1.1 INTRODUCTION

The colon is liable to various diseases such as Crohn’s disease, inflammatory bowel disease, ulcerative colitis, carcinomas and infections. The drugs recommended for these problems include anti-inflammatory drugs, corticosteroids, immunosuppressive agents, antibiotics and anti cancer drugs, which must be released in the colon. (1) Site-specific drug delivery to the colon is considered for the past few years in order to develop drug delivery systems that are able to release drugs specifically in the colon in a predictable and reproducible manner. The importance of site specific drug delivery to colon is for the treatment of diseases associated with the colon, reducing the side effects and reducing the dose. The pharmaceutical formulations available for this treatment are slow release oral formulations or enemas and foams for rectal administration. The formulations, however, are not truly site-specific, and the treatments are connected with a high frequency of systemic side effects. The side effects appear to be more frequent after administration of oral formulations compared with rectal formulations because of the large degree of systemic absorption from the upper gastrointestinal tract.

The main advantages of colon targeting are near neutral pH, longer transit time, relatively less proteolytic enzyme activity, and a much greater responsiveness to absorption enhancers. These criteria favour this distal part of the gastrointestinal tract (GIT) as a site for the delivery of various drug molecules, including protein-peptide drugs such as insulin, calcitonin, met-enkaphalin etc. and even for other nonpeptide drugs such as cardiovascular and antiasthmatic agents (e. g. Nifedipine, Theophylline, Isosorbide etc.) that are liable to first pass metabolism, gastric irritation and enzymatic degradation in upper part of GIT. (2, 3)

1.2 FACTORS IMPORTANT IN THE DESIGN OF COLON TARGETED DRUG DELIVERY SYSTEMS:

pH in the Colon: The pH of the GIT gradually increases as one moves down the GI tract from the stomach (1.0-2.5) to the terminal ileum (pH 7-8). However, the pH of the colon drops to 5.5-7 because of the acidification of the colonic contents caused by the products of bacterial fermentation. The highest level of pH (7.5±0.5) was found in terminal ileum. On entry to colon, the pH dropped to 6.4±0.6. The pH in the mid-colon was measured at 6.4±0.6 and in the left colon 7.0±0.7. (4) This pH variation in different segments of the GIT has been exploited for Colon
specific delivery. However, the pH of the GIT is subject to both inter and intra-individual variations, depending on the diet, disease, age, sex and the fed/fasted stage.\(^{5}\)

**Colonic Microflora:** There are over 100 billion bacteria in the gut and 400 different species which ferment undigested material e.g. polysaccharides, are metabolically active and affect the redox potential and pH of the lower gut. \(^6\) The upper part of GIT i.e. the stomach and the duodenum has a microflora of less than \(10^3\) to \(10^4\) CFU/ml. These are mainly gram +ve facultative bacteria. The microflora of the colon on the other hand is in the range of \(10^{11}\) to \(10^{12}\) CFU/ml consisting of mainly anaerobic bacteria e.g. *Bacteroides*, *Bifidobacteria*, *Eubacteria*, *Clostridia*, *Enterococci*, *Enterobacteria*, etc.\(^7\)

**Gastro-intestinal Transit Time:** Gastric transit of single unit non-disintegrating dosage form has been reported to vary from 15 min to more than 3 h. However, it is widely agreed that the small intestine residence time is fairly constant at 3-4 h. The mean colonic transit time in humans is reported to be 33h while in women it is 47h.\(^8\) The total time for transit tends to be highly variable and is influenced by number of factors such as diet, in particular dietary fiber contents, mobility, stress, disease and drugs.

### 1.3 APPROACHES FOR COLON TARGETED DRUG DELIVERY

**pH-dependent Systems:** The action of the pH-dependent delivery systems are based on the pH differences between the stomach and ileum. The use of pH-dependent polymers is based on the difference in the pH levels.\(^9,10\) The polymers described as pH-dependent in the colon-specific drug delivery systems are insoluble at low pH levels but become increasingly soluble as the pH rises. Widely used pH polymers are methacrylic resins, glycidyl methacrylate dextran.\(^11,12\)

**Time-dependent systems:** Time dependent formulations are designed to resist the release of drug in the stomach with an additional non-disintegrating or log phase included in the formulation (which equals to the small intestine transit time) and the release of the drug takes place in the colon e.g. Pulsincap. Variation in the gastric emptying and small intestine transit time are two limitations of this type of system. There is considerable variability in the in-vivo performance in the time-dependent systems by virtue of variations in the small intestine transit time.\(^13,14\)

**Pressure controlled systems:** Pressure strategy relies on the strong peristaltic movement in the colon and that leads to a temporary increased luminal pressure. Pressure sensitive drug
formulations release the drug as soon as a certain pressure limit is exceeded. The pressure and the destructive force induced by peristaltic waves are certainly high in the distal part of the large intestine. However, knowledge about the reproducibility and duration of this high-pressure phase is incomplete.\(^{(12,15)}\)

**Microflora activated systems:** The vast microflora fulfils its energy needs by fermenting various types of substrates that have been left undigested in the small intestine e.g. di and tri saccharides, poly saccharides, etc. For this fermentation, microflora produces a vast number of enzymes such as \(\beta\)-glucuronidase, \(\beta\)-xylosidase, \(\alpha\)-arabinosidase, \(\beta\)-galactosidase, nitroreductase, azoreductase and urea dehydroxylase.\(^{(16)}\) Because of the presence of these biodegradable enzymes only in the colon the use of bacterial degradable polymers for colon specific drug delivery seems to be a more specific approach as compared to other approaches. These polymers shield the drug from the environment of the stomach and the small intestine and are able to deliver the drug to the colon. On reaching the colon these undergo assimilation by the microorganism or degradation by enzyme or breakdown of the polymer backbone leading to a subsequent reduction in their molecular weight and thereby loss of the mechanical strength. They are then unable to hold the drug entity any longer\(^{(17)}\).

### 1.3 POLYMERS USED FOR COLON DRUG DELIVERY

Various polymers like Eudragit, chitosan, chondroitin sulfate, gelatin, alginate, cyclodextrins were tried to target the drug to the colon. Some of these were used for pH dependent systems and some for microflora-activated system. Microflora-activated system is highly advantageous due to considerable variability in the \textit{in vivo} performance in time dependent, pressure controlled system and pH dependent systems. Therefore, efforts are being made by the researchers to explore the colonic microflora for targeting drugs to colon. For this biodegradable polymers are preferred so that they can shield the drugs from the environment of the stomach and the small intestine and are able to deliver the drug to the colon. However, some biodegradable polymers are liable to acid degradation in stomach as well as in intestinal environment conditions. Therefore, they are to be made insoluble either by modification or by cross-linking with other polymers.