

IN VITRO -IN VIVO EVALUATION OF ORAL CONTROLLED DRUG DELIVERY SYSTEM



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INTRODUCTION

- Novel oral drug delivery systems are broadly classified into two categories as they may controlled release dosage forms as well as targeting dosage forms.
- Generally controlled drug delivery preparations release the drug in a controlled manner in the GIT for systemic uptake and no particular area of GIT specified.
- Targeted preparations are releasing the drug in a specified area or ,tissue of GIT.

Oral controlled drug delivery system

ADVANTAGES:-

- Increased patient compliance
- Reduction in dosing frequency
- Reduced fluctuations in circulatory drug levels
- Employ less total drug and eliminate local side effects
- Better utilization of the drugs
- More uniform effect
- Better control over the drug absorption.

DISADVANTAGES:-

- High cost
- Dose dumping
- Unpredictable or poor invitro-in vivo correlation
- Reduced potential for dosage adjustment
- Increased first pass clearance
- poor systemic availability.

ATTRIBUTES OF DRUG CANDIDATE FOR CONTROLLED RELEASE SYSTEMS

- The drug must be effective in a relatively small dose.
- Drugs with biological half-life's less than one hour or greater than 12 Hrs are viewed as questionable candidate for controlled release formulations.
- Very insoluble drugs whose availability is controlled by dissolution may not benefit from formulation in controlled release forms.Ex:griseofulvin.
- Drugs not effectively absorbed in the lower intestine as drugs with extensive first pass clearance are also difficult to formulate in controlled release system.

Various sites of gastrointestinal tract for oral drug delivery systems

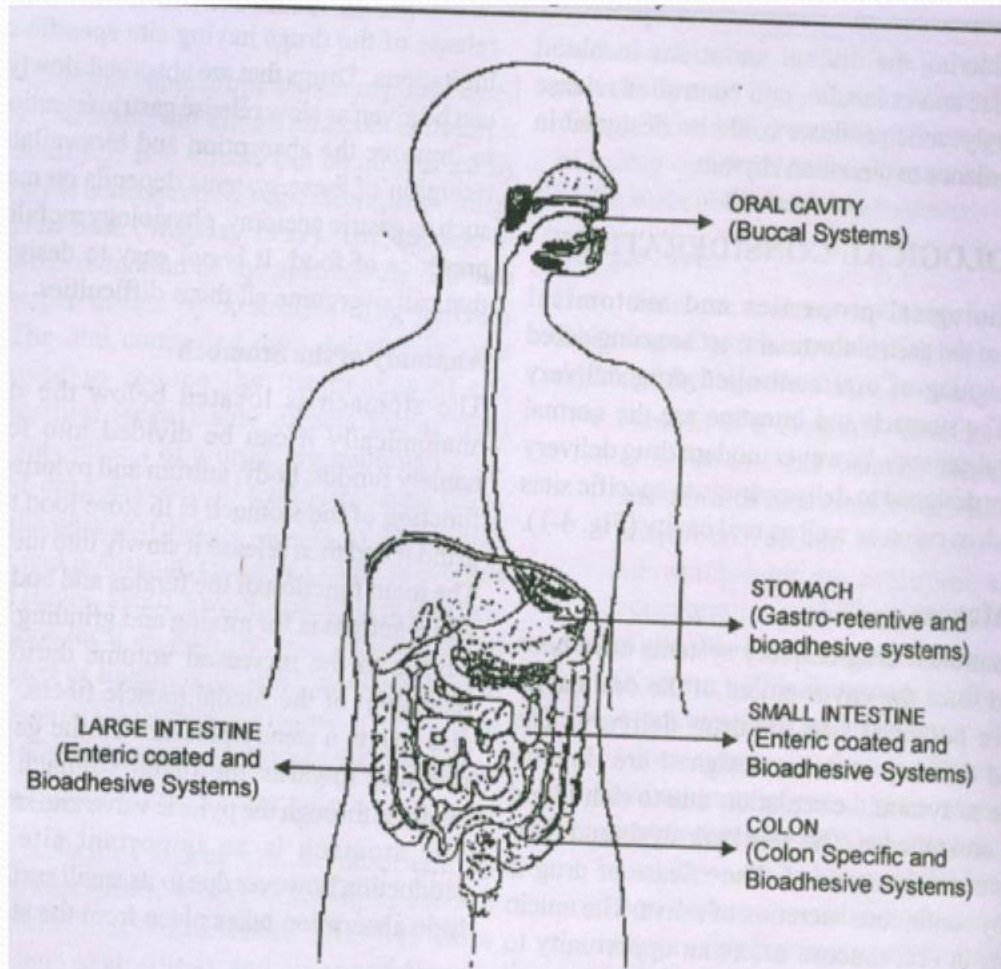


Fig. 4-1 Various Sites of Gastrointestinal Tract for Oral Drug Delivery Systems

GASTRO RETENTIVE DRUG DELIVERY SYSTEM

- ❖ Orally administered controlled release dosage forms suffer mainly from two adversities.
- Short gastric retention time(GRT)
- Unpredictable gastric emptying time(GET)
- ❖ This can be overcome by altering the physiological state and designing the formulations, by which gastric emptying process can be extended from few minutes to 12 Hrs.
- ❖ Various approaches has been worked out to improve the retention of oral dosage forms in the stomach.

Ex: Floating DDS , Bioadhesive DDS

FLOATING DRUG DELIVERY SYSTEM

Floating systems have the bulk density lower than that of gastric fluid, and therefore remain floating in the stomach for a prolonged period.

Three major requirements for FDDS formulations are

1. It must form a cohesive gel barrier
2. It must maintain specific gravity lower than gastric contents
3. It should release contents slowly to serve as a reservoir.

• **FLOATING SYSTEMS:**

Invitro-Invivo Evaluation:

Various parameters that need to be considered are,

1. **Physiological Parameters:** Age, sex, posture, food, bioadhesion, health of subject and GIT condition.
2. **Galenic Parameters:** Diametrical size, flexibility and density of matrices
3. **Geometric Parameters:** Shape
4. **Control Parameters:** Floating time, specific gravity, dissolution, content uniformity, hardness and friability

Evaluation of Floating Systems:-

1. Specific Gravity: Displacement method using benzene
2. Floating time: Usually performed in simulated gastric and intestinal fluids.

900 ml of 0.1 N HCl at 37°C in USP dissolution apparatus

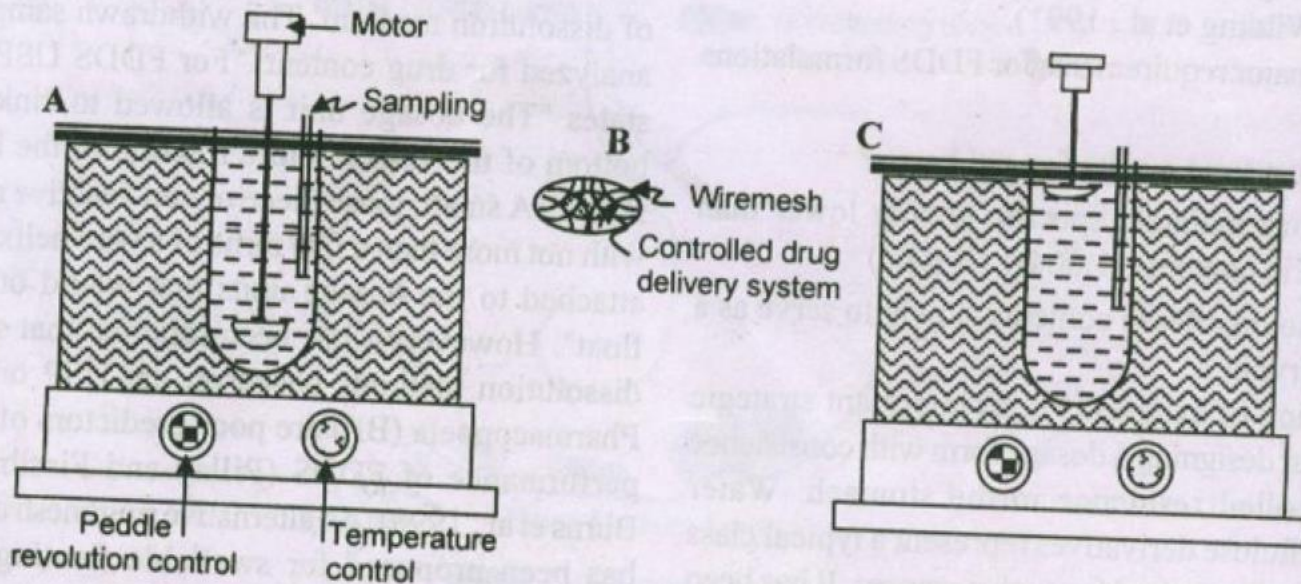


Fig. 5-3 (A) USP Paddle Type Dissolution Apparatus (B) Controlled Drug Delivery System in Wire Mesh (C) Modified USP Dissolution Apparatus

Marketed Preparations of Floating Drug Delivery System

S. no	Product	Active Ingredient
1.	Madopar	Levodopa and benserzide
2.	Valrelease	Diazepam
3.	Topalkan	Aluminum magnesium antacid
4.	Liquid gavison	Alginic acid and sodium bicarbonate

In Vitro Floating and Dissolution Performance

Drug (Polymer Used)	Floating Media/Dissolution Medium and Method
Pentoxifyllin (HPMC K ₄ M)	500 mL of artificial gastric fluid pH 1.2 (without pepsin) at 100 rpm using USP XXIII dissolution apparatus. The time taken by the tablet to emerge on the water surface (floating lag time) and time until it floats on water surface was measured
Piroxicam (microspheres) (Polycarbonate)	For dissolution: 900 mL dissolution medium in USP paddle type apparatus at 37°C at 100 rpm
Furosemide	Tablet were placed in a 400-mL flask at pH 1.2 and both the time needed to go upward and float on surface of the fluid and floating duration were determined.
Ampicillin (Sodium alginate)	For dissolution: 500 mL of distilled water, JP XII disintegration test medium No.1 (pH 1.2) and No.2 (pH 6.8) in JP XII dissolution apparatus with paddle stirrer at 50 rpm

In Vivo Evaluation

Drug (Polymer)	Method
Tranilast (Eudragit S (BaSo ₄))	Two healthy male volunteers administered hard gelatin capsules packed with microballons (1000 mg) with 100 mL water. X-ray photographs at suitable intervals were taken.
Floating beads	Gamma scintigraphy: In vivo behavior of coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers of mean age 34 yrs
Pentoxifyllin	Four healthy beagle dogs (fasted for 24 hours). Tablet was administered with 100 mL of water for radiographic imaging. The animal was positioned in a right lateral/ventrodorsal recumbency
Sulphiride	Three 3.5-kg white male rabbits 10 mg of the drug/kg body weight was administered in a crossover manner with a 14-day washout period between dosing. Both IV and oral dosage form were given.

BIO ADHESIVE DRUG DELIVERY SYSTEM

- Bio-adhesive is the term that describes the adhesion of a polymer to a biological substrate.
- If adhesion is restricted to the mucosal surface – Mucoadhesion.
- Immobilization of drug at the mucosal surface would result in;
 - ✓ A prolonged residence time
 - ✓ A localization of the drug at a target site
 - ✓ Increase in drug concentration gradient due to the contact of particles with mucosal surface.
 - ✓ Prevents the enzymatic degradation in the GIT.

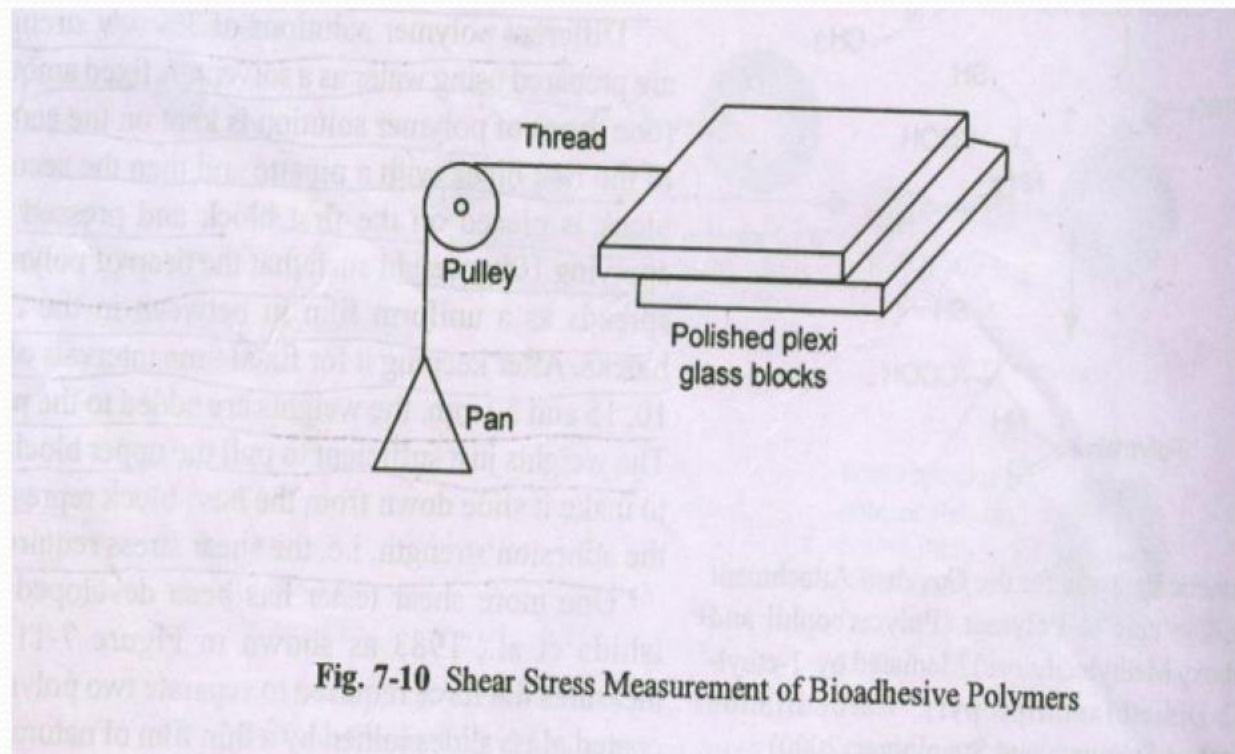
Evaluation of Bioadhesive system:

Invitro Evaluation:-

- Dissolution apparatus either paddle or basket
- Diffusion membrane method
- Simple incubation of the formulation in the medium.

Evaluation of bio-adhesion properties:

1. Shear Stress Measurement of Bioadhesive Polymer:



2. Detachment force measurement:

- Used to measure muco-adhesive capacity of different polymers.
- $F = 0.00981 W/2$

F-the force required to pull the tablet

W-amount of water.

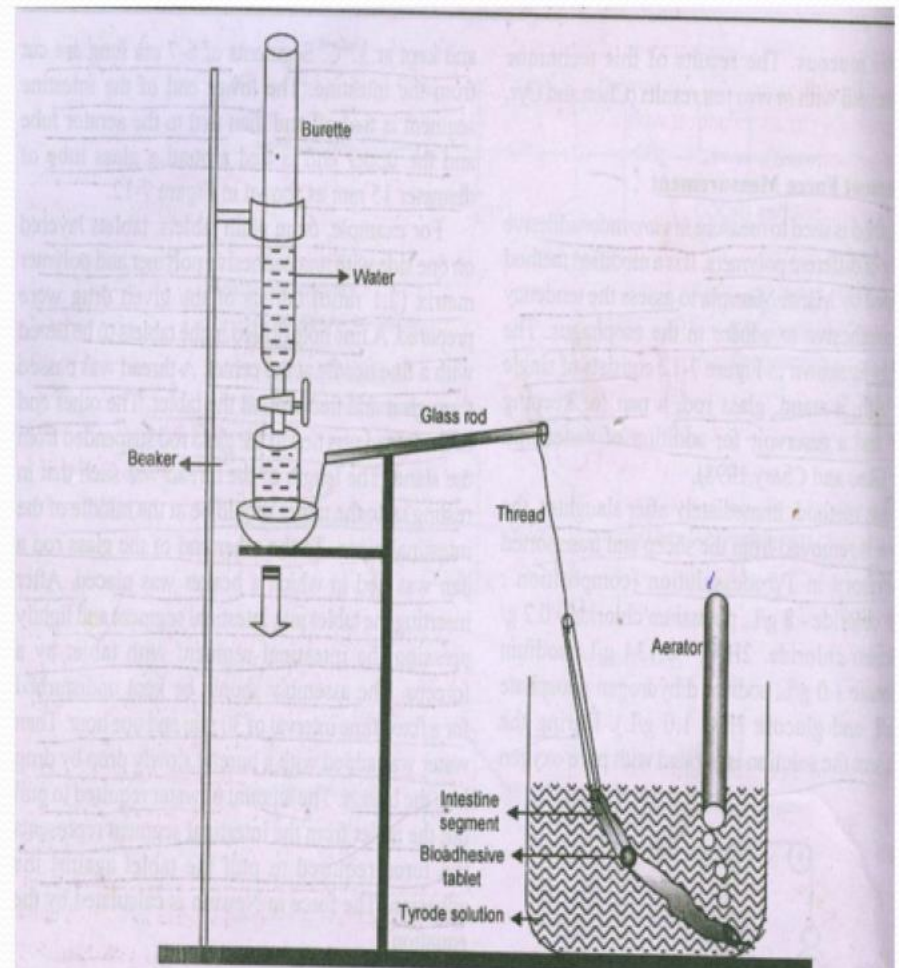
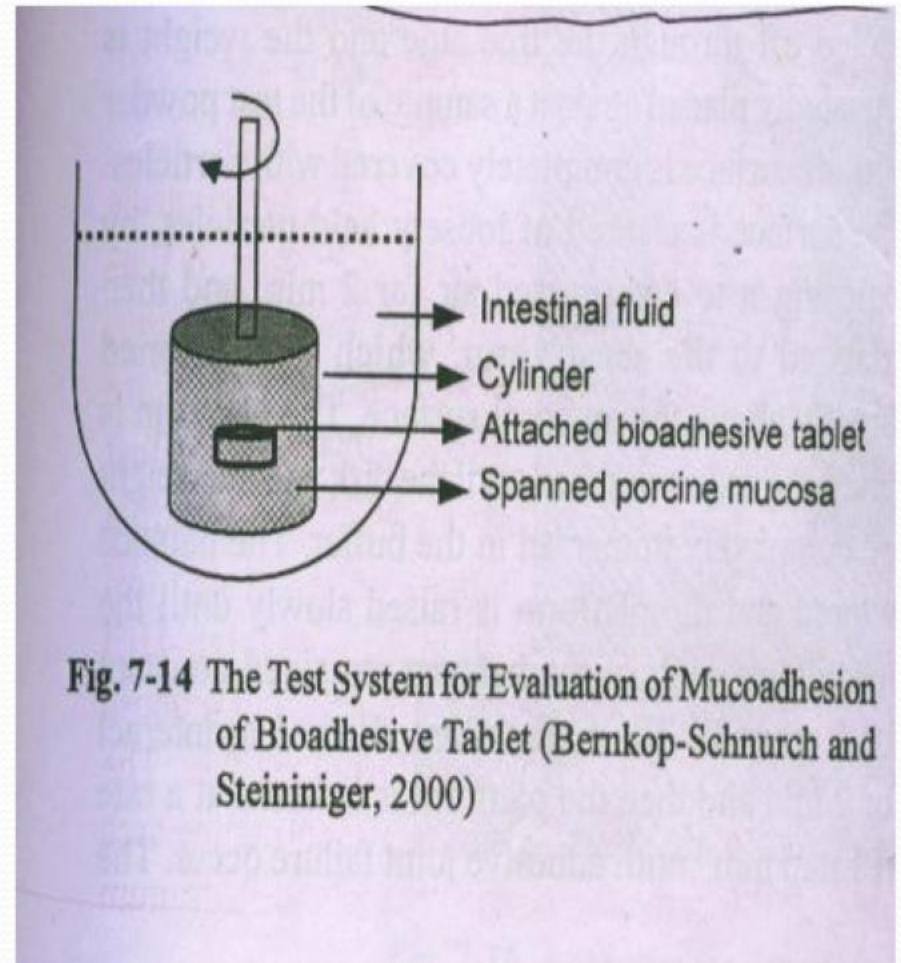


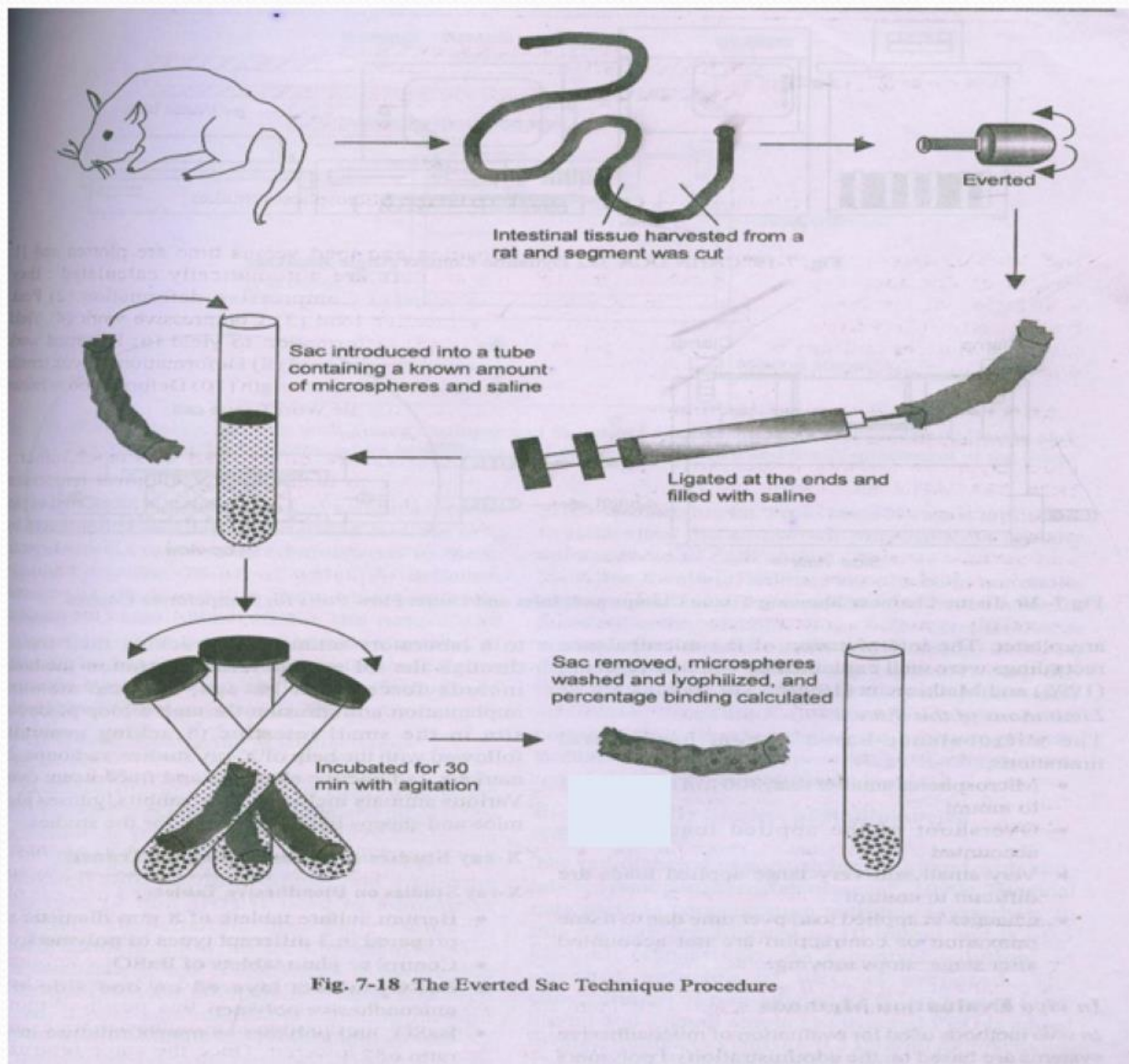
Fig. 7-12 Assembly Developed for Detachment Force Measurement (Rao and Chary, 1998)

3. Muco-adhesion studies:

- To evaluate the binding to the mucosa as well as the cohesiveness of the tablet.
- 100mM TBS pH6.8 at $37 \pm 0.5^{\circ}\text{C}$, cylinder rpm 250.



4. EVERTED SAC TECHNIQUE



In vivo Evaluation of Bioadhesive system :-

- Based on the administration of polymers to a laboratory animal and tracking their transit through the GI system.
- Tracking followed with the help of X-ray studies, radioopaque markers, radioactive elements and fluorescent dyes.

X-ray studies for monitoring GI transit:

1.X-ray studies on bioadhesive Tablets:

- Barium sulfate tablets of 8 mm diameter are prepared in 3 different type of polymers
- Control or plain tablets of BaSO_4 .
- BaSO_4 tablets layered on one side with mucoadhesive polymer
- BaSO_4 and polymer as matrix mixture in the ratio of 2:1.

2.X-ray GI Transit Monitoring of Radioopaque Microspheres:

- 200 mg barium sulfate loaded microspheres are suspended in a 1 ml 0.9% NaCl.
- Male rats are anaesthetized with methoxyflurane .

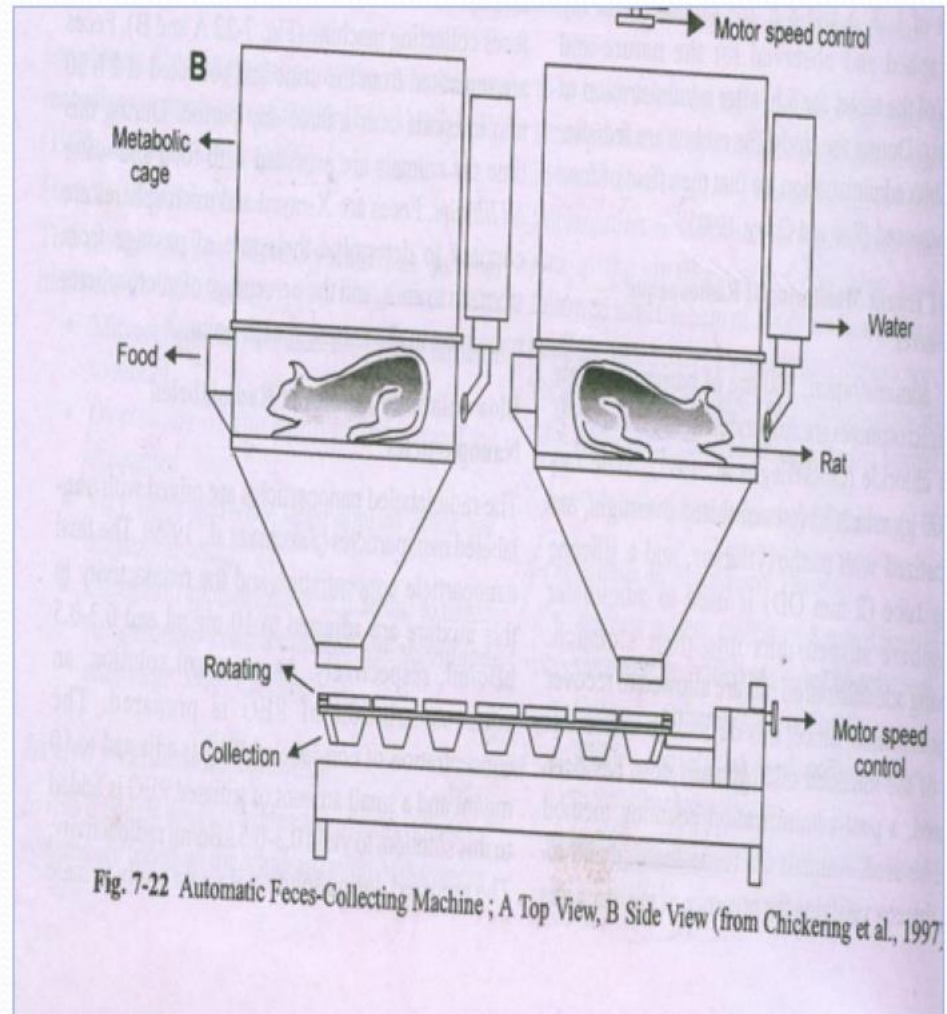


Fig. 7-22 Automatic Feces-Collecting Machine ; A Top View, B Side View (from Chickering et al., 1997)

Buccal Bioadhesive Drug Delivery

- Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery
- Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver.
- Commercially available buccal bioadhesive delivery systems:
 - a) Sublingual mucosal delivery of Nitroglycerin tablet: Susadrin[®]
 - b) Buccal mucosal delivery of Prochlorperazine tablet: Buccastem[®]
 - c) Buccal mucosal delivery of Nicotine: nicorette[®]

Evaluation of Buccal Delivery System

Evaluation of buccal patches:

Patch hydration: The unprotected patch was covered by an aqueous medium and its weight was plotted as function of time to evaluate the rate of water uptake by the patches. The swelling ratio and rate were calculated.

- The extent of hydration after 10 hr was approximately 200% with pH 2.6 and around 1000% with pH 7.

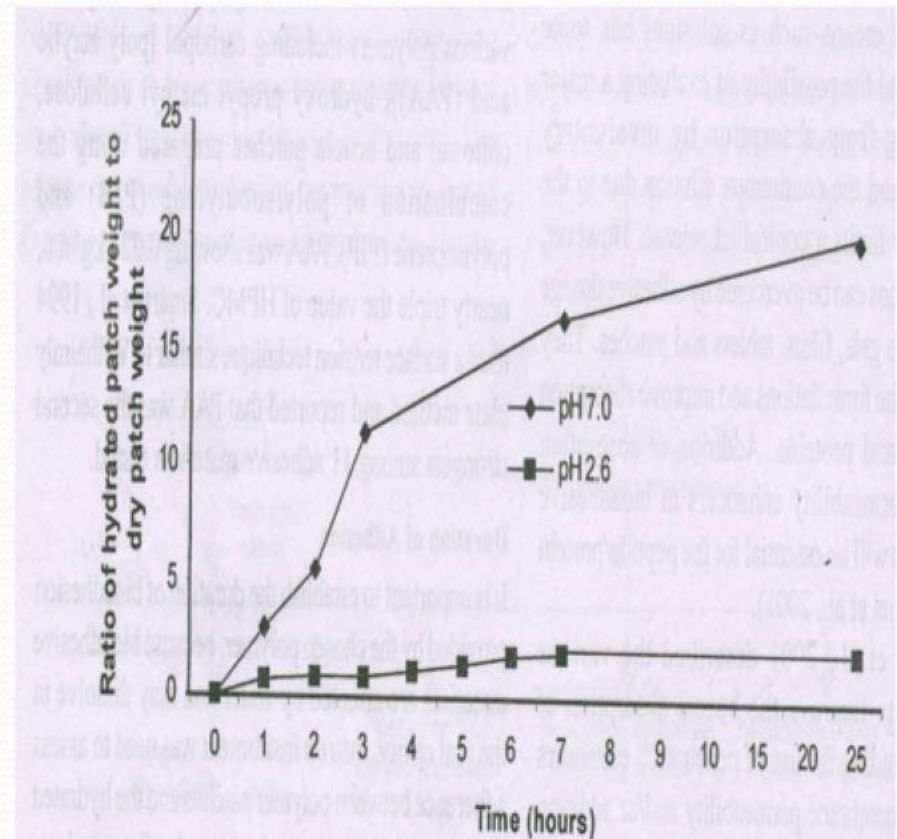


Fig. 7-30 Rate of Uptake of Water into PAA/PIB/PIP Patches at pH 2.6 and 7.0

- Evaluation of Buccal patches:

Drug release: Two methods are used to assess the drug release from patches.

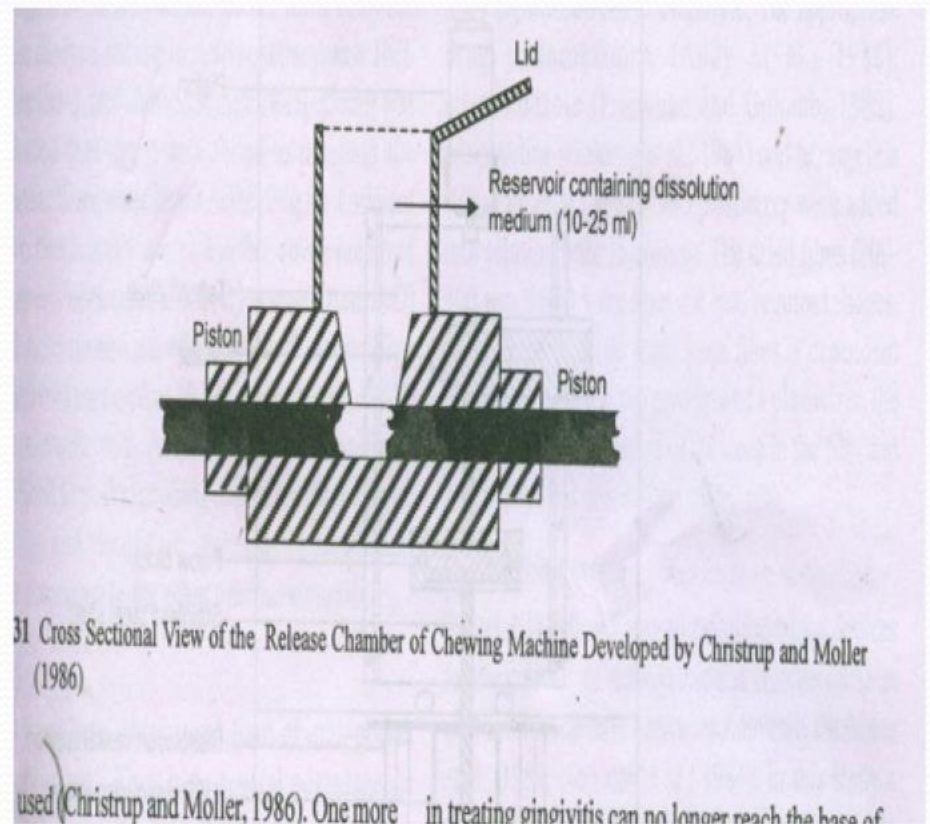
a) Dissolution using modified paddle apparatus.

b) Diffusion cell method:

Diffusion cell for determining drug release is considered an improvement over dissolution in that only one face of the patch is in contact with the medium, that mimics the moist surface of the buccal cavity.

Evaluation of drug release from chewing gums:

The cycle rate (chewing rate) is usually set at 60/min, and 20 ml of medium equilibrated to 37°C is used.



COLON SPECIFIC DRUG DELIVERY SYSTEM

- Colon specific drug delivery systems significantly differ from other systems by not releasing the drug in the stomach and small intestine. They release the drug specifically in the colon.
- Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases of the colon, but also the delivery of proteins and therapeutic peptides.
- The site specific delivery of the drugs to the target receptor sites has the potential to reduce the side effects and improve the pharmacological response.
- The colon has a longer retention time for poorly soluble drugs.
- Protect peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum which leads to greater systemic bioavailability.

- Evaluation of colon drug delivery system:

Various invitro -invivo evaluation techniques have been developed and proposed to test the performance and stability of the colon specific drug delivery system.

Invitro models:

- A) In vitro test for intactness of coatings and carriers in simulated conditions of the stomach and intestine

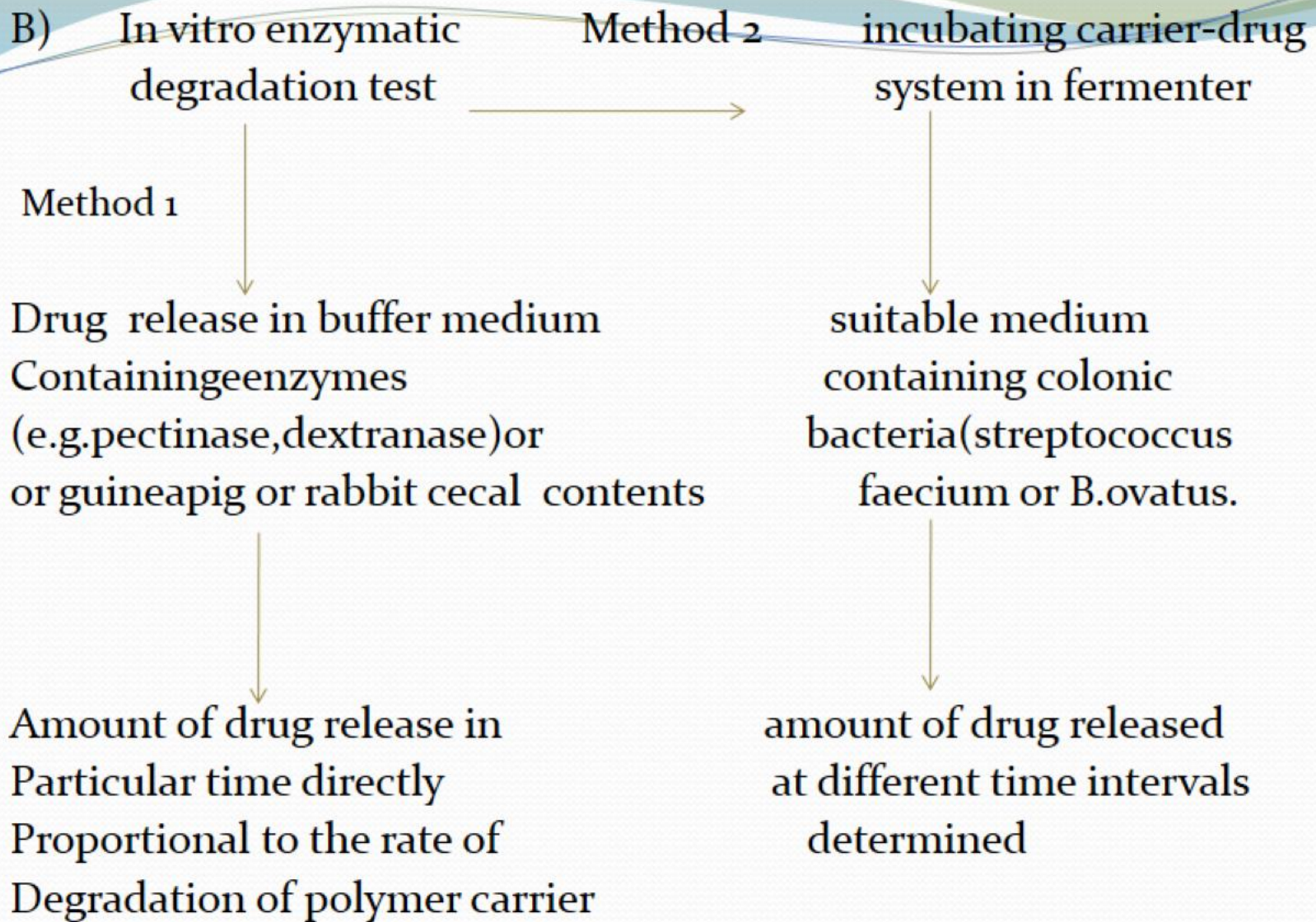
↓ Step 1

Drug release study in 0.1N HCl for 2 Hrs
(mean gastric emptying time)

↓ Step 2

Drug release study in phosphate buffer in 3 Hrs
(mean small intestine transit time)

- Invitro model:



Evaluation of colon drug delivery system:

- In-vivo animal models:
 - A number of animals have been used to evaluate the delivery of drugs to the large intestine of mammals.
 - While choosing a model for testing a colon drug delivery system, relative model for the colonic disease should also be considered.

For Ex. Guinea pigs are commonly used for experimental IBD model. The eating behavior ,anatomy, and physiology of GIT of guinea pigs are comparable to human.

The distribution of azo reductase and β -glucuronidase activity in the GIT of rat and rabbit.

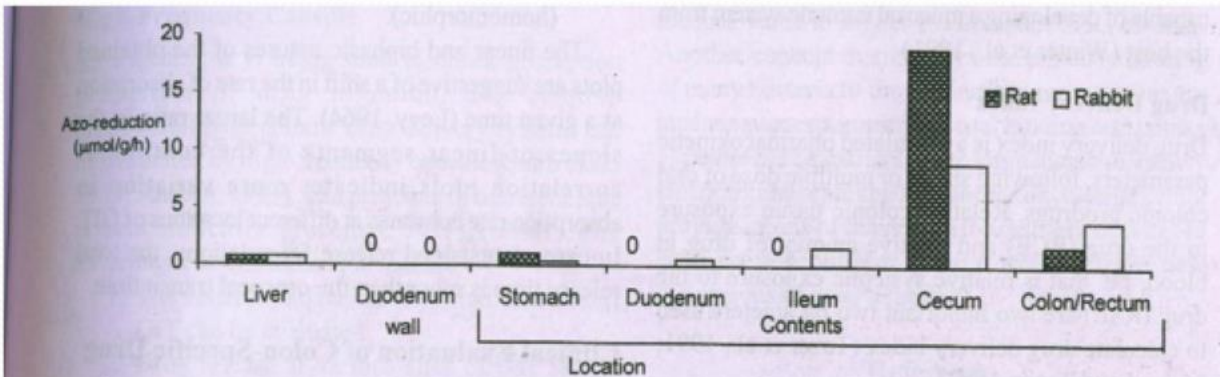


Fig. 6-39 The Distribution of Azo-reductase Activity in the GIT of Rat and Rabbit, 0 = not Detected. The results are expressed as μmol of product formed per g of tissue per h using the substrate 1,2 dimethyl-4-(4-carboxyphenylazo)-5-hydroxybenzene under anaerobic conditions upto 1 hour with homogenate of the tissue in 0.1 mol/l phosphate buffer (Renwick, 1982)

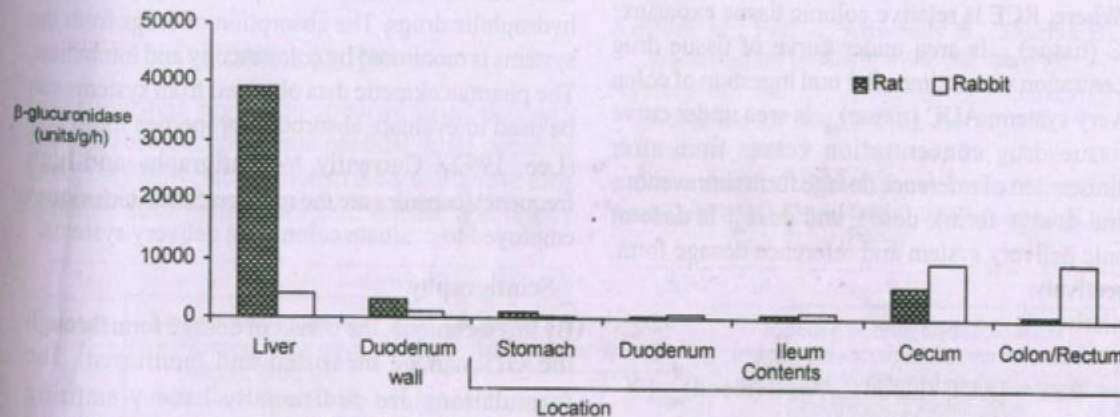


Fig. 6-40 The Distribution of β -Glucuronidase Activity in the GIT of Rat and Rabbit, Measured by Using Phenolphthalein β -D-Glucuronide as Substrate Under Anaerobic Conditions upto 1 h with an Homogenate of the Tissue in 0.1 mol/l Phosphate Buffer (Renwick, 1982)

Clinical evaluation of colon specific drug delivery system:

- Currently γ -scintigraphy and high frequency capsules are the preferred technique are employed to evaluate colon DDS.

γ -scintigraphy :

- The transit of dosage form through the GIT can be measured and monitored.
- The γ -radiations that emerge from the subject are collimated and detected by a crystal. The energy is transformed to light scintillation and amplified to give digitalized results.

Clinical evaluation of colon specific drug delivery system:
High -frequency capsule:

Smooth plastic capsules containing small latex ballon,
drug and radiotracer taken orally.



Triggering system
(High Frequency Generation)

release of drug and radio tracer
triggered by an impulse, the release
is monitored in different parts of
GIT by Radiological localization

CONCLUSION

- The primary aim of oral controlled DDS is to achieve more predictable and increased bioavailability.
- Now a days most of the pharmaceutical scientists are involved in developing the ideal oral DDS. This ideal system have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site.
- In vitro-in vivo evaluation of a drug product is a tool to ensure
 - Performance characteristics
 - Control batch to batch quality

REFERENCES

- Donald.L.Wise.,Handbook of Pharmaceutical Controlled Release Technology.,
- Yie.W.Chien.,Novel Drug Delivery Systems.,
- S.P. Vyas and Roop.K.Khar.,Controlled Drug Delivery.,
- N.k.Jain.,Progress in Controlled and Novel Drug Delivery Systems.,
- Gangadharappa H.V.,Pramod Kumar T.M and Shiva Kumar H.G.,Gastric Floating Drug Delivery Systems:A Review.,Ind J.Pharm.Educ41(2007).
- Alka Gupta.Sanjay Garg,R.K.Khar.,Mucoadhesives Buccal Drug Delivery Systems:A Review Article.
- M.K.Chourasia.S.K.jain.,Pharmaceutical Approches to Colon Targeted Drug Delivery Systems.J Pharm Sci(2003).
- Arora S, Ali J, Ahuja A, Khar RK, Baboota S. Floating Drug Delivery Systems: A Review. *AAPS PharmSciTech*. 2005



THANK U