COLON SPECIFIC DRUG DELIVERY SYSTEM

CONTENTS

1. INTRODUCTION

DEFINITION: Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon).

Why is colon targeted drug delivery needed?

- Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects.
- Site-specific or targeted drug delivery system would allow oral administration of peptide and protein drugs, colon-specific formulation could also be used to prolong the drug delivery.
- Colon-specific drug delivery system is considered to be beneficial in the treatment of colon diseases.
- The colon is a site where both local or systemic drug delivery could be achieved, topical treatment of inflammatory bowel disease, e.g. ulcerative colitis or Crohn's disease. Such inflammatory conditions are usually treated with glucocorticoids and sulphasalazine (targeted).

- A number of others serious diseases of the colon, e.g. colorectal cancer, might also be capable of being treated more effectively if drugs were targeted to the colon.
- Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/or susceptible to chemical and enzymatic degradation in the upper GI tract, highly affected by hepatic metabolism, in particular, therapeutic proteins and peptides.

Advantages of Colon Targeted Drug Delivery System

1. Time dependent system: small intestine transit time fairly consistent.
2. pH dependent system : formulation is well protected in the stomach.
3. It has minimum side effect.
4. Unnecessary systemic absorption does not occur.
5. Colonic drug delivery can be achieved by oral and rectal administration.
6. Colon specific formulation could be used to prolong drug delivery.
7. Enhance the absorption of poorly absorbed drug.

8. By this poorly absorbed drug molecule may have improved bioavailability.
9. It helps in efficient vaccine delivery.

Disadvantages of Colon Drug Delivery

1.Time dependent system :

* Substantial variation in gastric retention times
* transit through the colon more rapid than normal in patients with colon disease.

2.pH-dependent system :

* pH level in the small intestine and colon vary between and within individuals.
* pH level in the end of small intestine and caecum are similar.
* Poor site specificity.

3.Microflora activated Systems :

* Diet and disease can affect colonic micro flora.
* Enzymatic degradation may be excessively slow.

Nocturnal Pathologies

4.Manufacturing of such formulation on an industrial scale is often complicated and expensive.

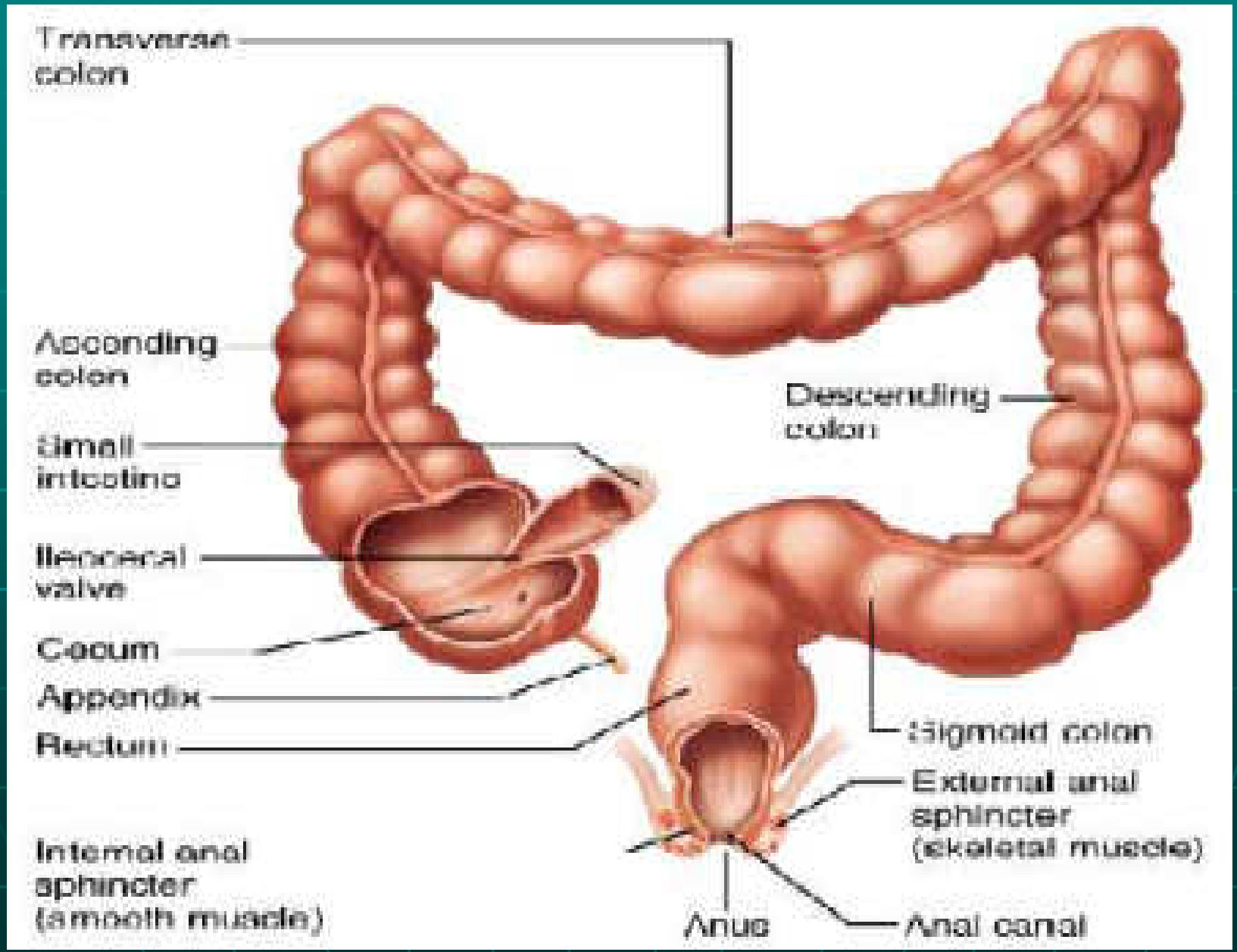
Limitations and Challenges in Colon Targeted Drug Delivery System

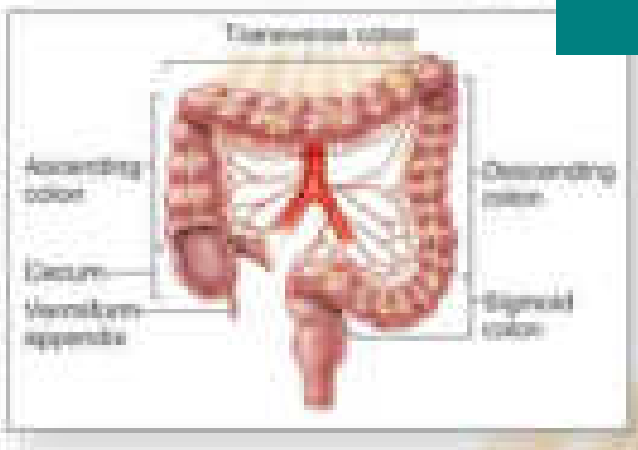
As a site for drug delivery, the colon offers

i) a near neutral pH,
ii) reduced digestive enzymatic activity,
iii) a long transit time and increased responsiveness to absorption enhancers;

- Successful delivery - the drug to be in solution form and the stability of the drug.
- The drug could potentially bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or fecal matter.
- The resident micro flora could also affect colonic performance via metabolic degradation of the drug.
- Lower surface area and relative 'tightness' of the tight junctions.
- Cytochrome P450 3A class of drug-metabolizing enzymes has lower activity in the colonic mucosa.

2.ANATOMY AND PHYSIOLOGY OF COLON

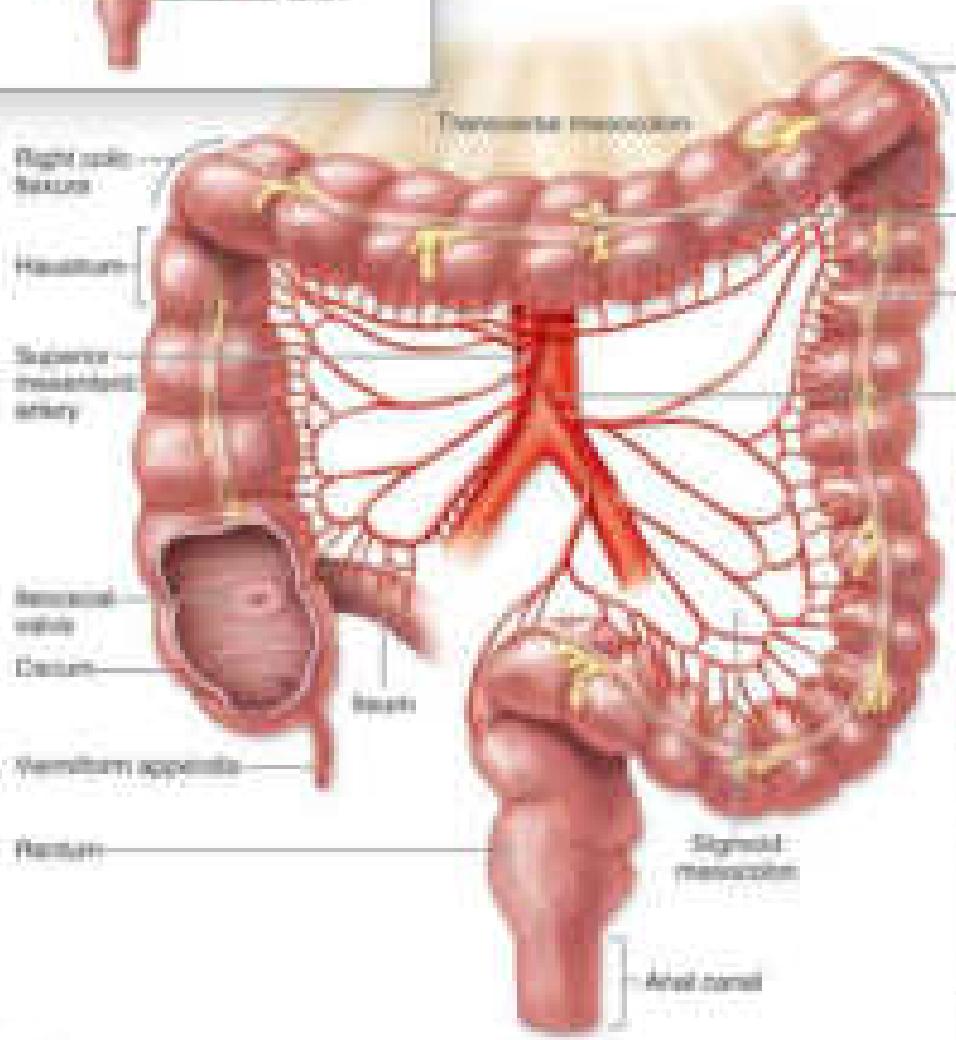


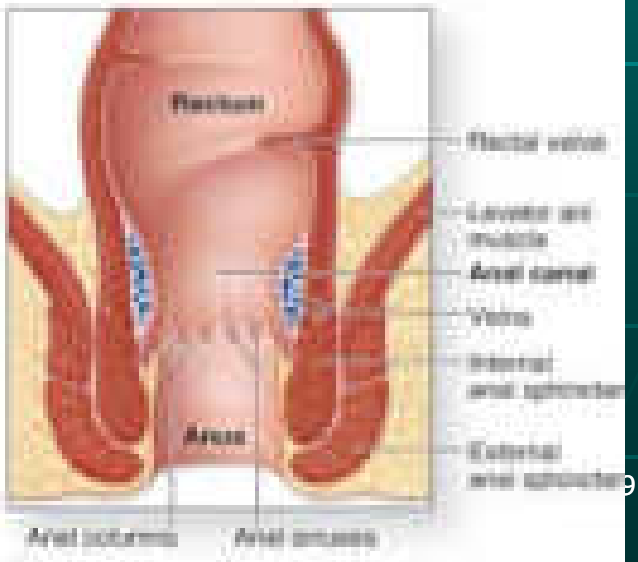


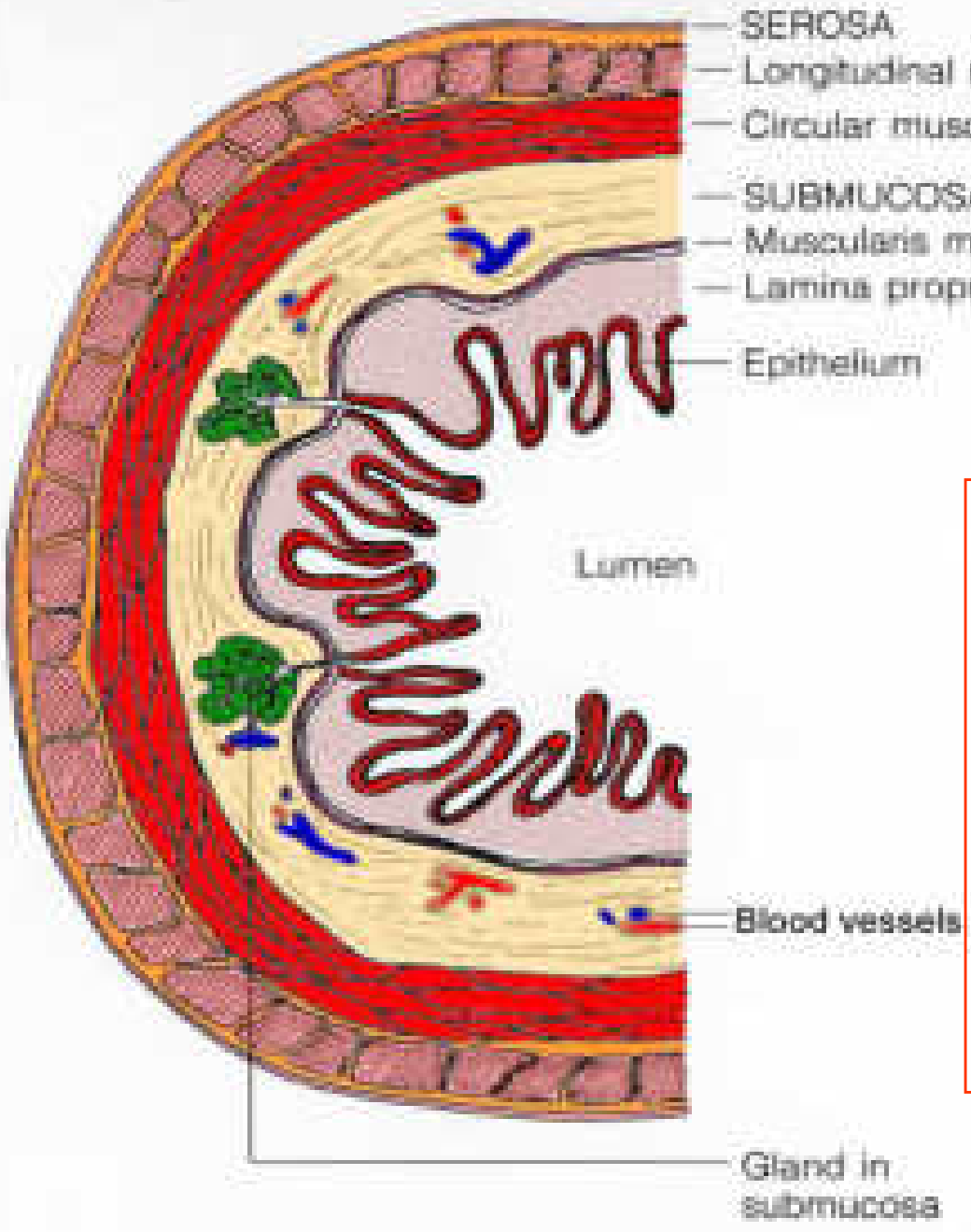
Length 1.5m

Diameter 9cm in caecum and 2cm in sigmoid colon.

Avg diameter – 6.5cm







Functions:

- Growth of colonic microbes.
- Storage reservoir for fecal contents.
- Expulsion of contents at appropriate time.
- Absorption of sodium, water from lumen, concentratating the fecal matter and secretion and excretion of potassium and bicarbonate.

The colon is a cylindrical tube which is lined by four layers:

i) **Serosa:** the external coat of the large intestine and consists of areolar tissue that is covered by single layer of squamous mesothelial cells.
ii) **Muscularis externa**: This is composed of an inner circular layer of fibers that surrounds the bowel.
iii) **Sub mucosa**: is the layer of connective tissue that lies immediately beneath the mucosa.
iv) **Mucosa:** it lines the lumen of the colon.

Location	pH	Location	pH
1)Stomach	1.5 – 2.0	Ileum	6.7 – 7.3
Fasted condition	1.5 – 2.0	3.Largeintestine Right colon	 6.4
Fed condition	5.0 – 6.5	Mid colon	6.6
2.Smallintestine	6.0 – 7.5	Left colon	7
Jejunum	6.4	Rectum	7

The major **functions** of the colon are as follows:

1) Creation of suitable environment for the growth of colonic microorganisms.
2) Storage reservoir of faecal contents.
3) Expulsion of the contents of the colon at a suitable time; and
4) Absorption of water and Na^+ from the lumen, concentrating the fecal content, and secretion of K^+ and HCO_3.

3.FACTORS GOVERNING THE COLONIC DRUG ABSORPTION

These factors include physiological, pathological and pharmaceutical.

Physiological Factors:

1) Gastrointestinal Transit:

In fasted state, the motility proceeds through 4 phases occurring in the stomach and small intestine that span over a period of 2-3hr.

Phase I: quiescent period of 40-60 min.

Phase II: intermittent contractions for a period of 40-60 min.

Phase III: a period of intense contractions sweeping material out of the stomach and small intestine.

Phase IV: dissipation of contractions.

2) Small Intestinal Transit:

•Normally, the small intestinal transit is not influenced by the physical state, size of the dosage form and the presence of food in the stomach.

•The mean transit time of the dosage form is about 3-4hr to reach the ileocecal junction and the time period is consistent.

•The dosage form is exposed to enzymes such as esterase, lipase, amylase, protease and brush border enzymes present in small intestine.

•The release of drugs from the prodrug based systems and stability of peptides can be affected by bacterial contents in the ileum.

3) Colonic Transit:

The total time for transit tends to be highly variable and influenced by number of factors such as diet, in particular dietary fiber content, mobility, stress, disease and drugs, gender, size of dosage form.

***b. Effect of diet on colonic transit*:** The effect of eating a meal on a colonic transit of radiolabelled tablet shows that the ingestion of food accelerates the movement of the tablet through the ileocecal junction of the colon.

c. Effect of the disease on the colonic transit: Diseases affecting colonic transits have important implications for drug delivery. The disease which cause narrowing of the small intestinal tract e.g. Crohn's disease may pose obstruction to solid formulations and hence increase the transit time; diarrhea will result in an increase in colonic motility and constipation in decrease in colonic motility.

4.Gastric Emptying:

The residence time in the stomach is important for single unit sustained release systems like tablets, which are designed to deliver drug in large intestine.

5. Stomach and intestinal pH:

•In the stomach the pH is 1.5-2 and 2-6 in fasted and fed state conditions, respectively.

•In small intestine, the pH increases slightly from 6.6-7.5 and decreases to 6.4 in right colon.

6. Colonic micro flora and enzymes:

•A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GI tract.

•Over 400 species of bacteria are found in the colon, which are predominantly anaerobic such as Bacteroids, Bifidobacterium, Eubacterium and Clostridium and a small number of fungi.

•The enzyme catalyzed metabolic reactions carried out by enzymes and secretary products released from micro flora can be used to deliver drugs selectively to colon.

- Azoreductase produced by the colonic micro flora plays an important role in development of a number of delivery systems, particularly in catalyzing the release of 5-amino salicylic acid from variety of prodrugs.

7.Colonic absorption:

- The absorption is influenced by the transport of water, electrolytes and ammonia across the mucosa, and it is more in proximal colon than distal colon.
- The absorption properties of colon are generally studied by invitro monolayers of colon carcinoma cell lines.
- Drug molecules pass from the apical to basolateral surface of the epithelial cells by

a) Passing through colonocytes (transcellular transport), or

b) Passing between adjacent colonocytes (paracellular transport)

- The colonic epithelial permeability of many drugs can be modified by the use of **absorption enhancers** which act by various mechanisms.

a) Disruption of the intracellular occluding junction complex opens the paracellular route

b) Modification of epithelial permeability by denaturing membrane proteins

c) Modification of lipid protein interactions and disruption of the integrity of lipid barrier by colonic enterocytes.

- Protease inhibitors such as aprotinin and bacitracin enhance the absorption of peptides and proteins by preventing their destruction from amino peptidase activity.
- The use of absorption enhancers in pharmaceutical formulations is limited since they are non-specific in action, produce local irritation and lead to irreversible changes in permeability of colon.

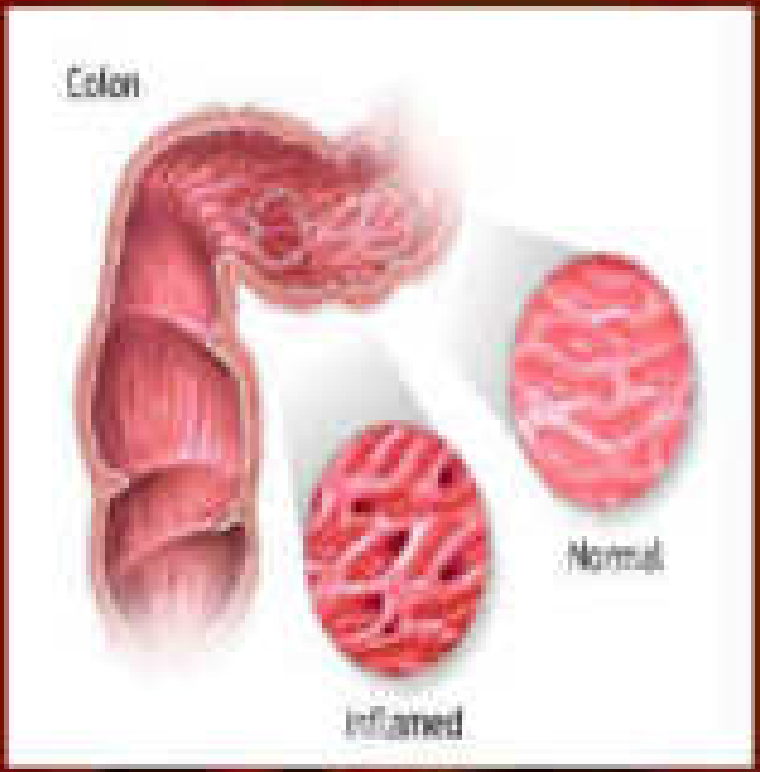
8.Gastrointestinal disease state:

General intestinal diseases such as IBD (inflammatory bowel disease), Crohn's disease, constipation, diarrhea and gastroenteritis may affect the release and absorption properties of colon-specific drug delivery system.

Disease	Effects on colonic absorption of drugs
IBD (Crohn's disease and ulcerative colitis)	Diarrhea, fever, anemia, obstruction of lymphatic drainage and hyperplasia of lymphoid tissue causing malabsorption of fats and highly lipophilic drugs.
Diarrhea	Hyper motility and frequent passage of hypertonic liquid feces.
Antibiotic associated colitis	Overgrowth of Clostridium difficile and its toxin production, which alters mucosal surface area may reduce absorption.
Gastroenteritis	Diarrhea due to increased mucosal secretion may effect the performance of formulations.

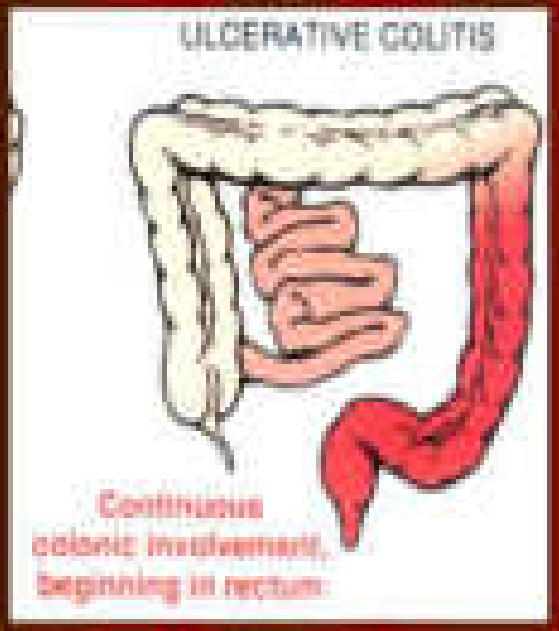
Disorders of Colon

- Inflammatory bowels disease

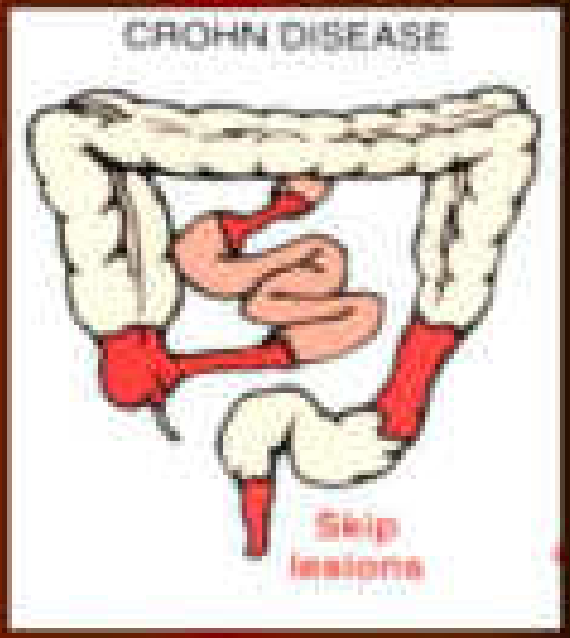


IBD

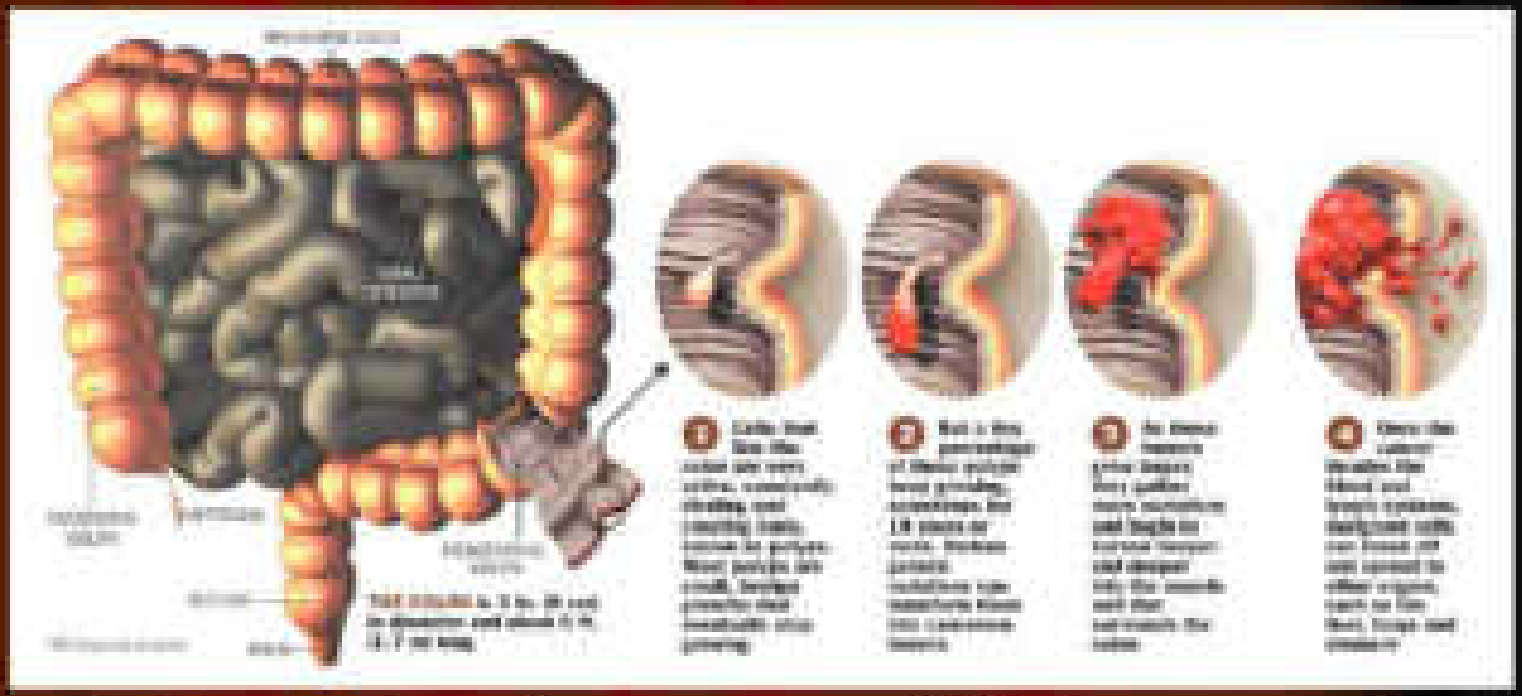
- Ulcerative colitis



- Chron's disease



Colon Cancer



- Colon and rectum cancer - 10% in men and 11% women
- >55,000 Total Colorectal Cancer Deaths

The pathological states also have pronounced effect on colonic absorption of drug molecules by affecting the colonic transit e.g. diarrhea will result in increase in the gastric motility and constipation results in decrease in colonic motility.

Pharmaceutical factors:

1.Drug carriers:

•The selection of carrier for particular drug candidate depends on the physicochemical nature of drugs as well as disease for which the system is to be used.

•The factors such as chemical nature, stability and partition coefficient of the drug and the type of absorption enhancer chosen influence the carrier selection.

•The choice of drug carrier depends on the functional groups of the drug molecule.

•The carriers, which contain additives like polymers (may be used as matrices and hydrogels or coating agents) may influence the release properties and efficacy of the systems.

2.CHARACTERISTICS OF DRUGS AND OTHER AGENTS THAT FAVOR COLONIC DELIVERY:

The permeability of the colonic epithelium may not be sufficient for achieving a transport rate required for therapeutic activity. This hurdle may be overcome, by using penetration enhancers.

Some common colonic drug absorption enhancers

- Non-steroidal anti-inflammatory agents (NSAIDS) (e.g., indomethacin and salicylates)
- Calcium ion-chelating agents (e.g., EDTA and citrate)
- Surfactants [e.g., polyoxyethylene lauryl ether (BL-9EX) and saponin]
- Bile salts (e.g., taurocholate and glycocholate)
- Fatty acids (e.g., sodium caprate, sodium caprylate, sodium laurate, and sodium oleate),Mixed micelles [e.g., monoolein–taurocholate, oleic acid–taurocholate, oleic acid–polyoxyethylene hydrogenated castor oil (HCO 60) and oleic acid–glycocholate]
- Other agents [e.g., acylcarnitine, azone (1-dodecylazacycloheptan-2-one), dicarboxylic acids and enamine]

Some enhancers that are more colon-specific include ethylacetoacetate, which must be first metabolically transformed to enamine.

Drug candidates for colonic drug delivery:

- Ulcerative colitis and crohn's disease - Sulfasalazine
- Pinaverium bromide - local treatment of irritable bowel syndrome.
- for colon cancer - 5- fluoro uracil, doxorubicin, and nimustine.
- drugs for amoebiasis – metronidazole
- Drugs which produce less side effects in colon.
  - Dexamethasone, Prednisolone and hydrocortisone.
  - Nicotine is under study (for ulcerative colitis).
- Peptide and protein drugs - like calcitonin, interferon, interleukins, erythropoietin, GH, and insulin. (under study)
- Drugs that are not stable or degrade in upper part of git.
- The drug should have good absorption from colon for sustained release and delayed release.

4.TARGETTING APPROACHES TO COLON

Various pharmaceutical approaches to colon targeted drug delivery systems are as follows.

1.Covalent linkage of a drug with a carrier

1.1. Azo conjugates

1.2. Cyclodextrin conjugates

1.3. Glycoside conjugates

1.4. Glucuronate conjugates

1.5. Dextran conjugates

1.6.Polypeptide conjugates

1.7. Polymeric prodrugs

2. **Approaches to deliver the intact molecule to the colon**

2.1. ***Coating with polymers***

2.1.1.Coating with pH sensitive polymers

2.1.2. Coating with biodegradable polymers

2.2***. Embedding in matrices***

2.2.1. Embedding in biodegradable matrices and hydrogels

2.2.2.Embedding in pH sensitive matrices

2.3. Time released systems
2.4.Redox sensitive polymers
2.5. Bioadhesive systems
2.6. Coating with micro particles
2.7.Osmotically controlled drug delivery

1.Covalent linkage of a drug with a carrier:

The type of linkage that is formed between the drug and carrier would decide the triggering mechanism for the release of the drug in the colon.

1.1. **Azo conjugates**:

•Microbial azo reductases are predominantly present in the colon which are capable of breaking the azo aromatic bonds.

•Sulfasalazine was introduced for the treatment of rheumatoid arthritis and anti inflammatory disease.

•Chemically it is Salicylazosulphapyridine (SASP), where sulfa pyridine is linked to a salicylate radical by an azo bond.

•The azo bond is broken by the colonial bacteria with the liberation of sulphapyridine and 5-ASA.
•Instead of using low molecular weight promoieties, macromolecular carriers are used to deliver 5-ASA to colon.
•The larger molecular size of polymers limit absorption in upper GIT.
•Polymeric carriers can accommodate large dose of drugs for local as well as systemic drug delivery.
•N-(2-hydroxy propyl) methacrylamide (HPMA) copolymers are used as colon specific drug carriers.
•These carriers designed for site specific drug(5-ASA) release the drug contents following enzymatic degradation or fragmentation of carrier polymer by the microbial azoreductase of the colon.

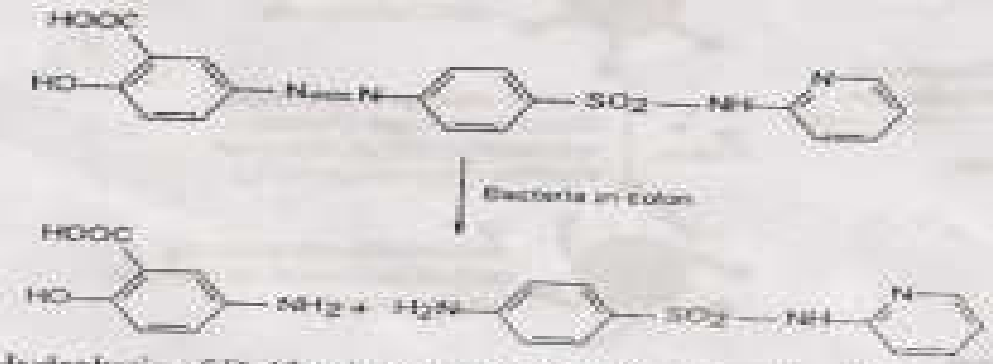


Fig. 6-18 Hydrolysis of Salfasalazine into 5-aminosalicylic acid and Sulphapyridine

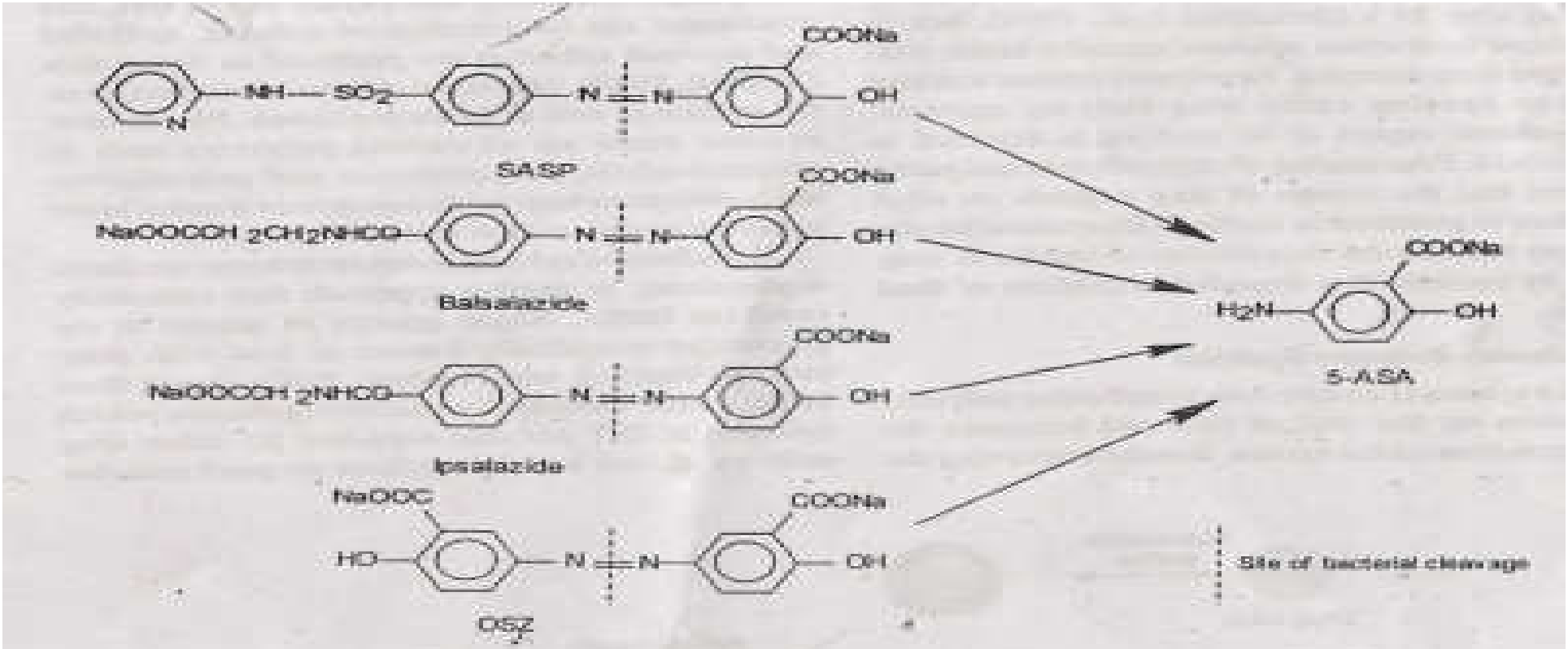


Fig. 6-19 Chemical Structures of SASP (Sodium sulphasalazine), Balsalazide, Ipsalazide and OSZ (Olsalazine) Showing Site of Bacterial Cleavage Leading to Liberation of Active Agent 5-ASA

1.2. Glycoside conjugates:

- The glycosidases produced by human micro flora are β-D-galactosidase, α-L-arabino furanosidase, β-D-xylo-pyranosidase and β-D-glucosidase.
- Particularly, β-glucosidase and β-glucuronidase activity is extensive in human micro flora.

•In colon, glycosides are cleaved by glycosidases of microflora, to liberate aglycon, the active constituent that acts on colon.
•On the basis of this mechanism, numerous prodrugs of dexamethasone, prednisolone and hydrocortisone -with β-D-galactosidases and β-D-glucosides were developed.
•Dexamethasone- β-glucoside conjugate is one of the examples of these prodrugs.
•Budenoside and dexamethasone conjugates of glucuronic acid and dextran prodrugs were synthesized for the treatment of ulcerative colitis

•.

The problems associated with β-glucuronidase activity are: 1.Since β-D-glucuronidase activity is located in intracellular compartment that is inaccessible to its substrates.
2.The hydrolysis of β-D-glucuronides in the luminal contents by mammalian β-D-glucuronidase is insignificant.

4.Cyclodextrin conjugates:

•Cyclodextrins are cyclic oligosaccharides having 6-8 dextrose units linked through 1-4 bonds.

•The cyclodextrin absorption from GIT is limited due to its bulky molecular size and hydrophilic nature.

•They are used as drug carriers for some drugs, which are released in aqueous fluid and remain in GIT.

•The α and β cyclodextrins are more resistant to gastric, salivary and pancreatic enzymes as well as gastric pH than cyclodextrin, which is slowly digested in small intestine, but completely degraded by colonic microflora.

•Hydrophilic cyclodextrins are used to formulate controlled release preparations of many water soluble drugs including peptides and proteins.

•Chemical derivatives of cyclodextrins are more resistant to intestinal hydrolases, absorption is low and they are almost completely excreted in feces.

2.Approaches to deliver the intact molecule to the colon:

2.1. ***Coating with polymers*:**

2.1.1.Coating with pH sensitive polymers:

•The ideal pH sensitive polymers for colon drug delivery are able to withstand the acidic pH of stomach and proximal part of small bowel, and selectively disintegrate in intestinal pH, preferably in ileocecal junction.

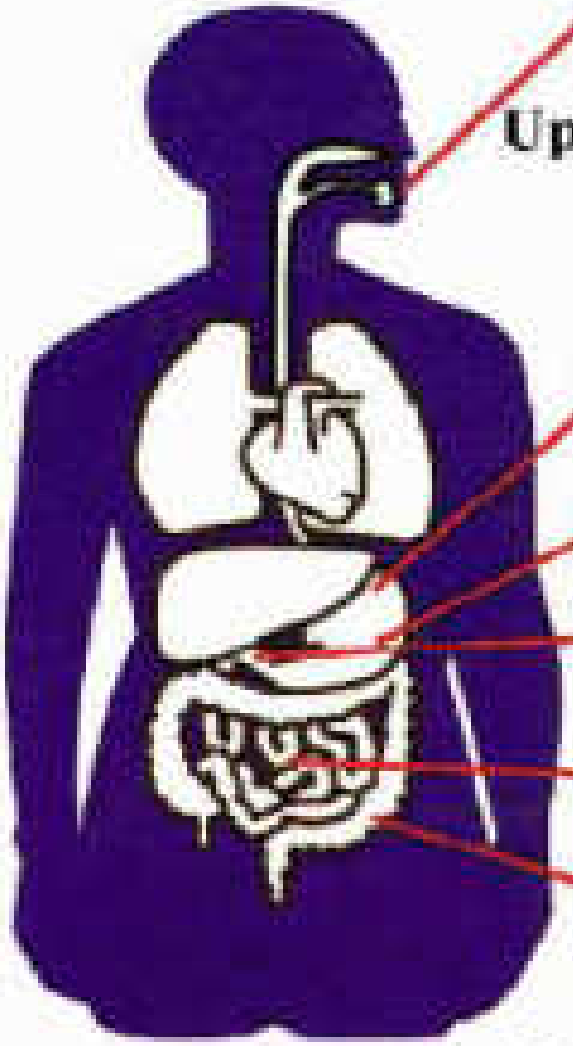
•Most commonly used pH dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit S and Eudragit L.

•Eudragit L100 and S100 are copolymers of methacrylic acid and methyl methacrylate.

•Eudragit L and Eudragit S are soluble at pH 6 and 7 respectively, hence they are used to make acid resistant film coating.

•These polymers were used to develop systems containing drugs such as Salsalzine, pednisolone, insulin and quinolones.

The Human Digestive Tract pH Range Chart



Saliva
6.5 - 7.5 pH
up to 1 minute

Upper Stomach (fundie)
4.0 - 6.5 pH
30 - 60 minutes

Lower Stomach
1.5 - 4.0 pH
1 - 3 hours

Duodenum
7.0 - 8.5 pH
30 - 60 minutes

Small Intestine
4.0 - 7.0 pH
1 - 5 hours

Large Intestine
4.0 - 7.0 pH
10 hours - Several days

Lag phase of ~ 5 h is observed.

•The coating of pH sensitive polymers to the tablets, capsules or pellets provide delayed release and protect the active drug from gastric fluid.

•The threshold pH commonly employed pH sensitive polymers are depicted in the table.

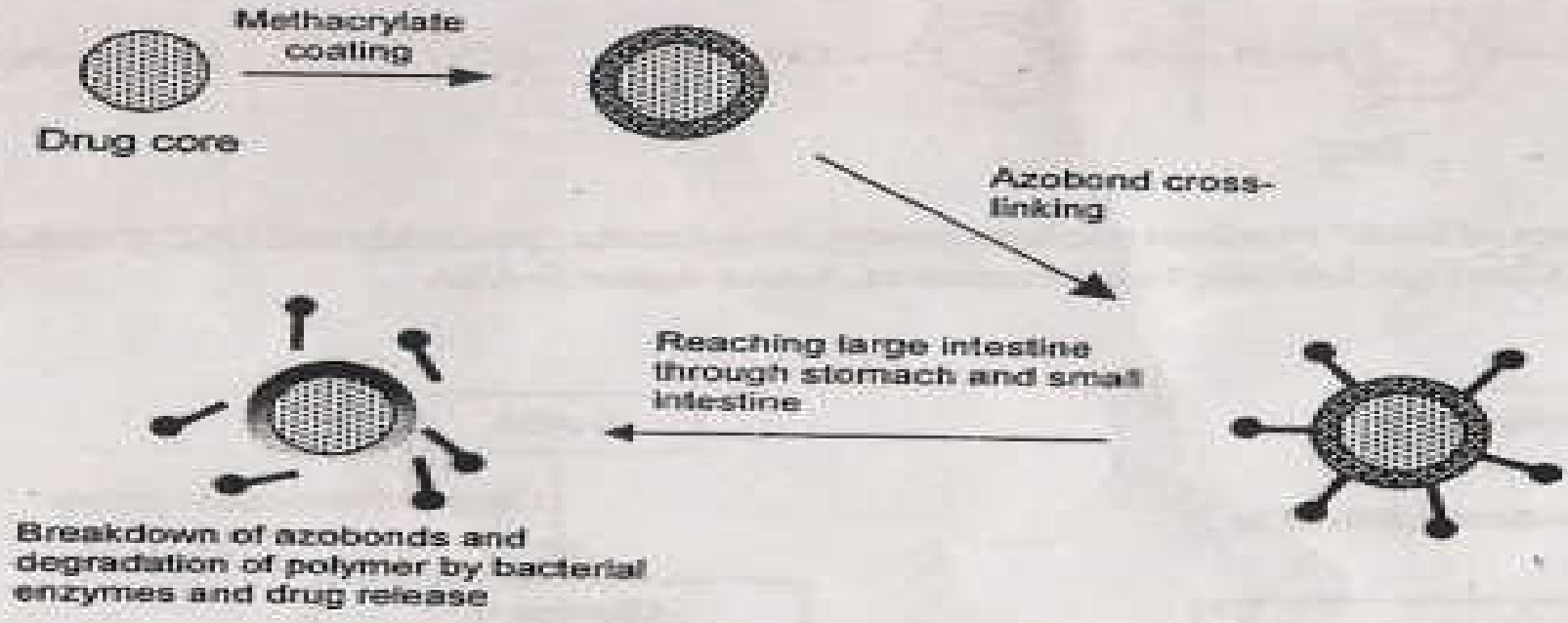
Polymer	Threshold pH
Eudragit® L 100	6.0
Eudragit® S 100	7.0
Eudragit® L –30D	5.6
Eudragit® FS 30D	6.8
Eudragit® L 100-55	5.5
Polyvinyl acetate phthalate	5.0
Hydroxy propyl methyl cellulose phthalate	4.5–4.8
Hydroxy propyl methyl cellulose phthalate 50	5.2
HPMC 55	5.4
Cellulose acetate trimelliate	4.8
Cellulose acetate phthalate	5.0

Microbially degradable polymers used for Colonic drug delivery system.

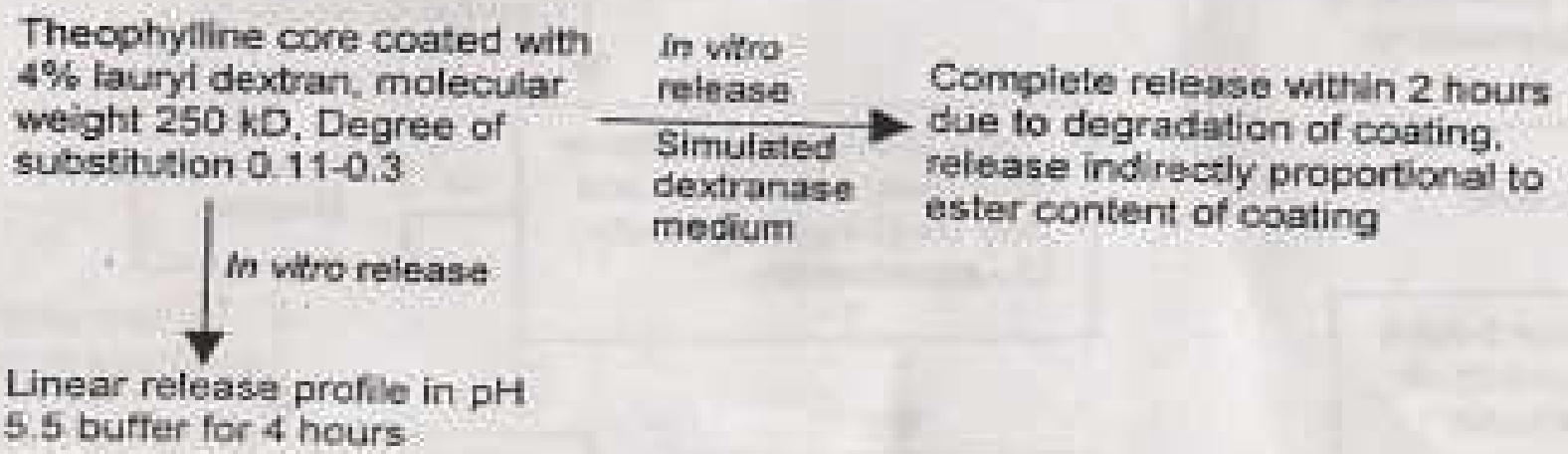
Class	Examples
Disacharides	Lactose
	Maltose
Oligosaccharides	Cellobiose
	Cyclodextrins
	Lectulose
	Raffinose
	Stachyose
Polysaccharides	Alginates
	Amylose
	Arabinogalactan
	Arabinoxylan
	Cellulose
	Chitosan
	Chondroitin sulfate
	Xextran
	Galactomnam (guar gum, locust bean gun)
	Inulin
	Karaya gum (kadaya gum)
	Laminarin
	Pectins and pectates
	Starch,Tragacanth gum

2.1.2. Coating with biodegradable polymers:

- The degrading property of enzymes produced by microflora of the colon, particularly azoreductase activity is taken as advantage in developing biodegradable polymer coated drug delivery systems.
- This approach totally depends on the metabolic activity of bacteria in colon, which is influenced by dietary fermentation precursors, co administration of chemotherapeutic agents and type of food consumed.
- Glassy amylose and suspension of natural polygalactomannose in polymethacrylate are used to form biodegradable coating.
- Polymethacrylate copolymers were used to strengthen the film forming properties of polygalactomannans.
- Ester based dextran, polyurethane was also used to develop colon drug delivery systems.
- Paracetamol cores were coated using aqueous dispersion consisted of pectin and ethyl cellulose. The drug release was controlled by the reaction of ethyl cellulose to pectin in film coat.



ig. 6-15 Working Principle of Biodegradable Azopolymer System (Van den mooter et al.



5 Schematic Representation of Biodegradable Ester Based Dextran System (Bauer and Kesselhut Hirsch et al., 1997)

2.2. *Embedding in matrices*

2.2.1. Embedding in biodegradable matrices and hydrogels:

- The drug is embedded in the matrix core of biodegradable polymer by compressing the blend of active drug, a degradable polymer and additives.
- Polysaccharides are the family of natural polymers used in drug delivery as it is comprised of polymers with large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, low toxicity, biodegradability and high stability.
- A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans are used in colon drug delivery systems.
- The gelling properties of pectin offer several advantages, including the formation of viscous diffusional barriers and fermentability in the large intestine, which are useful aspects in colonic drug delivery systems.

- Calcium pectinate-indomethacin compressed tablets are reportedly degraded by enzymes of *Aspergillus* and colonic bacteria *Bacteroids ovatus.*

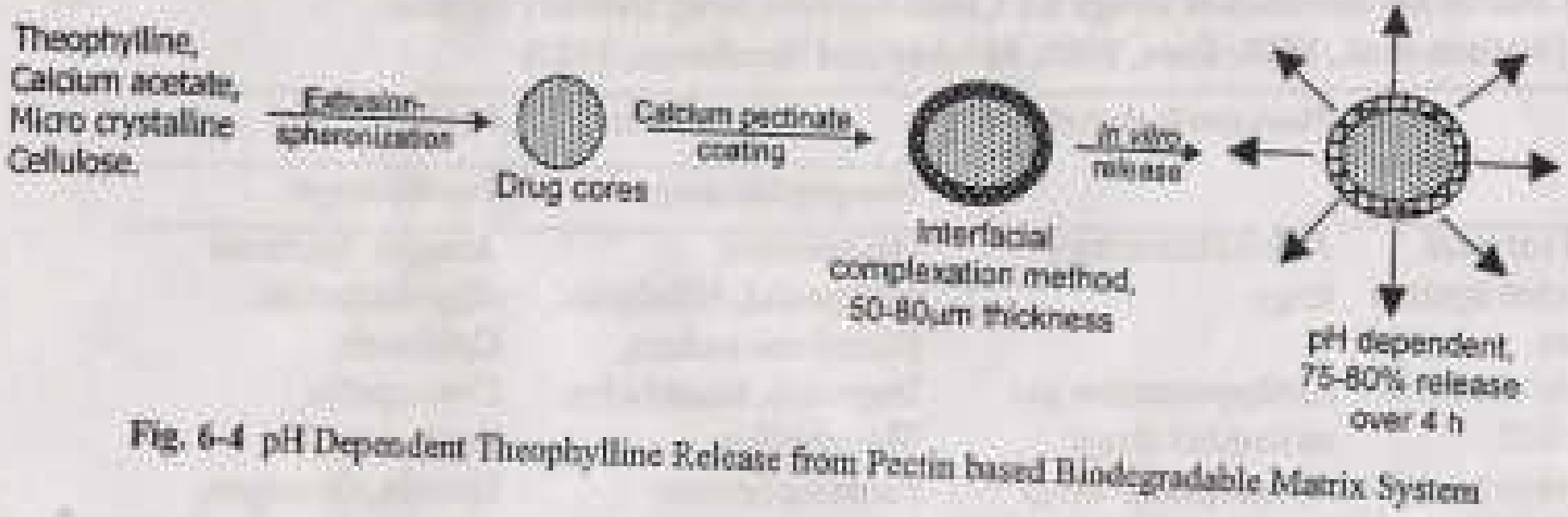


Fig. 6-4 pH Dependent Theophylline Release from Pectin based Biodegradable Matrix System

- Drug carriers made up of natural and modified polysaccharide hydrogels tend to swell following their hydration.
- Amidated pectins are more tolerant to pH variations and fluctuations in calcium levels.
- Amidation of pectin affects the release rate through slow and controlled matrix erosion.

Eudragit-coated pectin microspheres of 5-fluorouracil for colon targeting

Amol Paharia, Awesh K. Yadav, [...], and Govind P. Agrawal

Additional article information

Abstract

An objective of the present investigation was to prepare and evaluate Eudragit-coated pectin microspheres for colon targeting of 5-fluorouracil (FU). Pectin microspheres were prepared by emulsion dehydration method using different ratios of FU and pectin (1:3 to 1:6), stirring speeds (500–2000 rpm) and emulsifier concentrations (0.75%–1.5% wt/vol). The yield of preparation and the encapsulation efficiencies were high for all pectin microspheres. Microspheres prepared by using drug:polymer ratio 1:4, stirring speed 1000 rpm, and 1.25% wt/vol concentration of emulsifying agent were selected as an optimized formulation. Eudragit-coating of pectin microspheres was performed by oil-in-oil solvent evaporation method using coat: core ratio (5:1). Pectin microspheres and Eudragit-coated pectin microspheres were evaluated for surface morphology, particle size and size distribution, swellability, percentage drug entrapment, and in vitro drug release in simulated gastrointestinal fluids (SGF). The in vitro drug release study of optimized formulation was also performed in simulated colonic fluid in the presence of 2% rat cecal content. Organ distribution study in albino rats was performed to establish the targeting potential of optimized formulation in the colon. The release profile of FU from Eudragit-coated pectin microspheres was pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7.4. It is concluded from the present investigation that Eudragit-coated pectin microspheres are promising controlled release carriers for colon-targeted delivery of FU.

KeyWords: 5-Fluorouracil, pectin, microspheres, Eudragit coating, colon targeting

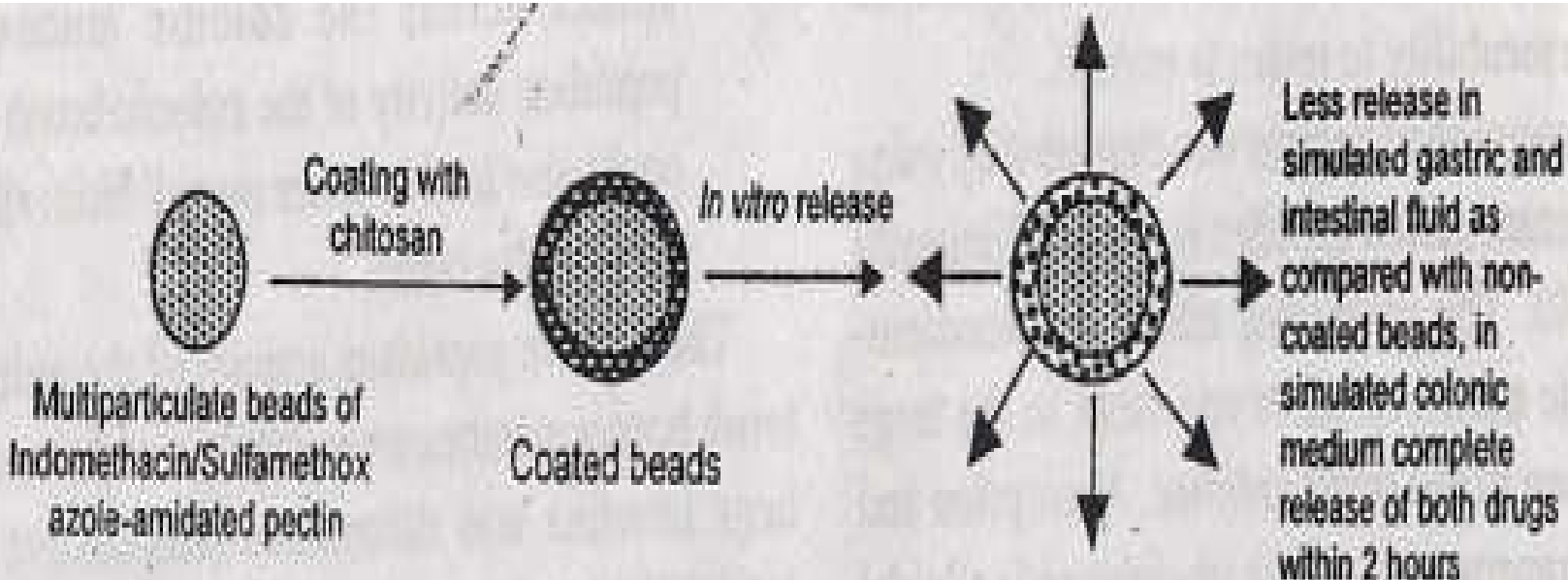
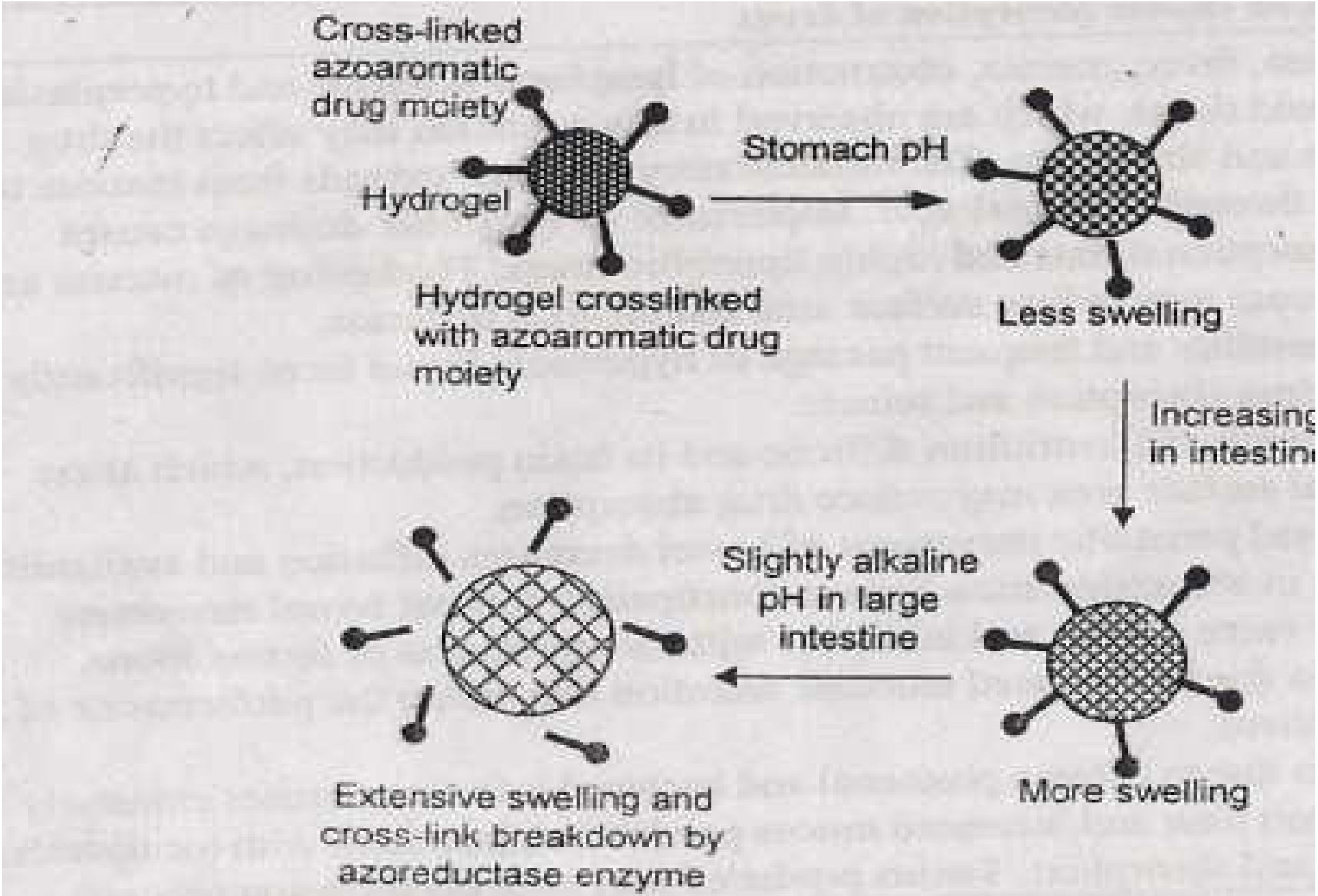


Fig. 6-6 Working Principle of Multiparticulate System Based on Amidated Pectin (Munjeri et al., 1997)

- Hydrogels with azoaromatic cross linking are developed to deliver drugs to colon.
- Various polymers such as cellulobiose derived monomers, carbopol 974P and copolymerized methacrylates are used in the delivery of mesalamine and 5-flurouracil.



Working Principle of System Based on Hydrogel-Azoaromatic Cross-Linking

•The results of insulin colon delivery from chitosan capsules suggest that chitosan based systems can be useful carriers for peptide delivery.

2.2.2.Embedding in pH sensitive matrices:

•Extrusion-spheronization and pelletization have been used for the preparation of pH sensitive matrix pellets for colon targeted drug delivery.

•Ibuprofen as a model drug and Eudragit S and Aqcoat AS-HF as enteric polymers are used for developing site specific systems for release of a drug in the lower part of intestine or colon.

2.3. Time released systems:

•This approach is based upon the theory that the lag time equates to the time taken for the dosage form to reach the colon.

•The lag time is dependent on size of dosage form and gastric motility associated with the pathological condition of the individual.

•The first formulation introduced based on this principle was Pulsincap. It is similar in appearance to hard gelatin capsule.

•A novel delivery system was developed for delivering drugs to the colon by selecting polymethacrylates with appropriate pH dissolution characteristics for the distal end of the small intestine.

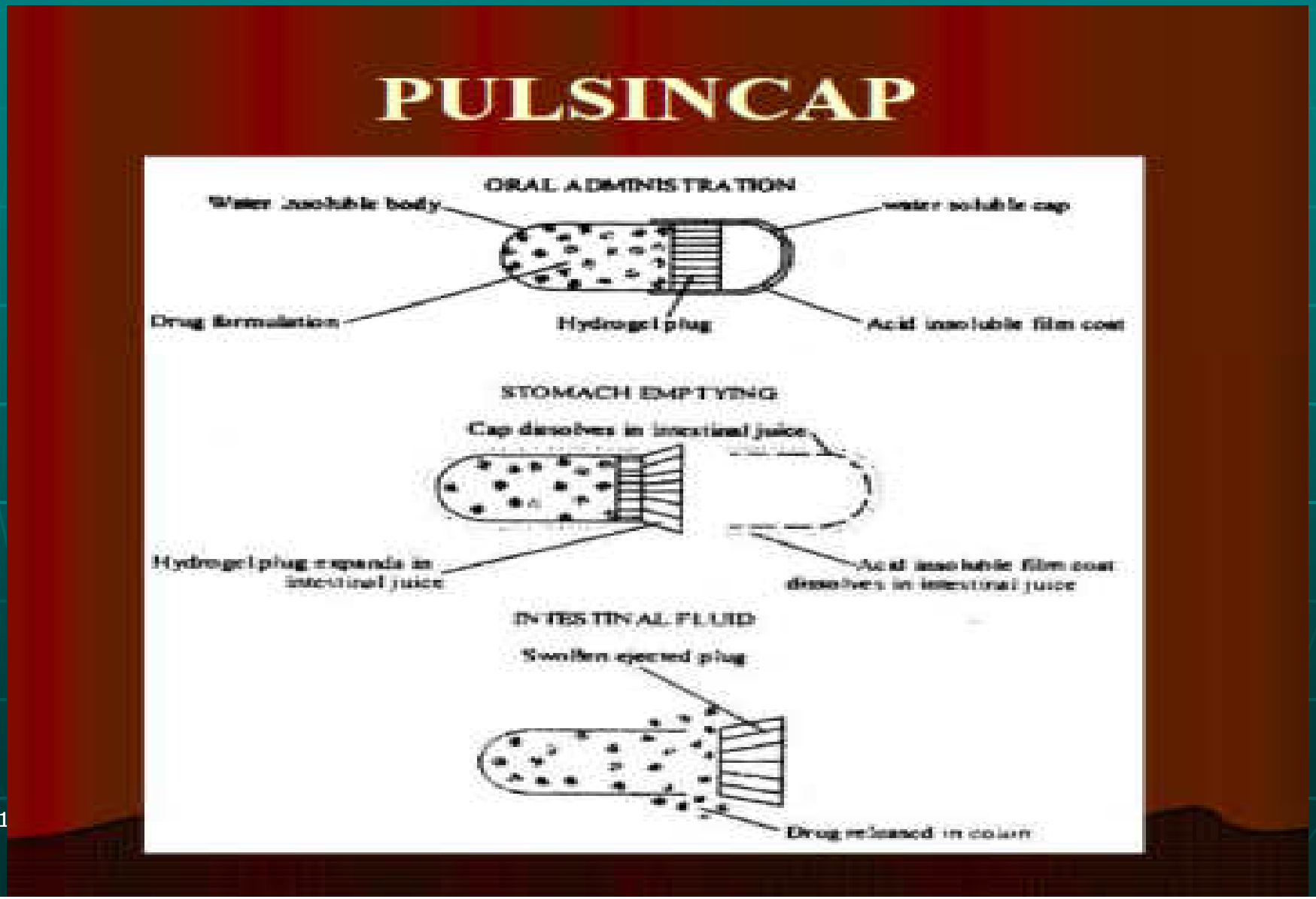
•Pellets were prepared by powder layering of 5-ASA on nonpariels in a conventional coating pan.

•Drug layered pellets were coated with an inner layer of a combination of two pH independent polymers Eudragit RL and Eudragit RS and an outer layer of pH dependent polymer, Eudragit S.

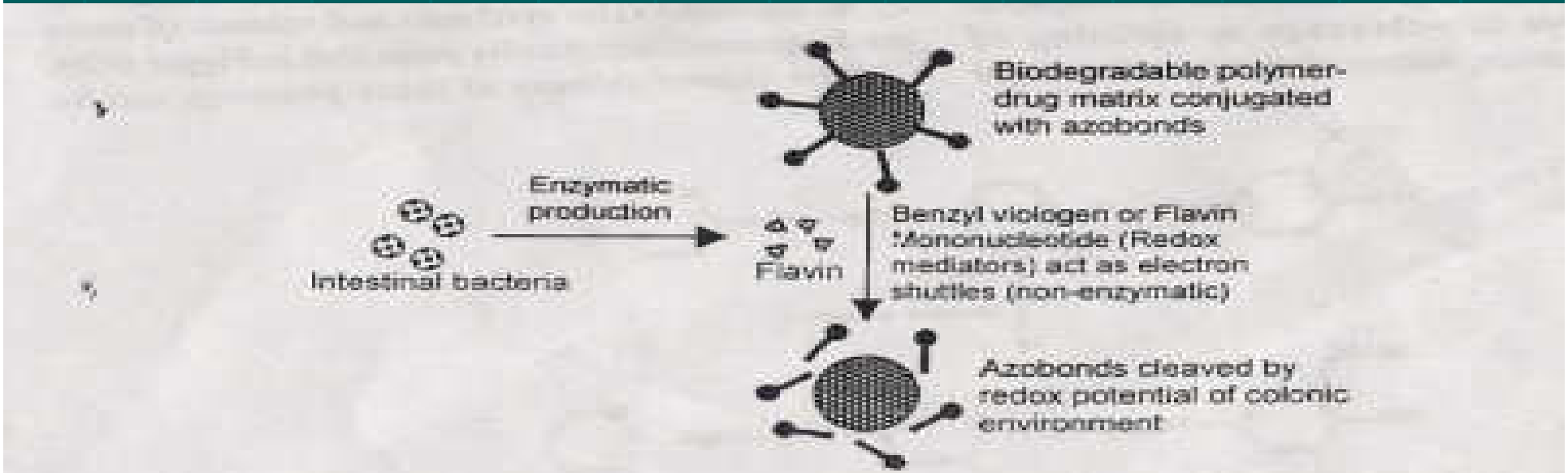
•To develop a new colon targeting formulation, which can suppress drug release completely during 1-2hr in the stomach and release the drug rapidly after a lag time of 3±1hr in the small intestine, the use of press coated tablets with hydroxypropylmethylcellulose acetate succinate in the outer shell was used.

•A delivery system called the **Time clock** has been exploited to release the drug in the colon . It is composed of a solid dosage form coated with hydrophobic surfactant layer to which a water soluble polymer is added to improve adhesion to the core.

•The outer layer redisperses in the aqueous environment in a time proportional to the thickness of the film and the core is then available for dispersion.



- **2.4.Redox sensitive polymers:**
- Novel polymers, which are hydrolyzed nonenzymatically by enzymatically produced flavins, are being used for colon targeting.
- Redox potential is an expression of total metabolic and bacterial activity in the colon and intestine determined by dietary changes.
- Based on redox mechanism, systems bearing peptides coated with polymers cross linked via azoaromatic groups were developed.



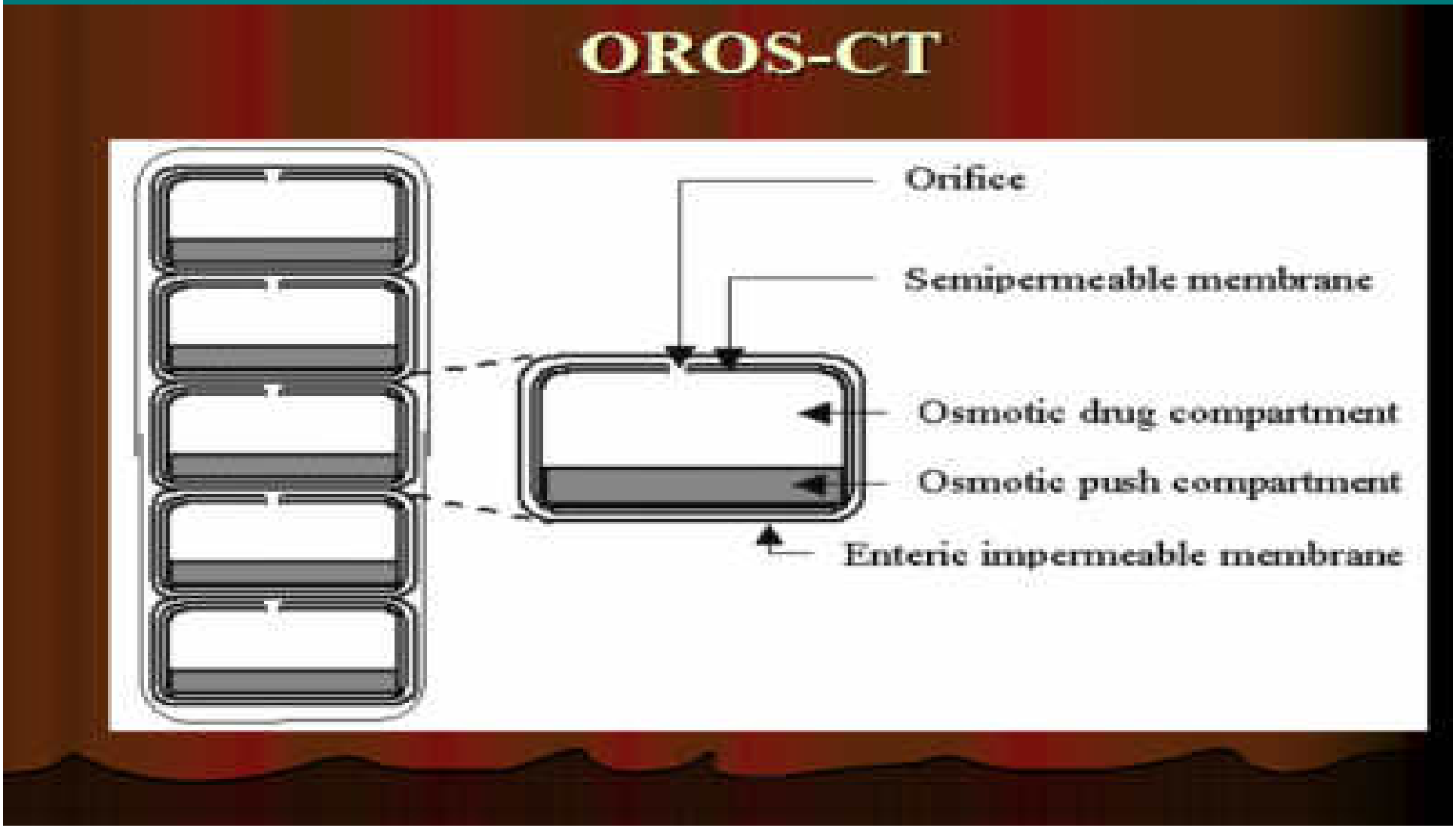
6-17 Release Mechanism of Drug From System Based on Redox-Sensitive Polymers (Grim and Kops

2.5. Bioadhesive systems:

- Bioadhesion has been proposed as a means of improving the performance and extending the mean residence time of colonic drug delivery systems.
- Various polymers include polycabophils, polyurethanes and polyethylene oxide-polypropyline oxide copolymers have been used.
- Amino acids and polymers have used as drug carriers for colon targeted delivery of 5-ASA.
- Epithelial and mucosal adhesion are preferred as target sites.
- Bioadhesive systems based on receptor mediated mechanisms, is another approach that essentially involves lectin.
- Bioadhesive microorganisms such as E.coli is able to adhere to small intestine by producing a protein(fimbriae) on the surface of the organism.
- The specific bioadhesive region of the fimbrial structure of E.coli was identified as Film-H, which is characteristically polyvalent in nature.

2.7.Osmotically controlled drug delivery:

The OROS-CT (Alza corporation) can be single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4mm in diameter, encapsulated in hard gelatin capsule.



5.GENERAL COSIDERATIONS FOR DESIGN OF COLONIC FORMULATIONS

The proper selection of a formulation approach is dependent upon several important factors which are listed below:

a)Pathology and pattern of the disease or physiological composition of the healthy colon if the formulation is not intended for localised treatment.

b)Physicochemical and bio pharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery and

c)The desire release profile of the active ingredient. The most common physiological factor considered in the design of delayed release colonic formulations is pH gradient of the GIT.

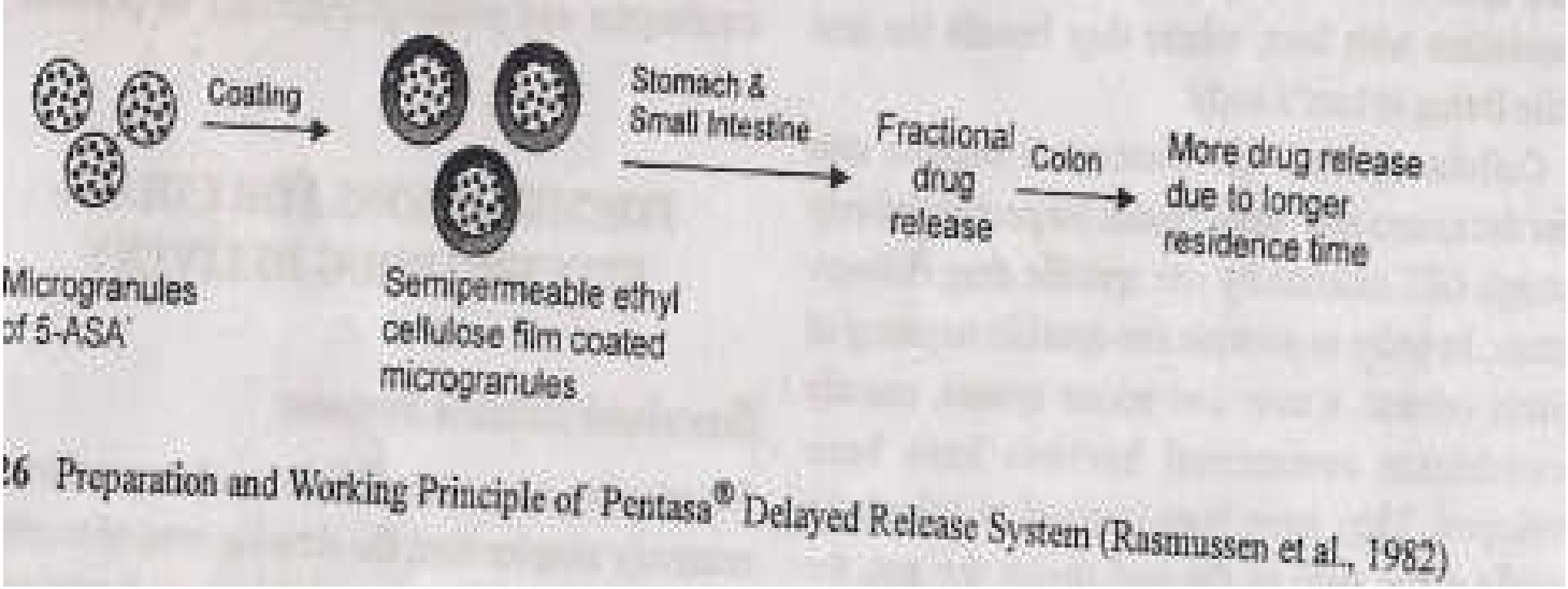
Formulation of drugs for colonic delivery also requires careful consideration of drug dissolution and/or release rate in the colonic fluids.

•Generally, the dissolution and release rate from colonic formulations is thought to be decreased in the colon , which is attributed to the fact that less fluid is present in the colon than in the small intestine.

•Consequently, such drugs need to be delivered in a presolubilised form, or formulation should be targeted for proximal colon, which has more fluid than distal colon.

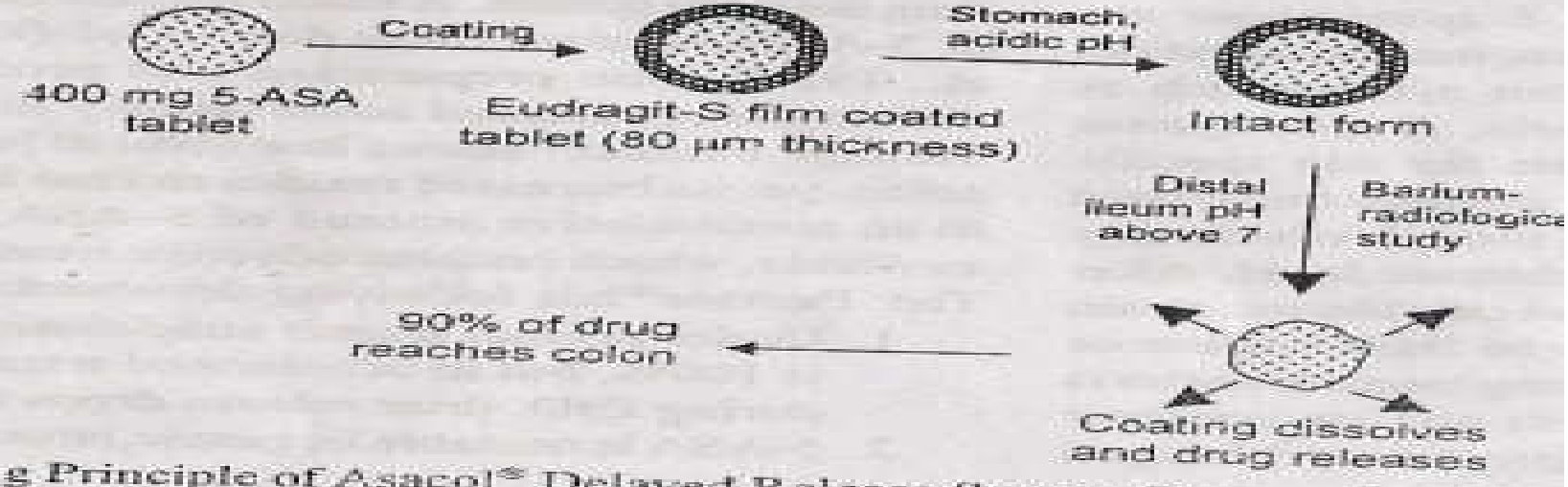
6.FORMULATION FOR COLON SPECIFIC DRUG DELIVERY

Sustained release formulation:



26 Preparation and Working Principle of Pentasa® Delayed Release System (Rasmussen et al., 1982)

Delayed and time release dosage forms



-27 Working Principle of Asacol® Delayed Release System (Dew et al., 1982)

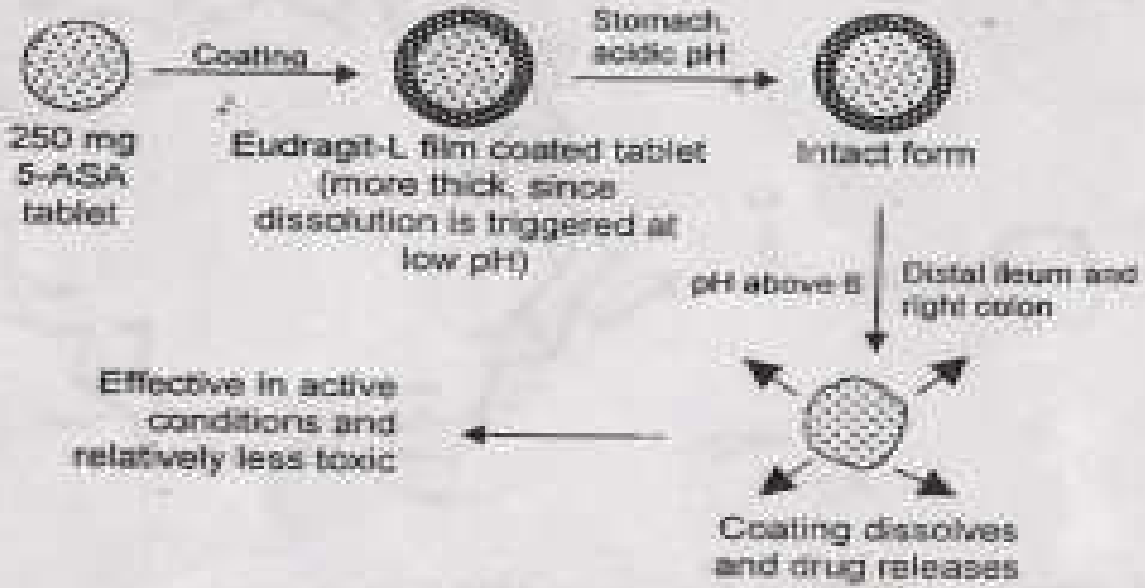
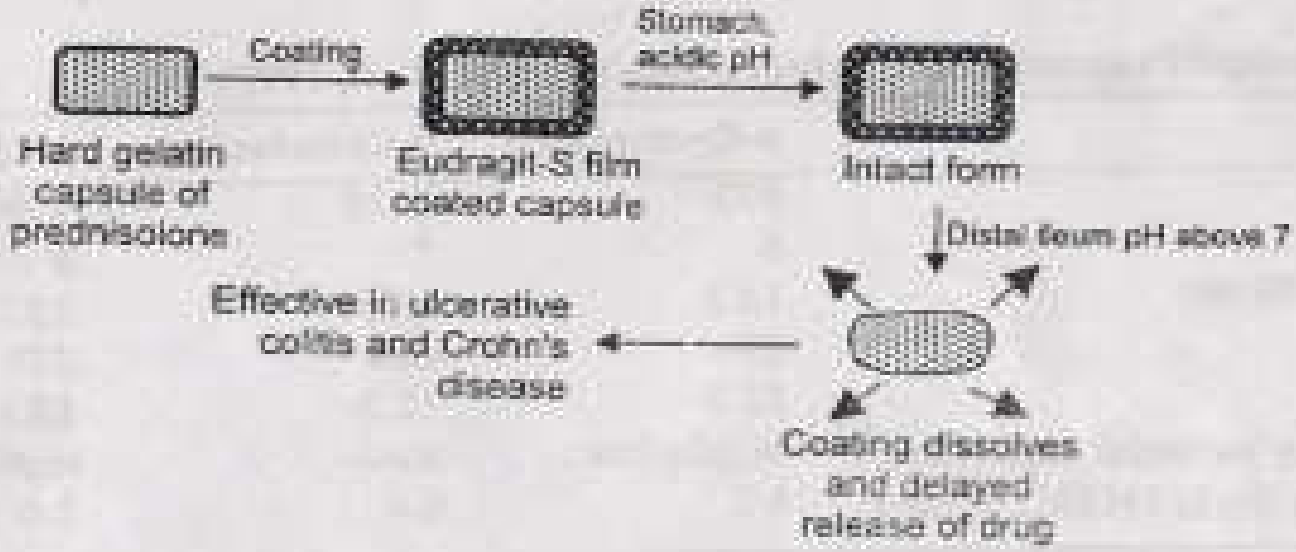


Fig. 6-28 Working Principle of Claversal® Delayed Release System (Rutgeerts, 1989; Rachmilewitz, 1988)



9 System Components and Release Mechanism of Prednisolone Delayed Release System (Thomas et al., 1985)

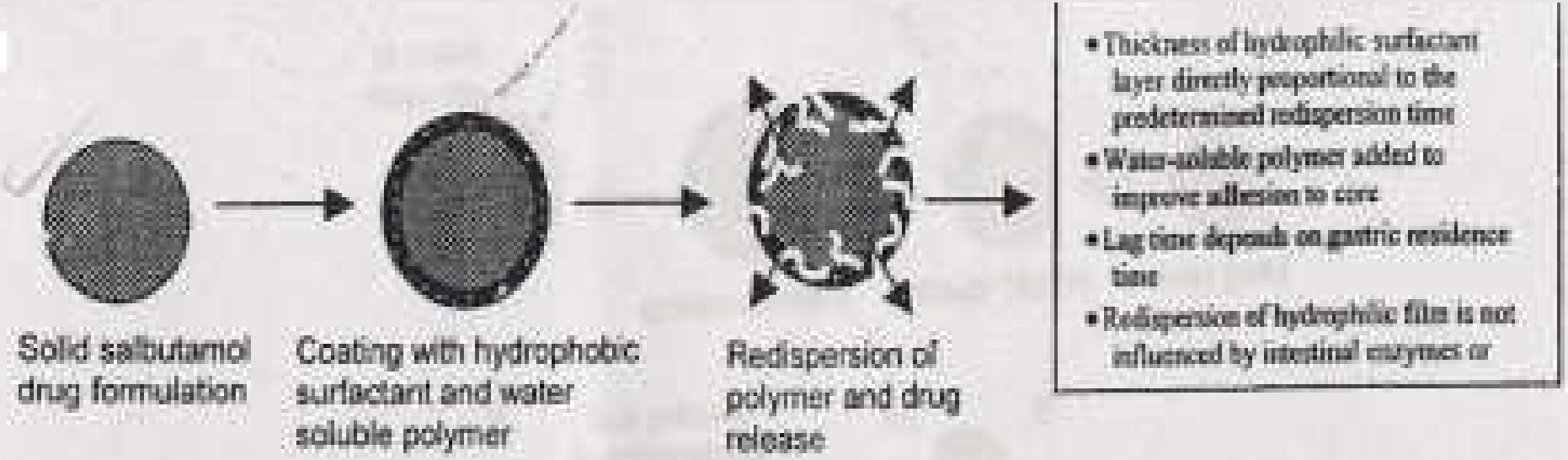


Fig. 6-32 Components and Working principle of Time Clock® (Pozzi et al., 1994)

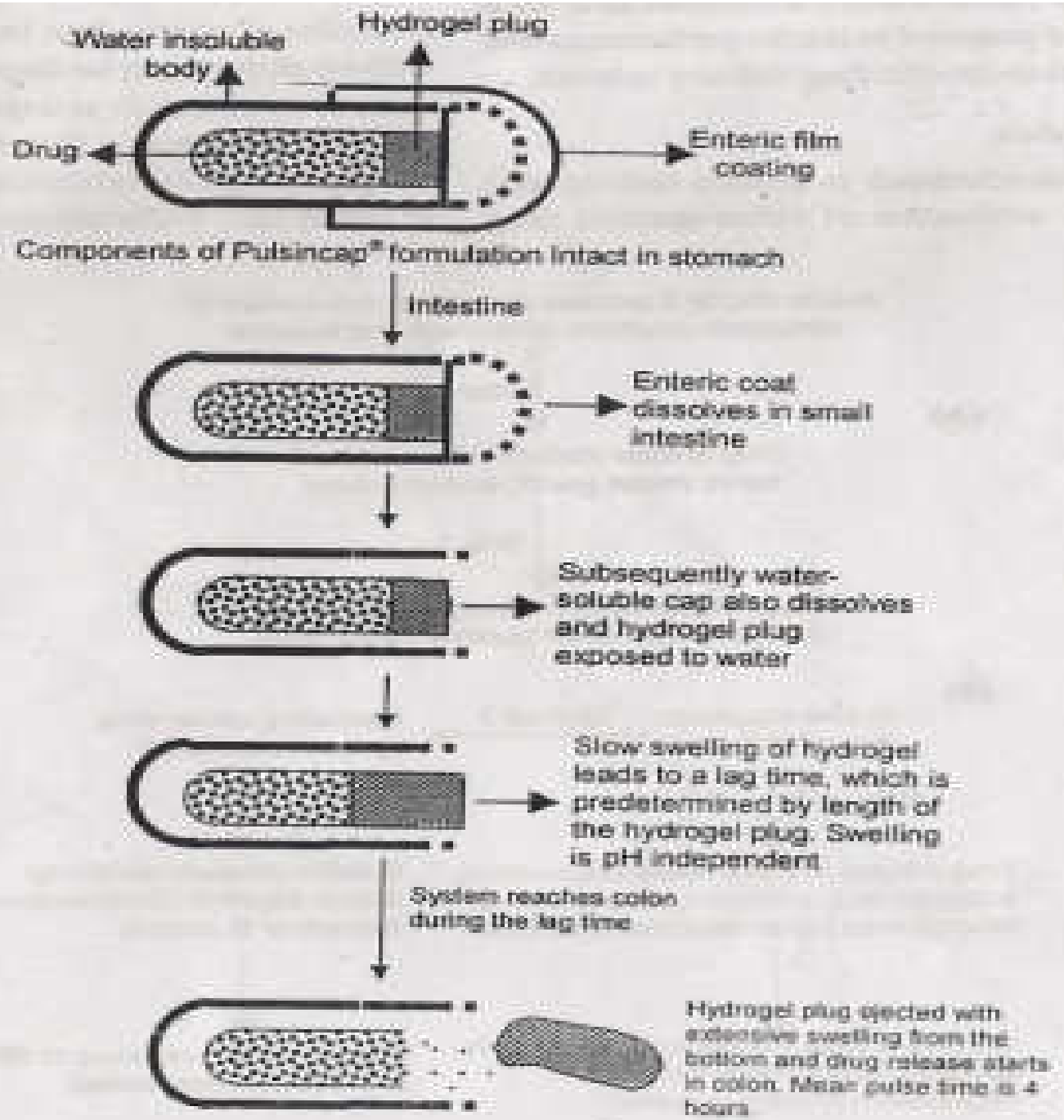


Fig. 6-31 Components and Working Principle of Pulsincap® Time-Dependent Release System

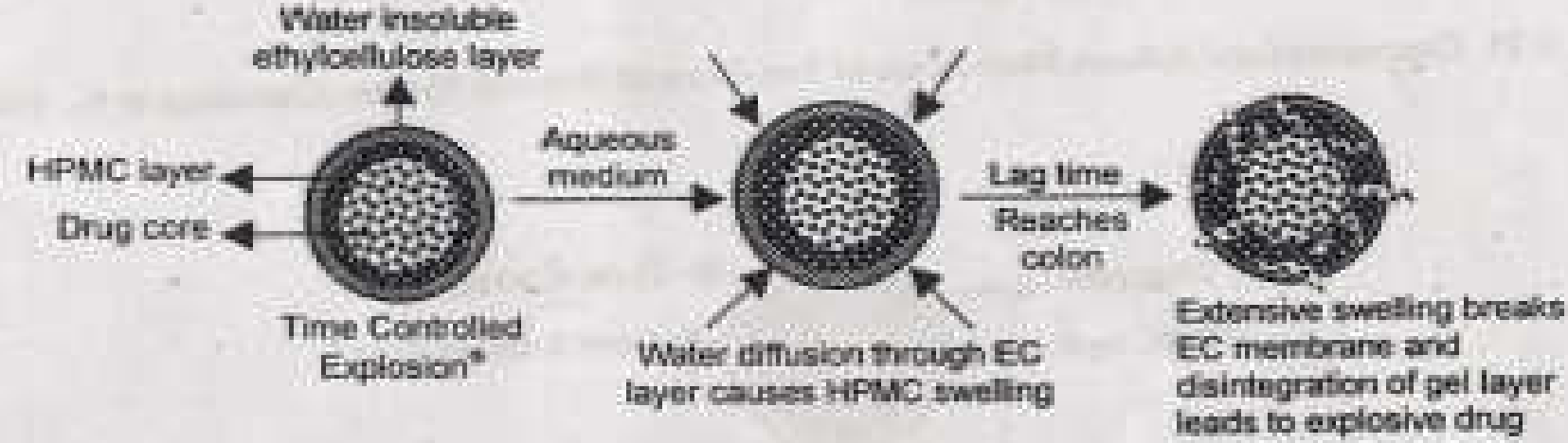
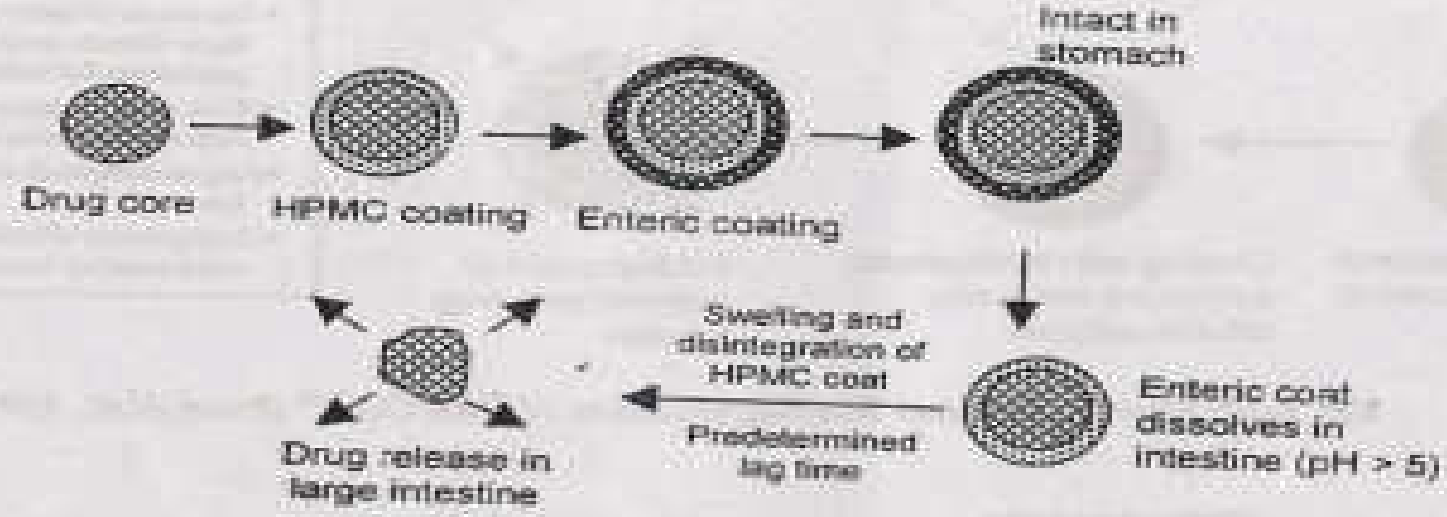


Fig. 6-33 Components and Release Mechanism of Time Controlled Explosive® System (Ueda et al., 1994)



ig. 6-35 Components and Release Mechanism of Two-Layered Polymer System (Gazzaniga et al., 1994)

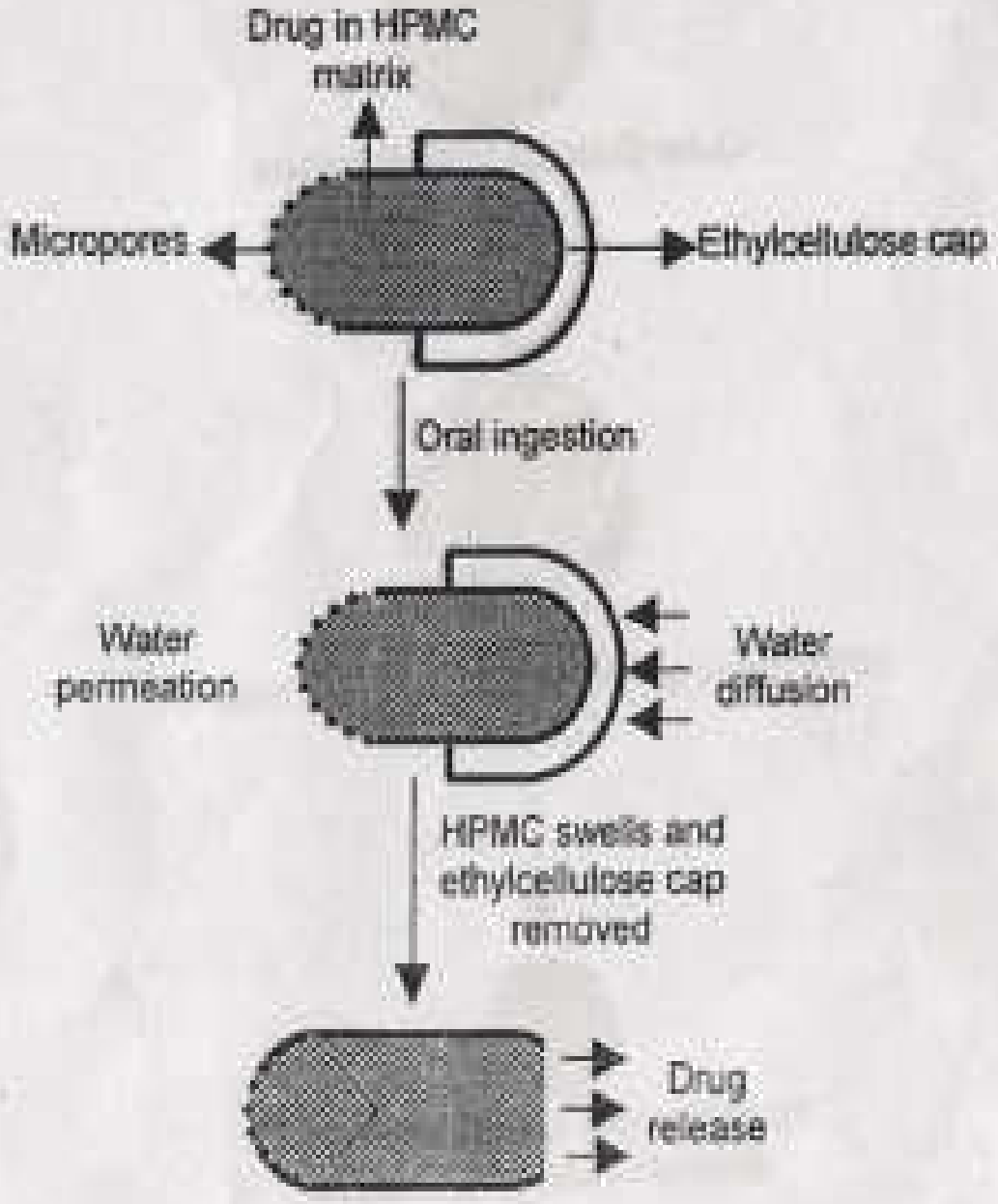
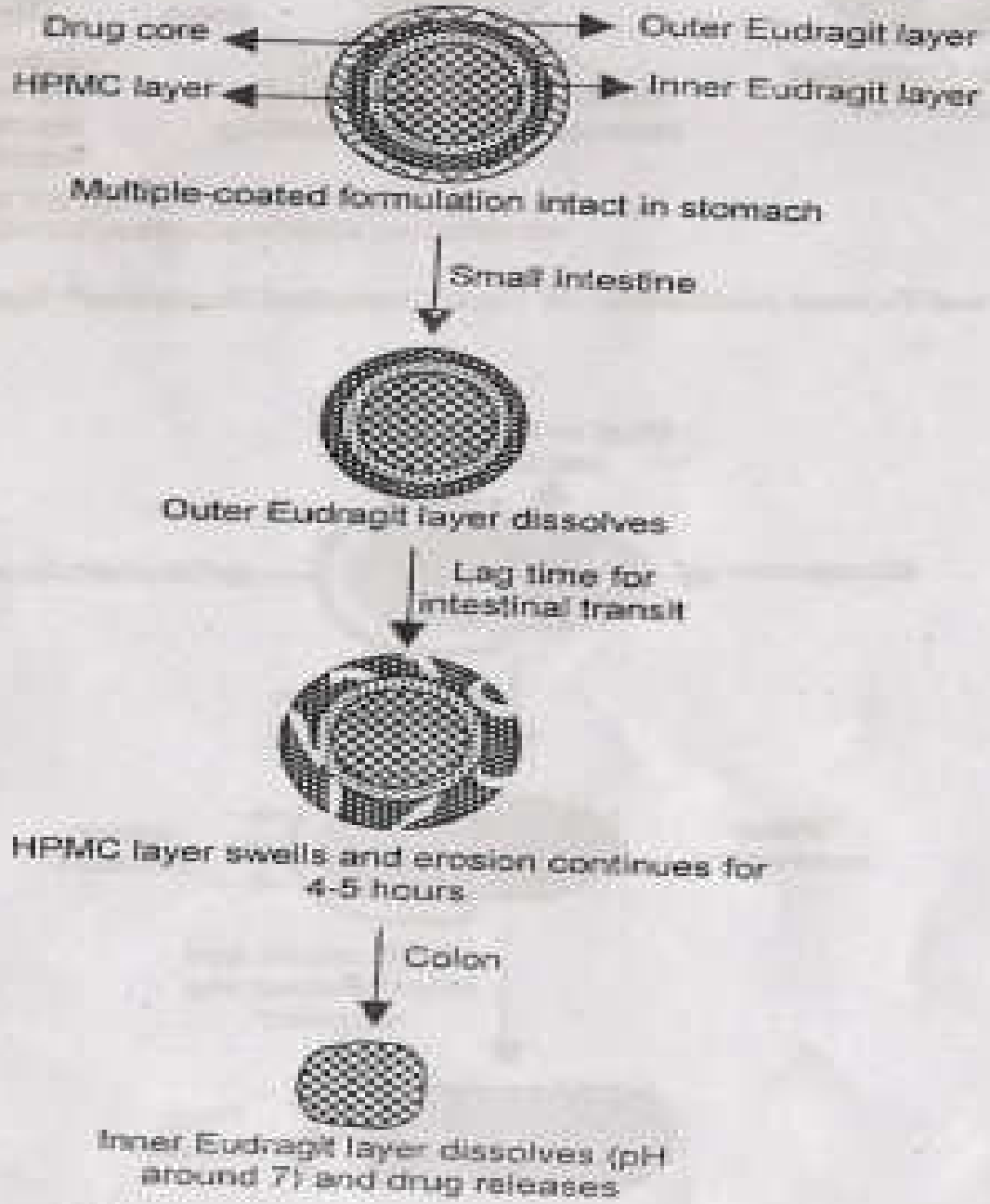


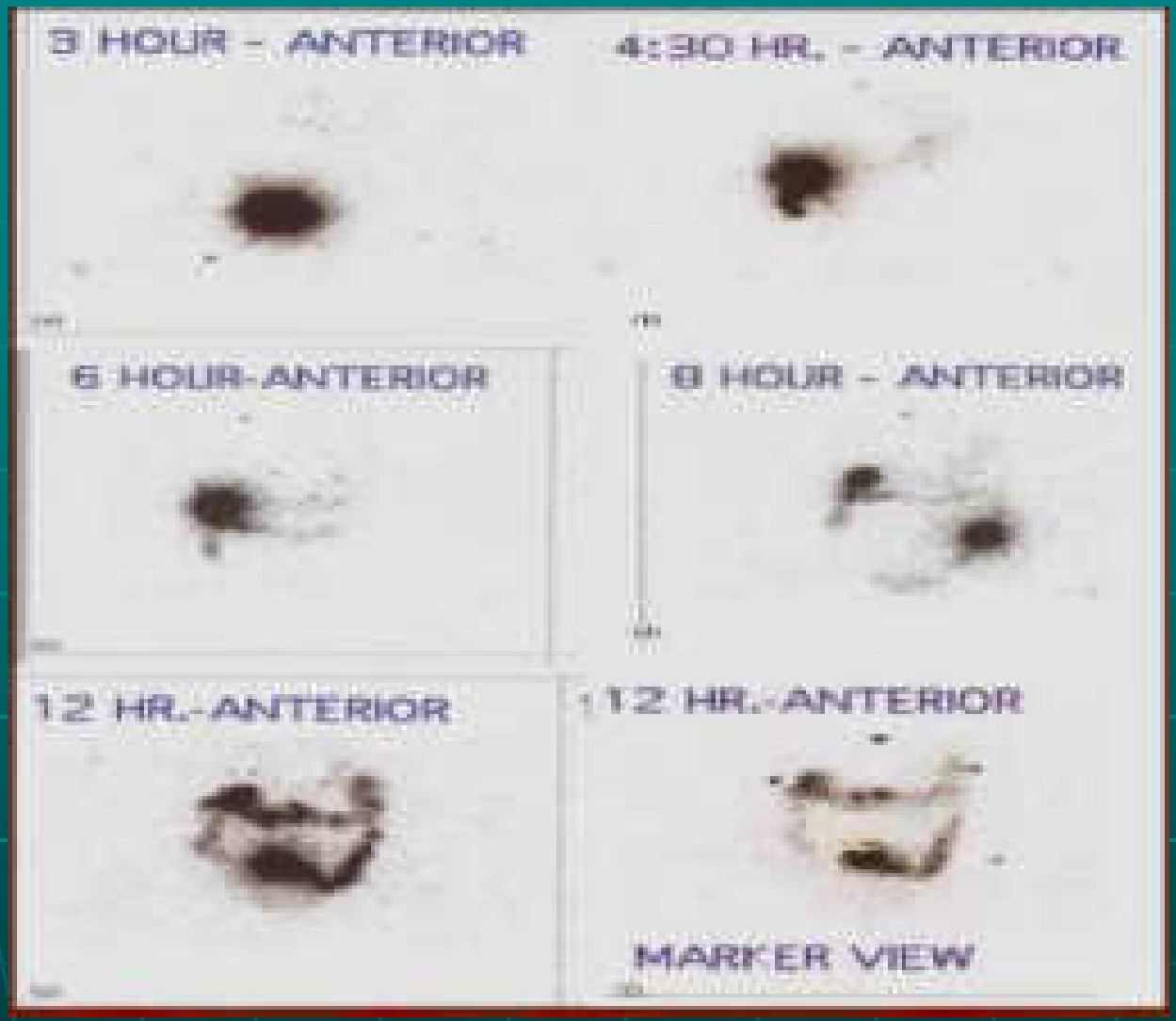
Fig. 6-34 Components and Working principle of Ethylcellulose Capsule system (Niwa et al., 1995)



Components and Release Mechanism of Delayed-Release Multiple Coated Tablet (Reddy et al., 1999)

7.EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM

- *in-vitro* method involves incubation of the drug delivery system in a fermentor with commonly found colonic bacteria.
- *In vivo* methods offer various animal models.
- Guinea pigs were used to evaluate colon- specific drug delivery from a glucoside prodrug of dexamethasone.
- *In vivo* gamma scintigraphic studies were carried out on the guar gum matrix tablets, using technetium 99 m- DTPA as a tracer.
- Scintigraphs taken at regular intervals have shown that some amount of tracer present on the surface of the tablets was released in stomach and small intestine.
- Radio telemetry, Roentegenography are the other *in vivo* evaluation methods for colon-specific drug delivery systems.



Gamma Scintigraphy showing the spread of the tracer all along the ascending, transverse, descending and sigmoid colon

REFERENCES

1.James Swarbrick, Drug Delivery: Oral Colon-Specific, Encyclopedia of Pharmaceutical Technology, third edition, volume2, pg.no.1228-1240.

2.SP.Vyas, Roop K. Khar, Targeted and controlled drug delivery concepts and advances, Systems for Colon Specific Delivery, pgno.218-253.

3.www.uaberta.ca/CSPS/JPPS6(1)/S. Chourasia/colon.htm

4.www.pharma info. net/…/colon targeted-drug delivery-system-overview.

5.www.pharma info.net/pharma…/colon-specific-drug delivery.

6.www.colon targeted drug delivery systems an overview diet delivery NY.mht.

7.www.kem.edu/…/Dr%20 V.R.%20 sinha%20 specific%20 drug%20 delivery%20 colon. pdf.