TARGETED DRUG DELIVERY TO COLON

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CHIPS

DEFINITION

Colon: The long, coiled, tube like organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. Also known as large bowel and large intestine.

Colon drug delivery system: It refers to targeted delivery of drug in to the lower parts of GI tract , mainly large intestine.

Objectives

- Oral route is considered to be most convenient for administration of drug to patient.
- Colon is used as site of Targeted drug delivery.
- Colon was considered as a BLACK-BOX , as most of the drug are absorbed from the upper part of the GI tract.
- Prime objective-Beneficial in the treatment of colon diseases.
  - Increase the pharmacological activity.
  - Reduce dosing & side effects.
  - Prevent drug from degradation.

WHY COLON TARGETED DRUG DELIVERY IS NEEDED?

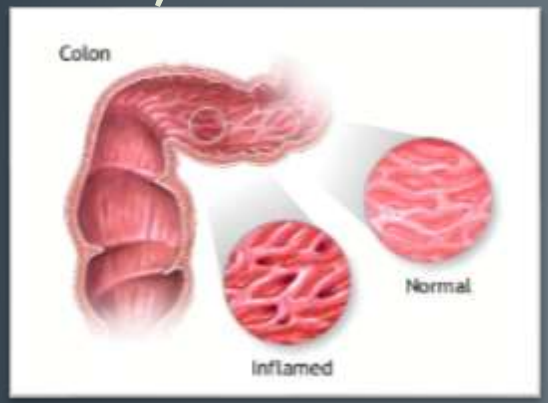
- As most of the conventional drug delivery systems for treating colon disorders such as inflammatory bowel diseases, infectious diseases and colon cancer are failing as the drugs don't reach the site of action in appropriate concentration.
- In recent times the colon-specific delivery systems(CSDDS) are also gaining importance for the systemic delivery of protein and peptide drugs . This is because,

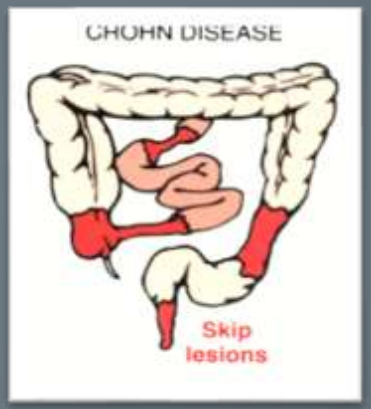
i)As the peptide and protein drugs are destroyed and inactivated in acidic environment of stomach or by pancreatic enzymes (or) by parenteral route which is inconvenient and expensive.

ii) Due to the negligible activity of brush border membrane peptidase activity and less activity of pancreatic enzymes the colon is considered as the most suitable site.

ADVANTAGES

- The site specific delivery of drug to lower part of GIT, for localized treatment of several colonic diseases. (ulcerative colitis, Crohn's disease, carcinomas and infections)





- Prevent drug from degradation
- Ensure direct treatment at disease site.
- Suitable absorption site for Protein & Peptide drug.
- Used to prolong the drug therapy.
- Improved drug utilization.

LIMITATIONS

- Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or fecal matter.
- Non availability of an appropriate dissolution testing method to evaluate the dosage form in-vitro.
- Drug should be in solution form before absorption and there for rate limiting step for poor soluble drugs.
- Substantial variation in gastric retention time may affect drug delivery.
- Diseased condition may affect the colonic transit time and drug release profile.
- pH level of colon may vary between individuals due to disease, state and temperature of food consumed.

COLON TARGETING DISEASES, DRUGS AND SITES

TARGET SITES	DISEASE CONDITIONS	DRUG AND ACTIVE AGENTS
Topical action	Inflammatory Bowel Diseases, Irritable bowel disease and Crohn's disease. Chronic pancreatitis	Hydrocortisone, Budenoside, Prednisolone, Sulfaselazine, Olsalazine, Mesalazine, Balsalazide
Local action	Pancreatactomy and cystic fibrosis, Colorectal cancer	Digestive enzyme supplements 5-Flourouracil
Systemic action	To prevent gastric irritation To prevent first pass metabolism of orally ingested drugs Oral delivery of peptides Oral delivery of vaccines	NSAIDS Steroids Insulin

CRITERIA OF DRUG SELECTION

- Drugs used for local effects in colon against GIT diseases.
- Drugs poorly absorbed from upper GIT.
- Drugs for colon cancer.
- Drugs that degrade in stomach and small intestine.
- Drugs that undergo extensive first pass metabolism.
- Drugs for targeting.

Factors affecting Colon drug delivery

- Physicochemical parameters
- Intestinal transit time
- Colonic Microflora
- Role of absorption enhancers

PRIMARY APPROACHES FOR CDDS

- pH sensitive systems
- Microbially triggered system
  - Prodrugs
  - Polysaccharide based systems
- Delayed release systems

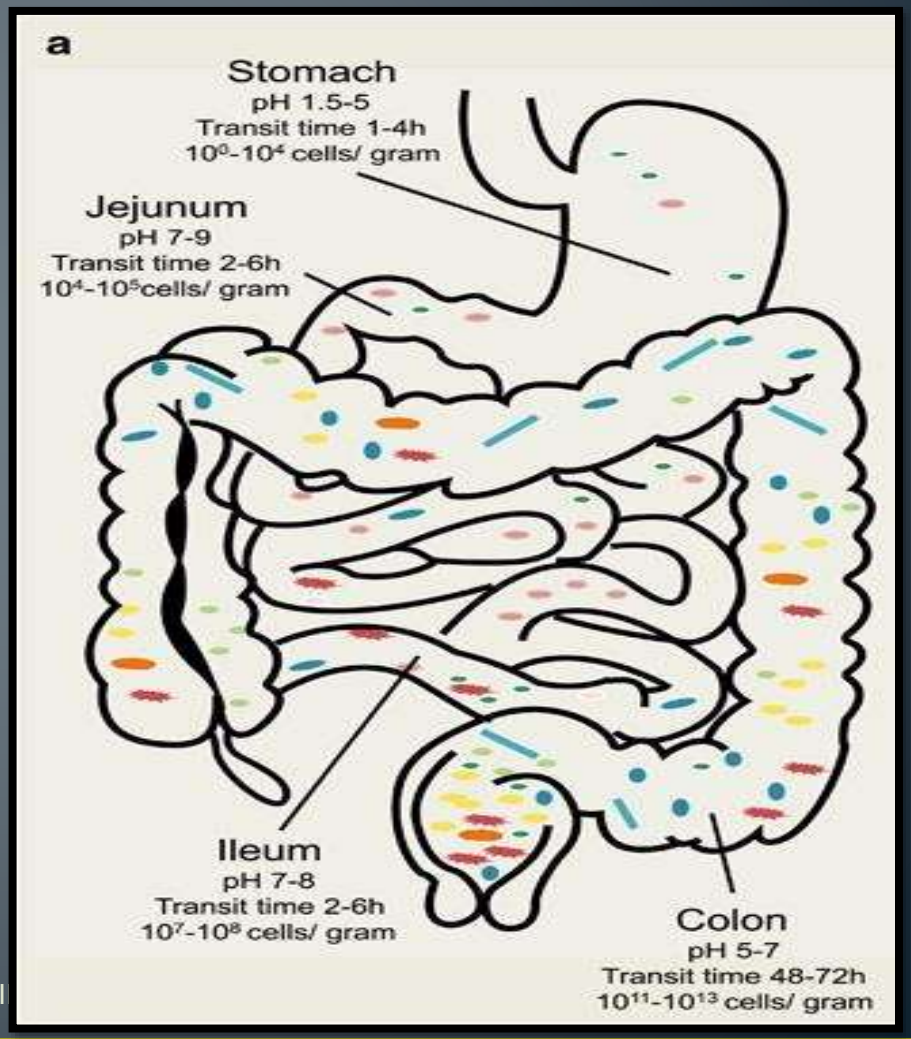
NEWLY DEVELOPED APPROACHES FOR CDDDS

- Pressure controlled drug delivery systems
- Novel colon targeted delivery systems
- Osmotic controlled drug delivery systems

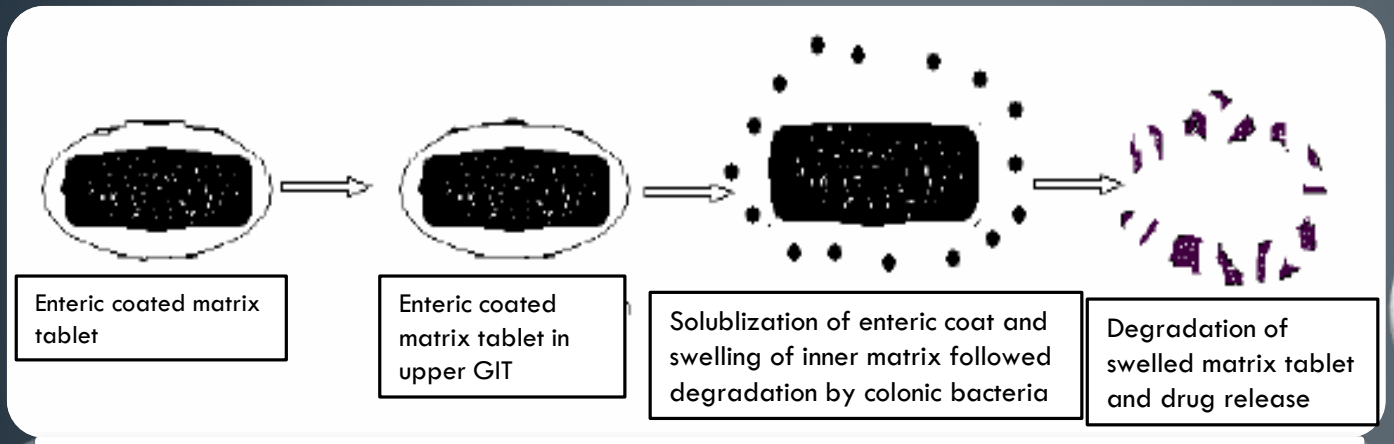
1. PRIMARY APPROACHES

a) pH sensitive polymer coated drug delivery to colon

LOCATION	pH
1. STOMACH:	1.5 - 2.0
Fasted	3.0 - 5.0
Fed	5.0 - 6.5
2. SMALL INTESTINE:	6.0 - 7.5
Jejunum	6.4
Ileum	6.7 - 7.3
3. LARGE INTESTINE:	6.5 - 7.0
Right colon	5.7
Mid colon	6.6
Left colon	7.0



b) Delayed release drug delivery to colon



Enteric coated time-release press coated (ETP) tablet

Disadvantages

- Gastrointestinal Transit
- Gastric emptying of various dosage form is highly inconsistent & depends primary on whether the subject is fed or fasting & properties of dosage form.
- Accelerated transit was observed in IBD and ulcerative colitis patients

c) Microbially triggered drug delivery to colon

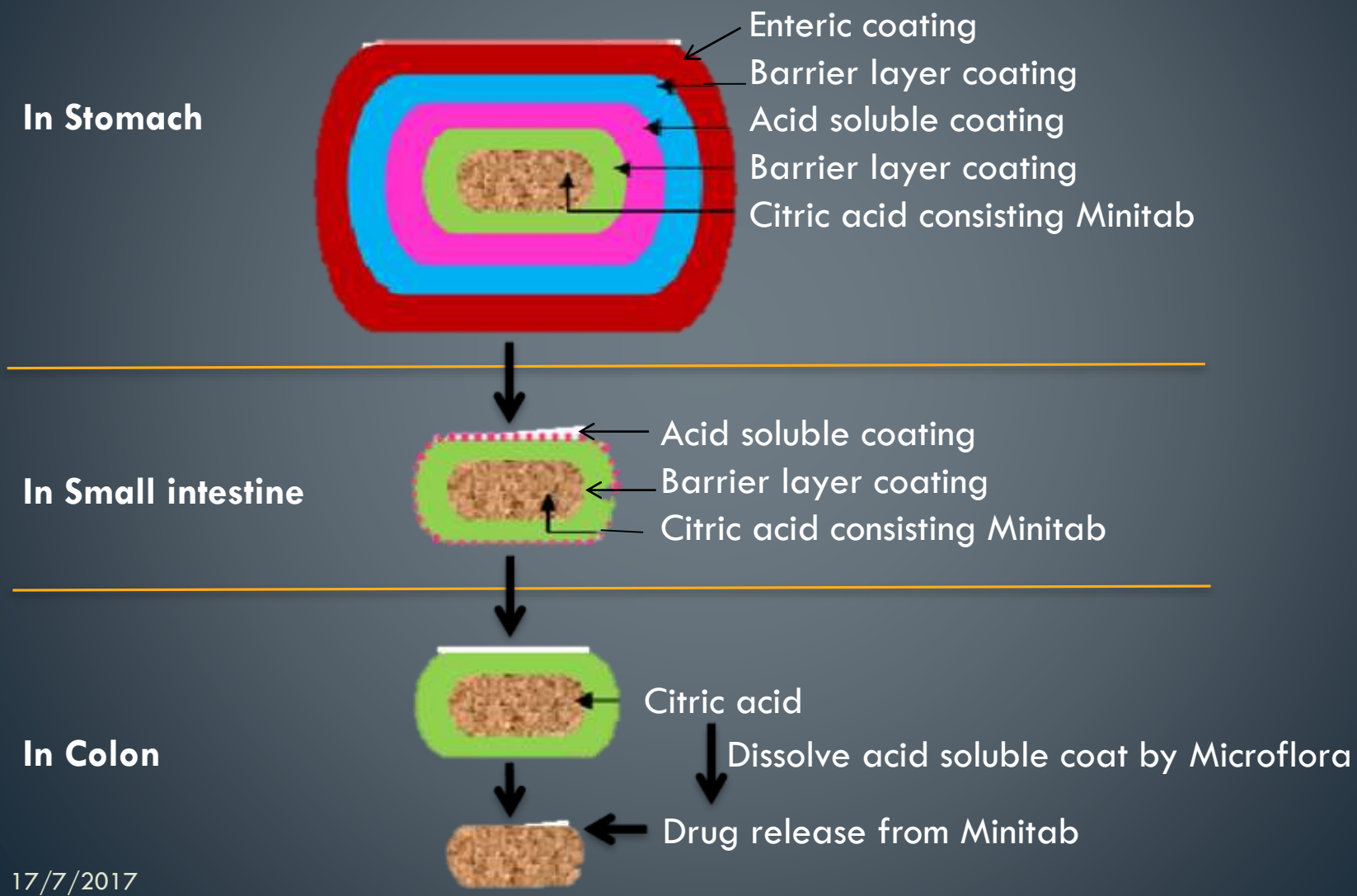
- The microflora of the colon is in the range of 1011 -1012 CFU/ mL, consisting mainly of anaerobic bacteria, e.g. bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria and ruminococcus etc.
- Microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase.
- Presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery.
- These polymers shield the drug from the environments of stomach and small intestine, and are able to deliver the drug to the colon.

1. Prodrug Approach – Not a versatile approach.
2. Azo-polymeric prodrugs
3. Polysaccharide based delivery - GRAS

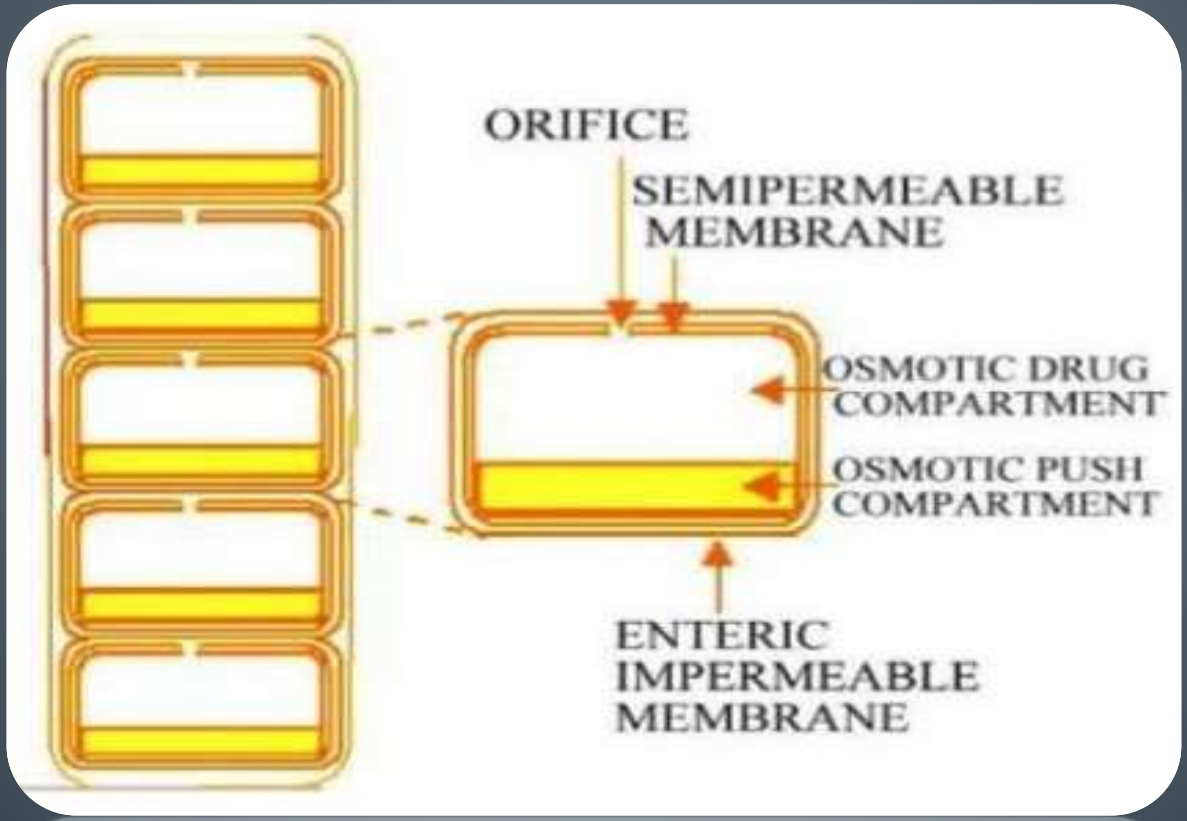
2. NEW DRUG APPROACHES
a) Pressure controlled delivery

- As a result of peristalsis, higher pressures are encountered in colon than in small intestine.
- Takaya et al. developed pressure controlled drug delivery capsules are prepared using ethyl cellulose, which is water insoluble.
- Thickness of polymer membrane and capsule size and its density are important factors for the disintegration of formulation.
- Due to reabsorption of water from colon, viscosity of luminal content seems to be higher in colon than in small intestine.
- Lag time of 3 to 5 hrs. in relation to drug absorption.

b) Novel colon targeted delivery



c) Osmotic controlled drug delivery



APPLICATIONS

- **LOCAL ACTIONS**

1. Ulcerative colitis.
2. CROHN'S disease.
3. Irritable bowel syndrome.
4. Metastatic human colon cancer.

- **SYSTEMIC ACTIONS**

1. Molecules degraded/poorly absorbed from upper GIT such as peptides and proteins are better absorbed from colon.
2. For achieving chemotherapy for diseases that are sensitive to circadian rhythm such as Asthma, angina, arthritis.

MARKETED PRODUCTS

Sr. no.	Marketed name	Company name	Disease	Drug content
1)	Mesacol tablet	Sun pharma, India	Ulcerative colitis	Mesalamine
2)	SAZO	Wallace , India	Ulcerative colitis, crohn's disease	Sulphasalazine
3)	BUSCOPAN	German remedies	Colonic motility	Hyoscine butyl bromide
4)	Entofoam	Cipla, India	Ulcerative colitis	Hydrocortisone acetate

EVALUATION TESTS

- For evaluation, not any standardized evaluation technique is available for evaluation of CDDS because an ideal in vitro model should posses the in-vivo conditions of GIT such as pH, volume, stirring, bacteria, enzymes, enzyme activity, and other components of food.
- These conditions are influenced by the diet, physical stress, and these factors make it difficult to design a standard in-vitro model.

1. In vitro dissolution study – Conventional basket method, BIO-DIS III
2. In vitro enzymatic degradation test
3. In vivo evaluation
4. Drug delivery index (DDI)
5. Clinical evaluation

BIO-DIS III

2. In vitro Enzymatic tests

Method 1:

- Drug release in buffer medium containing enzymes (ex. pectinase, dextranase) or rat or guinea pig or rabbit decal contents

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- Amount of drug release in particular time directly proportional to the rate of degradation of polymer carrier.

Method 2:

- Incubating carrier drug system in fermenter

↓

- Suitable medium containing colonic bacteria (streptococcus faecium or B.ovatus)

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- Amount of drug released at different time intervals determined.

3. In vivo Evaluation

- Rats, mice, pigs and dogs animal models were reported for colon targeted drug delivery systems.
- For simulating the human physiological environment of the colon, appropriate animal model selection is depends on its approach and design of system.
- For example, guinea pigs have glycosidase and glucuronidase activities in the colon and digestive anatomy and physiology is similar to that of human, so they are appropriate in evaluating prodrugs containing glucoside and glucuronate conjugated for colonic delivery.

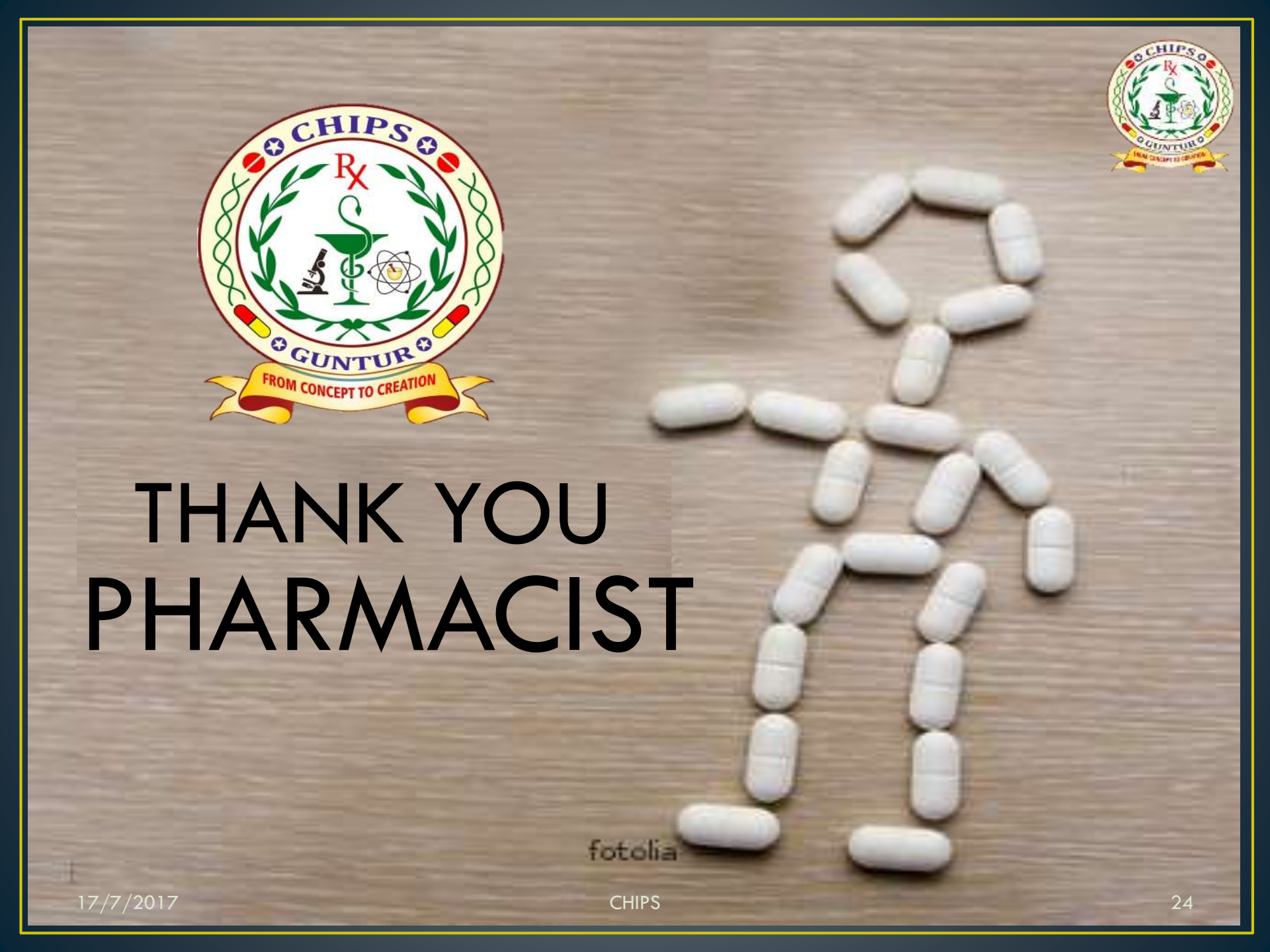
4. Drug Delivery Index (DDI)

$$DDI = \frac{Relative\ colonic\ exposure\ to\ the\ drug(RCE)}{Relative\ systemic\ exposure\ to\ the\ drug(RSC)}$$

- Absorption of drug from colon is monitored by
  - String technique
  - Endoscopy
  - Radiotelemetry
  - Roentegenography
  - Gamma scintigraphy

CONCLUSION

- The colonic region of the GIT has become an important site for drug delivery that considerably offers therapeutic benefits to patients in terms of both local and systemic.
- Colon specificity is more likely to be achieved with natural materials that are degraded by colonic bacterial enzymes.
- Uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, and remains as a challenge for the pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.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