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A REVIEW ON COLON TARGETING MULTIPARTICULATE SYSTEMS

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ABSTRACT

Site specific drug delivery has gained a lot of interest in the last decade. Colon targeting has potential opportunities and challenges in the area of research. Colon was considered as "BLACK BOX" as, most of drugs are absorbed from upper part of GIT tract. Colon-specific drug delivery has gained increased importance as it has large amounts of lymphoma tissue, lack of digestive enzymes and long transit time. Colon specific drug delivery is not only used for the delivery of the drugs for the local treatment of diseases associated with colon but also for the systemic delivery. Colon is the potential site for the delivery of the proteins and peptides. This article reviews the surge of focus on the colon targeting multiparticulate systems as they are having less inter and intra subject variability. Reports suggest that drug carrier systems larger than 200 µm possess very low gastric transit time due to physiological condition of the bowel in colitis. Thus considering the selective uptake of micron or sub-micron particles by cancerous and inflamed cells or tissues a multiparticulate approach based on pellets, granules, and microsphere or nanoparticle type formulation is expected to have better pharmacological effect in the colon.

Key words: Transit time, Multiparticulate systems, Lymphoma tissue, Inter and intra subject variability.

INTRODUCTION

The GIT (gastro intestinal tract) can be divided into various regions in terms of drug targeting. They are oral cavity, oesophagus, stomach, intestine, and the colon (Willams RO *et al*., 1997). There is a need for development of new drug delivery systems for delivering drugs to patients efficiently with fewer side effects. Colonic drug delivery refers to targeted delivery of drugs into the lower gastro intestinal tract, specifically to colon (i.e., part of the large intestine) (Davis S, 1990; Van den Mooter GV, 1995). In the beginning delivery of drugs to the colon was tried through the rectal route using suppository and enema formulations. In such formulations the spreading of drug beyond the descending colon is rare, with little or no drug reaching the proximal colon (Jay M and Beihn RM, 1985; Hardy JG *et al*., 1985). Moreover, the rectal route is unacceptable and inconvenient for most of the patients. Therefore the oral route is the preferable route for targeting colon.

For developing a reliable colonic drug delivery system, the transit time of dosage forms through the gastrointestinal tract and the anatomy of the colon need to be understood very well. The transit time of orally administered dosage form through the GI tract is highly variable and depends on factors (Devereux, 1990; Hunter E, 1982; Meier R, 1990; Price JMC *et al*., 1993) like disease state of the lumen (diarrhea, diabetes, peptic ulcer etc), simultaneous administration of other drugs (domperidone, cisapride, metoclopromide etc), body posture (vertical or supine) and type of food (protein and fat content) can influence the gastric emptying rate.

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Anatomy of colon

The large intestine is approximately 1.5 m in length and extends from the ileum to the anus. Its width decreases gradually from the caecum (approximately 7 cm in diameter) to the sigmoid (approximately 2.5 cm in diameter) (Keshav S *et al*., 2003). The large intestine forms a three-sided frame around the small intestine. It absorbs water from the contents that pass into it from the small intestine. The small intestine absorbs some water but this process is intensified in the large intestine until the semisolid consistency of faeces is achieved. The caecum, colon, rectum and anal canal are the parts of the large intestine. The colon is further divided into four parts. They are ascending colon, transverse colon, descending colon and sigmoid colon.

Ascending colon

The ascending colon (approximately 15 cm long) joins the caecum at the ileocaecal junction. The anterior part of the ascending colon is covered with peritoneum on both sides, while, the posterior surface is devoid of peritoneum. It ascends on the right side of the abdomen up to the liver where it bends acutely to the left. At that point the ascending colon forms the right colic or hepatic flexure and then continues as the transverse colon (Thibodeau G *et al*., 2002).

Transverse colon

The transverse colon is a loop of colon (approximately 45 cm long) that continues from the left hepatic flexure across to the left side of the abdomen to the left colic flexure. It passes in front of the stomach and duodenum and then curves beneath the lower part of the spleen on the left side as the left colic or splenic flexure and then passes acutely downward as the descending colon (Watson R *et al*., 2000)

Descending colon

The descending colon (approximately 25 cm in length) passes downwards on the left side of the abdomen to the level of the iliac crest. The descending colon is narrower and more dorsally situated than the ascending colon.

Sigmoid colon

The sigmoid colon (approximately 36 cm long) begins near the iliac crest and ends at the centre of the mid-sacrum, where it becomes the rectum at the level of the third sacral vertebra. The sigmoid colon is completely covered by peritoneum.

Functions of colon (Christine Edwards *et al*., 1997)

- The caecum and proximal colon are the major sites for bacterial carbohydrate metabolism and therefore act as fermentation chamber.
- The transverse colon may also be an important site for the absorption of water and the formation of faeces. The predominant motor patterns of the transverse colon hold material in the proximal colon for further fermentation or propel it distally, emptying the proximal colon.
- The distal colon and rectum are reservoirs for fecal material allowing defecation to be delayed until socially convenient.
- The pH is different throughout the GIT and the variability depends upon factors such as food intake, intestinal motility and disease states. This inconsistency in the gastric pH makes it more challenging for the specialists to develop a delivery system that would be robust enough to withstand these changes (Spitael, 1980; Devereux JE *et al*., 1990).The colonic drug delivery system uses this difference in pH along the GIT to target the drug (Thomas P *et al*., 1985). The pH of the stomach is 1.2and pH of the small intestine from the proximal part to the distal small intestine ranges from 6.6 – 7.5(Evans DF *et al*., 1988). The fall in pH in the colon is due to the production of short chain fattyacids from the bacterial fermentation of polysaccharides (Tomlin J *et al*., 1988).

Microflora in the colon

- Drug release from the colon targeting dosage forms in various parts of gastro intestinal tract depends upon the existence of intestinal enzymes that are derived from gut microflora residing in high numbers in the colon. These enzymes are used to destroy coatings/matrices and to convert prodrug into active agent by breaking the bonds between an inert carrier and an active agent resulting in the drug release from the formulation.

- Nearly 400 distinct bacterial species have been discovered, out of which genus Bacteroides ranges from 20% to 30% **(**Sarasija S Hota A.,**).** A small number of fungi are also present. Others are facultative anaerobes **e.g.:** E.Coli. The concentration of bacteria in human colon is 10^{11}-10^{12} CFU/mL (colony forming unit/mL) in colon (Ramaprasad YV, 1995; Simon, GL and Gorbach SL, 1984). Most of these microfloras are anaerobes. **e.g.:** Bacteroides, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Ruminococcus, Propionibacterium, and Clostridium (Krishnaiah YSR *et al.*, 2002).

- Carbohydrates and proteins, which escaped digestion in the upper GIT, are metabolized by the enzymes secreted by colonic bacteria (Molly K *et al.*, 1993) Colonic microflora produces a large number of Hydrolytic

(Hawksworth G *et al*., 1971) as well as reductive enzymes (Rowland IR *et al.*, 1988) which can be utilized for colon-specific drug delivery. Prodrugs (Ryde EM *et al.*, 1992) and coatings of azoaromatic polymer (Saffran, M *et al*., 1986) and matrices (Brondsted H *et al*., 1981) containing azoaromatic cross-links are degradable by reductive enzymes released by colonic bacteria (Jain A *et al*., 2006). The microflora releases other polysaccharidases like glucosidases and glycosidases are also released by colonic microflora, which are responsible for the degradation of polysaccharides (Larsen, 1989; McLeod AD *et al*., 1983). Pectin and its combination with other polymers have been studied for colon-specific drug delivery (Schacht E *et al*., 1996). A summary of the metabolic reactions carried out by intestinal bacteria is provided in Table no 2 (Lee VHL *et al*., 2002).

Colon targeted drug delivery system

The proper selection of a formulation approach is dependent upon several important factors like pathology and pattern of the disease (especially the affected parts of the lower GIT) or physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment, physicochemical and biopharmaceutical properties of the drug such as solubility, stability and permeability at the intended site of delivery and the desired release profile of the active ingredient.

Advantages of the colonic drug delivery system

1. Drugs can be directly targeted to the colon for the treatment of several colonic diseases like inflammatory bowel diseases (Crohn's disease and ulcerative colitis), irritable bowel syndrome and colon cancer.

2. The formulations such as proteins and peptides which are susceptible to chemical and enzymatic degradation in the upper part of the GIT can be given by colonic drug delivery as relatively low proteolytic enzyme activity (Jitendar Mor, 2011; Luck M, 2000; Watts PJ, 2001)**.**

3. The colon contains high amount of lymphoid tissue and uptake of antigen into mast cells
of the colonic mucosa leads to rapid local production of antibodies and helps in efficient delivery of vaccines (Yang H *et al.*, 1999).

4. The metabolizing enzyme, cytochrome P450 3A class, is comparatively lower in the colonic mucosa than in the small intestine therefore the bioavailability of drugs can be improved (Basit A *et al.*, 2003).

5. A much longer transit time of colon offers a much greater responsiveness to absorption enhancers for the delivery of drugs for colon (MacFarlane GT *et al*., 1989).

6. Colon targeting can be utilized for the chronotherapeutic delivery of drugs for the treatment of diseases like asthma, arthritis, and hypertension (Singh BN *et al*., 2002).

7. Comparatively lesser amount of required dose.

8. Decreased side effects.

9. Improved drug utilization

Limitations of the colonic drug delivery

1. The main limitation for colon drug delivery is to preserve the formulation and drug from degradation. It should prevent the release and also the absorption from the upper part of GIT due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access (Ashford M, 1994; Tarak Jayraj Mehta *et al*., 2011).

2 Enzymatic stability is essential for successful colonic uptake of a drug.

3 Relative 'tightness' of the tight junctions in the colon causes insufficient epithelial permeability.

4 Designing of appropriate dissolution method for the *invitro* evaluation is the one of the major challenge because of the rationale after a colon specific drug delivery system is quite diverse.

5 The drug to be in solution form before it reaches in the colon or it should dissolve in the luminal fluids of the colon. It is the main limitation for the delivery of poorly soluble drugs as the fluid content is much lower and viscosity also higher than the upper part of the GIT (Kollam Prasad AV *et al*., 2011).

***DRUGS SUITABLE FOR CDDS* (**Sateesh Kumar Vemula and Prabhakar Reddy Veerareddy, 2010**)**

Drugs used for the treatment of local diseases of colon

1. For the treatment of IBD

E.g. sulfasalazine, olsalazine, mesalazine, steroids like fludrocortisone, budesonide, prednisolone and dexamethasone.

2. For the treatment of colon cancer

E.g. 5-fluorouracil, doxorubicin, and methotrexate.

3. Protein and peptide drugs - eliminating drug degradation

E.g. Growth hormones, calcitonin, insulin, interleukin, interferon and erythropoietin.

4. To treat infectious diseases (amoebiasis & helminthiasis) - requires site specific delivery

E.g. metronidazole, mebendazole and albendazole,

5. To treat rheumatoid arthritis (NSAIDS), nocturnal asthma, angina require delay in absorption due to circadian rhythms

6. Drugs showing more selective absorption in colon than small intestine due to small extent of paracellular transport
E.g. Glibenclamide, diclofencac, theophylline, ibuprofen, metoprolol, and oxyprenolol.

Colon targeting drug delivery is divided into 2 types
They are 1. Single unit systems
2 .Multiparticulate systems

COLON TARGETING SINGLE UNIT SYSTEMS

Single unit systems are formulated as capsule based and osmosis based systems. Single unit systems are designed by coating the system either with eroding/soluble or rupturable coating with suitable polymers (Ali AF, 2006; Ashford M *et al.*, 1994).

Advantages
1. The manufacturing process is simple due to less number of formulation steps.

Disadvantages
Such kind of delivery systems may suffer from the following limitations:
1. Unintentional disintegration of the formulation due to manufacturing deficiencies or unusual gastric physiology may lead to decreased systemic drug bioavailability and there by therapeutic action in the colon decreases (Shidhaye SS *et al*., 2011).
2. The gastric residence time is variable.

MULTIPARTICULATE DRUG DELIVERY SYSTEMS

Multiparticulate drug delivery systems are reservoir type of oral dosage forms consisting of a collection of small discrete units and their diameter is ranging from 0.05-2.00 mm. In these systems, the dosage of the drug is divided into many subunits consists of thousands of spherical particles (Roy P *et al.*, 2009). To deliver the total dose, these subunits are filled into a capsule or compressed with additional excipients to form a tablet (Daumesnil R, 1994; Ueda Y *et al*., 1989).

In 1985 Hardy and co-workers (Hardy JG *et al*., 1985) showed that multiparticulate systems reach the colon quickly and were retained in the ascending colon for a relatively long period of time. The multiparticulate systems perform better *in vivo* than single unit systems, as they spread throughout the length of the intestine causing less irritation, and also have slower transit through the colon and give a more reproducible drug release (Kramer A *et al*., 2003).

Multiparticulate drug delivery systems are reservoir type of oral dosage forms. These systems show various advantages as well as disadvantages over single – unit systems, which are as follows (Davis SS *et al.*, 1989)

Advantages
1. The gastric residence time is short, predictable, and reproducible.
2. The inter- and intra-subject variability is less.
3. The bioavailability can be improved.
4. Adverse effects are less and tolerability is improved.
5. Local irritation is less.
6. No dose dumping.
7. Flexibility in design.
8. Stability can be improved.
9. Patient comfort and compliance can be improved.
10. Unique release pattern can be achieved.

Disadvantages
1. Drug loading is low.
2. Higher need for excipients than single unit systems.
3. Lack of manufacturing reproducibility and efficacy.
4. Process variables are more.
5. Several formulation steps.
6. Production cost is high.
7. Advanced technology is needed.

MULTIPARTICULATE SYSTEMS ARE FORMULATED AS:

1. Reservoir system with rupturable polymeric coating:

In multiparticulate systems the devices with reservoir are coated with a rupturable polymeric layer. These reservoir systems comprised of many layers, some of them contain drug substance, while the remaining are rate controlling polymers. The effect of rupturing can be achieved by coating the individual units with osmotic or swelling agents. Various release profiles can be achieved using reservoir systems including sustained release of drugs for absorption throughout the gastrointestinal tract. Time delayed release of the active pharmaceutical ingredient can be either a burst release or sustained release profile achieved over a period of 1 – 12 h, with a lag – time of 4 – 10 h. The duration of drug release depends on the composition and also the thickness of the polymer barrier. The lag time depends on coating. Optimal release profiles for either single drugs or for a combination of drugs can be achieved by the multiparticulate systems. (Meyer JH *et al.*, 1985) Ueda *et al.*, attempted for the first time to develop a time dependent system for colon delivery. Those inventers developed a time controlled explosion system (TES) in which drug released is by the explosion of a membrane after a definite lag time, which is

programmed precisely. Both single and multiple unit dosage forms can be prepared by using timed explosion systems. In TES, the core contains drug plus inert osmogen and suitable disintegrating agents. The core is coated by a protective layer and then by a semipermeable layer, which is the rate controlling membrane for the entry of water into osmotic core. The osmotic pressure buildup by water access causes explosion of the core, with an immediate release of the active ingredient. Swelling agents also leads to the explosion. (Ueda S, 1994; Ueda S and Yamaguchi H, 1994)

2. *Reservoir systems with soluble or eroding polymer coatings*

Another class of reservoir type multiparticulate pulsatile systems is based on coating of soluble or erodible polymer. In this after a specific lag time the barrier dissolves or erodes followed by burst release of drug from the reservoir core. Thickness of the coating layer controls the lag time before drug release. The basic principle involved is that pH – sensitive polymers solubility increases to their large extent at same pH in the gastro intestinal tract. It prevents the release of drug in the stomach and completely releases the drug in intestine. The release mechanism from these systems is dissolution, for this a higher ratio of drug solubility to the dosing amount is necessary for rapid release of drug after the lag period.

3. *System with changed membrane permeability*

In order to diminish the nocturnal symptoms or the symptoms in the early morning for certain diseases which are based on the circadian biorhythms (hypertension, ischemic heart disease, asthma and arthritis), the dosage forms should be administered in such a way that the desired therapeutical plasmatic level is reached only during sleep or in the early morning hours (Kalantzi LE *et al*., 2009). The release profile in this system depends on physicochemical properties of active ingredient and its interaction with the membrane. Each individual unit contains a drug containing core, and a water soluble osmogen (NaCl) enclosed in a water-insoluble and permeable film. Incorporation of hydrophobic, insoluble agent in to the polymer alters the permeability of the polymer film. The osmogen dissolves in the water, causing the pellet to swell and regulates the rate of diffusion of drug from the core. Sigmoidal release pattern is observed coating systems which is therapeutically beneficial for timed release and colonic drug delivery. The Sigmoidal release pattern is based on the permeability and water uptake of polymers and also influenced by the presence of different counter ions in the release medium (Bodmeier R *et al*., 1996). Narisawa *et. al.* (Narisawa S, 1996; Narisawa S, *et al.*, 1993) developed a system with this type of ion exchange. Eudragit RS 30D is the polymer of choice for this purpose. It consists of positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied with a negative hydrochloride counter-ion. As the quaternary ammonium group of the polymer is hydrophilic, it facilitates the interaction with water, thereby changing its permeability and allowing water to permeate the core in a controlled way.

RECENT INNOVATIONS IN MULTIPARTI CULATE SYSTEMS:

1. *pH- and time- dependent systems*

The pH in the terminal ileum and colon (except ascending colon) is higher than in remaining regions of the gastro intestinal tract. Therefore the dosage form that disintegrates preferentially at high pH levels is suitable for site-specific delivery to the colon.

Formulating the enteric coated granules is one of the simplest approaches for designing pH dependent multiparticulate colon specific delivery system. It has been used to prevent drug release in the upper GIT. Their use as binders and coating materials for granules have been reported (Marvola M *et al*., 1999) Incorporation of organic acids in granule matrices also influences the drug release (Nykanen P *et al*., 1999) In one such study, incorporation of citric acid into both the granules as well as the matrix of the enteric coated tablets of ibuprofen showed retardation in the *in vitro* release and *in vivo* absorption of the pharmaceutically active ingredient because of the prolongation in disintegration time of the core system because of the presence of the acid (Nykanen P *et al*., 2001).

Most commonly used pH-dependent coating polymers are methacrylicacid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratios makes it possible to influence the drug release within 6.0-7.0 pH range. Earlier reports showed that usage of Eudragit S alone is not apt for colonic delivery. (Nykanen P *et al.*, 1997) Studies in human volunteers have shown that the pH drops from 7.0 at terminal ileum to 6.0 of ascending colon. (Chu JS *et al*., 2003)In order to overcome this problem, a proper combination of polymers Eudragit S100 and Eudragit L100 is used to prevent the failure of drug release.

2. *Microbially controlled systems*

Microbially controlled delivery system is the

most interesting for colon targeting as it relies on the unique enzymatic ability of the colonic micro flora and enables a more specific targeting, independent of the variations in pH throughout the gastro intestinal tract. Many natural polysaccharides such as chitosan, xanthan gum, chondroitin sulphate, pectin, dextran, guar gum etc. have been investigated for their potential use in colon targeting. (Sinha VR *et al.,* 2003)

Pectin is the one of the most widely used polysaccharide for the delivery of drugs to the colon. The capacity of amidated low methoxy pectin to form rigid gels with divalent cations has been exploited to produce calcium pectinate gel beads, for controlled delivery of drugs and also as a carrier for colonic delivery of proteins. (Sria mornsalk P *et al.,* 1988) Pectin has high water solubility. To overcome the problem of high dissolution of pectin in the upper GI tract, pectin has been reacted with calcium salts since calcium pectinate (the insoluble salt of pectin) is not degraded by enzymes present in the stomach and intestine. But they are degraded by colonic pectinolytic enzymes. El-Gibaly *et al* studied the comparative efficacy of zinc pectinate gel microparticles against calcium pectinate gel beads for colon targeting (ElGibaly I *et al.,* 2002).The drug loaded beads were prepared by the ionotropic gelation method and the cross linking agent used were calcium chloride and zinc acetate. The comparison of *in vitro* drug release properties showed significant retardation in the case of zinc-pectinate microparticles (t50% of 7.33 h) against calcium-pectinate based beads (t50% of 35 min). The observed differences were because of the differences in degree of cross linking of the two gel types, which inturn affects the penetration of solvent into the microparticles, swelling rate of the microparticles, and consequently the drug release.

3. *Microparticulate systems*

In IBD treatment, because of the symptoms like diarrhoea the sustained release devices like pellets, capsules or tablets have less efficiency, which enhances their elimination and reduces the total time available for drug release. It has been shown that drug carrier systems whose size is larger than 200 µm would be subjected to rapid bowel evacuation because of diarrhoea, ensuing in a decreased gastrointestinal transit time and decreased efficiency (Watts PJ *et al*., 1992). Therefore, a multiparticulate system in the µ size range could be a better option in the designing a suitable dosageform for IBD. Among pH-sensitive Eudragit polymers belongs to the group of polyacrylates and possesses a dissolution threshold at pH slightly above 7.2. As ulcerative colitis mainly affects the distal parts of the colon and also to prevent early drug loss towards the non-inflamed tissue Eudragit P-4135 F is very useful. Now a day's most of the pH-based colonic drug delivery systems utilize Eudragit S and L which dissolve in the pH range of 6-7 and liberate the drug at the terminal ileum, which may lower the efficiency of dosage form and may increase risk of adverse effects. Eudragit P-4135 F is a useful alternative for targeting the distal colon.

4. *Nanoparticulate systems*

Nanoparticles for colon targeting are composed of natural or synthetic polymers have also been investigated. Orally administered nanoparticles are carriers for different types of drugs and also shown to increasing their solubility, permeability and bioavailability (Wilders *et al*., 1984). Protein and peptide drugs can also be delivered through nanoparticles (Seldenrijk *et al*., 1989).

For colonic diseases like IBD, nanoparticles tend to accumulate at the site of inflammation. Because of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of neutrophils, Natural Killer cells, macrophages and so on leads to the increased accumulation. Efficient uptake of microspheres and nanoparticles by the macrophages has been reported (Kreuter J *et al*., 1991). This uptake by the macrophages results in accumulation of the particulate carrier system for prolonged residence time in the desired area (Couvreur P *et al*., 1993).

The nanoparticles usage for bioadhesion purposes have also been investigated (Lamprecht A *et al*., 2001).Nanoparticles have high interactive potential with biological surfaces, which is due to their large specific surface. Bioadhesion can be induced by binding of nanoparticles with different molecules as the interaction is nonspecific in nature. The nanoparticle surface has to show free functional groups (carboxylic or amine residues) for attachment.

Loss of nanoparticle in the early transit through GI tract is an important area of concern in order to optimize therapeutic efficacy (Lamprecht A *et al.,* 2001). Particle uptake by Payer's patches and/or enzymatic degradation may cause the release of entrapped drug leading to systemic drug absorption and side effects are also one of the problem. In order to overcome this, entrapment of drug loaded nanoparticles into pH sensitive microspheres is done, which leads to deliver the incorporated nanoparticle to the site of action and prevents the early leakage of drug. The use of Eudragit P-4135F which is a pH sensitive polymer prevented drug release in

the upper gastrointestinal tract and during intestinal passage and permitted targeted delivery of drug to the colon (Krishnaiah YSR *et al.,* 2003).

Invivo behaviour of the colon targeting multiparticulate systems:

Animals such as dogs, guinea pigs, rats and pigs are used for evaluating the delivery of drug to colon because of the resemblance of the anatomic and physiological conditions as well as the microflora of human GIT. While selecting the model for testing colon targeting, suitable model for the colonic diseases should also be considered. Eg. Commonly for experimental IBD model guinea pigs are selected. The distribution and activity of enzymes azoreductase and glucouronidase in the GIT of rat and rabbit is comparable to that of the human (Asha Patel *et al*., 2011).

Gamma scintigraphy based imaging technology is in the good evidence of the actual *in vivo* behavior of colon targeted dosage forms (Kwabena OK *et al*., 2004). The parameters like gastro intestinal transit time, residence time in small intestine, colon arrival time, and residence time in colon represent vital information for *in vivo* evaluation and establishing *in vitro-in vivo* correlation of colon targeted dosage forms (Christensen FM, 1985, Billa N, 2000).

Abrahamsson and co-workers studied, that the GI transit of a multiparticulate dosage forms in the form of pellets and a non-disintegrating tablet of metoprolol (Abrahamsson B *et al*., 1996). The pellets and tablets of metoprolol were administered with breakfast to eight healthy male human subjects simultaneously. A statistically significant difference was reported between the mean gastric emptying time for the pellets (3.6h) and that for the tablet (9.6 h).

Figure 1. Anatomy of GIT

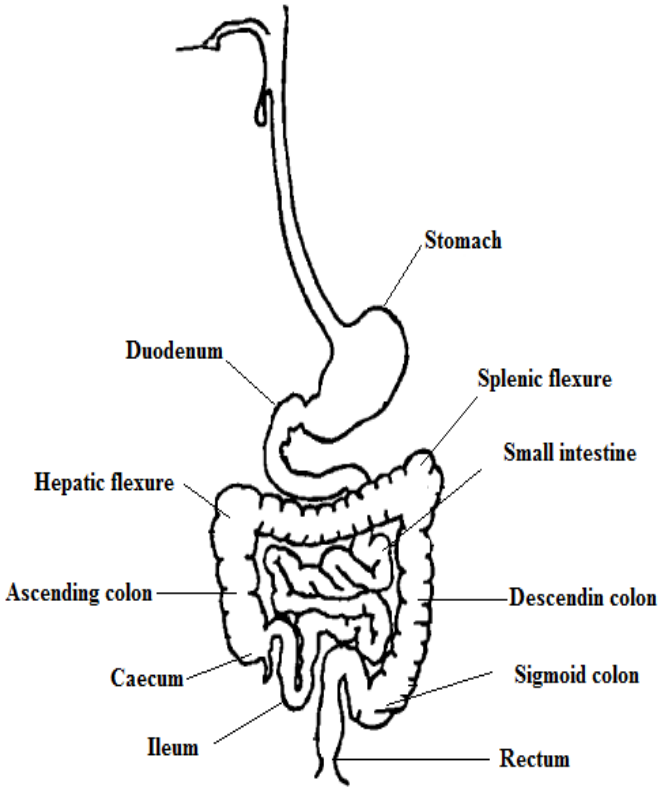

Table 1. Length and diameter of the different parts of GIT

	Length (cm)	Internal diameter
Small intestine		
Duodenum	20-30	3-4
Jejunum	150-250	3-4
Ileum	200- 350	3-4
Large intestine		
Cecum	6-7	8
Ascending colon	20	6
Transverse colon	45	5
Discending colon	30	5
sigmoid colon	40	5
Rectum	12	4
Anal canal	3	4

Table 2. pH of different parts of GIT

S. No	Part of the GIT	pH
1	Stomach	**1 – 3.5**
2	Duodenum	**5 – 7**
3	Jejunum	**6 - 7**
4	Ileum	**7**
5	Colon	**5.5 - 7**
6	Rectum	**7**

Table 3. Different metabolic reactions of microflora and their enzymes

S. No	Micro organisms	Enzymes	Metabolic reaction catalyzed
1	E.Coli, Bacteroids	Nitroreductase	Reduce aromatic and heterocyclic nitro compounds
2	Clostridia, Lactobacilli, E.Coli	Azoreductase	Reductive cleavage of azo compounds
3	E.Coli	N-oxide reductase, Sulphoxide reductase	Reduce N- oxides and Sulphoxides
4	Clostridia, Lactobacilli	Hydrogenase	Reduce carbonyl groups and aliphatic double bonds
5	E.Coli, P. vulgaris, B. subtilis, B. mycoides	Esterases and Amidases	Cleavage of esters and Amidases of carboxylic acid
6	E.Coli, A. aerogenes	Glucuronidase	Cleavage of β Glucuronidase of alcohols and phenols
7	Clostridia, Eubacteria	Glucosidase	Cleavage of β Glycosidase of alcohols and phenols
8	Clostridia, Eubacteria, Streptococci	Sulphatase	Cleavage of O-sulfates and sulfamates

CONCLUSION

However, the mean transit through the small intestine did not vary significantly for the two formulations - pellets (3.1 h) and tablet (2.0 h). The pellets were found to have a longer residence time in the colon in all subjects as compared with the tablet, with mean colon transit time of 28 h for pellets and 15 h for the tablet. This study helped to highlight the differences in the *in vivo* behavior of multiparticulate and single unit dosage forms.

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