  - Novel Dissolution test Apparatus for buccal and sublingual tablets.
  - Novel Dissolution test Apparatus for Floating and Muco adhesive delivery
  - systems.
  - Novel Dissolution test Apparatus for dosage form containing poorly soluble drugs.
  - Dissolution study of Lipid filled soft gelatin capsules.
  - Dissolution study of chewing gum as a dosage form.
  - Mini Paddle Apparatus- for dissolution study of Immediate-Release Dosage Forms
  - Importance & applications of dissolution testing. (Sept. 2005)
  - In vivo methods to determine permeability. (Sept. 2005)
  - Biorelevant dissolution testing. (Sept. 2006)
  - How is the dissolution profile of a test product matched with a reference pdt? (Sept. 2006)
  - What is dissolution testing? Justify its necessity?
  - Describe modification in dissolution testing to mimic in vivo condition in case of
  - a) TDDS b) GRDDS c) Topical DDS
  - What is Franz diffusion apparatus? Mention its applications?