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Review Articles

VARIOUS APPROACHES USED FOR COLONIC DRUG DELIVERY SYSTEM

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ABSTRACT

Aim: The review article is aimed at understanding the various features of the different primary as well as potential novel pharmaceutical approaches used for colon targeted drug delivery systems for better therapeutic action without compromising on drug degradation and its low bioavailability. Colon specific drug delivery has gained immense importance not only for the treatment of local diseases associated with the colon but also as potential site for systemic delivery of therapeutic proteins and peptides. **Material and method:** Literatures and reports were taken from research articles published in various journals, data from different books and other online available literature. **Results:** This review article compares the different approaches to colon targeted drug delivery like pH and time dependent, prodrug, microbial triggered drug delivery, azo hydrogels, pressure controlled drug delivery, pulsatile drug delivery system, osmotic controlled drug delivery system, etc. **Conclusion:** The review provides a systematic discussion of various conventional, as well as relatively newer formulation approaches/technologies currently being utilized for the development of colon specific drug delivery system.

Keywords: Colon specific drug delivery system, Advantages, Approaches.

Introduction:

COLON SPECIFIC DRUG DELIVERY SYSTEM (CSDDS)

Colon specific drug delivery system (CDDS) has attained the focus of various studies in recent years due to its potential to improve treatment of local diseases affecting the colon, while minimizing systemic side effects (Amidon et al., 2015). The colon targeted drug delivery is valuable for the localized treatment of several colonic diseases mainly inflammatory bowel diseases (IBD), irritable bowel syndrome and colonic cancer. The colon specific drug delivery system is capable of protecting the drug from acidic pH of stomach and delivers it to the colon (Philip and Philip, 2010). A colon specific drug delivery system (CDDS)should have the property of releasing the drug in to the colon i.e. drug release and absorption should be prevented in the stomach as well as the small intestine and the bioactive agent should be released and absorbed once it reaches to the colon (Prathap et al.). The colon is considered to be more suitable for delivery of peptides and protein in comparison to small intestine as the peptide and protein drugs are destroyed and inactivated in acidic environment of the stomach or by pancreatic enzymes (Anuj and Amit, 2010).As the colon has a long residence time up to five days and is highly responsive to absorption enhancers, thus colon-targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon which make this organ an ideal site for drug delivery (Philip and Philip, 2010).

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Certain drugs which are destroyed by the stomach acid and metabolized by pancreatic enzymes can be protected with the colon specific drug delivery. Sustained release of drugs into colon can be beneficial in the treatment of many diseases (Prathap et al.). Numerous approaches have been developed for colon targeted drug delivery. Most of these approaches utilize the physiological properties of the GIT and colon such as pH of GIT, transit time of small intestine and the presence of microbial flora existing in the colon (Anuj and Amit, 2010).The physico-chemical properties of drug, the type of delivery system and all other factors that can influence the GI transit time, along with the degree of interaction between the drug and the GI tract plays important role in success of a colon specific drug delivery. Therefore the approaches used in developing a CDDS are aimed at delaying the drug release until the system reaches the colon (Amidon et al., 2015). As a site for drug delivery colon offers diverse advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity, and a greater responsiveness to absorption enhancers. The longer residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancer are certain advantages which make the colon a promising site for the delivery of protein and peptide drugs for systemic absorption (Anuj and Amit, 2010).

ADVANTAGES OF CSDDS

1. Targeted drug delivery to the colon would ensure direct treatment at the disease site, lower dosing and fewer systemic side effects (Prathap et al.).
2. Used for the effective treatment of inflammatory bowel diseases like ulcerative colitis and crohn's disease (Sreelatha and Brahma, 2013).
3. Reduces dosage frequency. Hence, decreased cost of expensive drugs (Singh and Khanna, 2012).
4. It is a promising site for a drug which is unstable or poorly absorbed from upper GI tract (Singh and Khanna, 2012).
5. Prevents gastric irritation caused by administration of many drugs (e.g. NSAIDS) (Sreelatha and Brahma, 2013).
6. Bypass the first pass metabolism (Singh and Khanna, 2012).
7. Increased patient compliance (Sreelatha and Brahma, 2013).
8. Decreases the incidence of side effects and drug interactions in the treatment of colon diseases (Singh and Khanna, 2012).
9. Colon has low hostile environment, less peptidase activity. So peptides, oral vaccines, insulin, growth hormones, can be given through this route (Singh and Khanna, 2012).
10. A number of other serious diseases of the colon, e.g. colorectal cancer, may also be treated more effectively by colon specific drug delivery system (Prathap et al.).

ANATOMY AND PHYSIOLOGY OF COLON

The human large intestine is approximately 1.5 m long and forms the colon (ascending, transverse, and descending), with a small distal part forming the rectum. The large intestine extends from the ileocaecal junction to the anus which is divided into three main parts colon, rectum and anal canal (Prathap et al.).The average size of colon is 1.5 m long, the transverse colon is the longest and most mobile part and has an average diameter of about 6.5 cm. The colon constitutes caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon and sigmoid colon (Fig. 1).

Colon extracts water and salts from solid wastes before they are eliminated from the body (Sreelatha and Brahma, 2013). The parts of colon are located either in the abdominal cavity or behind it in retro peritoneum. The physiology and the physical properties of the colonic contents also differ between the ascending, transverse, descending, and sigmoid colon (Amidon et al., 2015). Factors such as viscosity and volume of colonic fluids, the presence of microbial enzymes, and the resulting colonic metabolism another important factors that influences the performance of colon targeted drug delivery (Amidon et al., 2015).

Figure: 1 Anatomy of colon

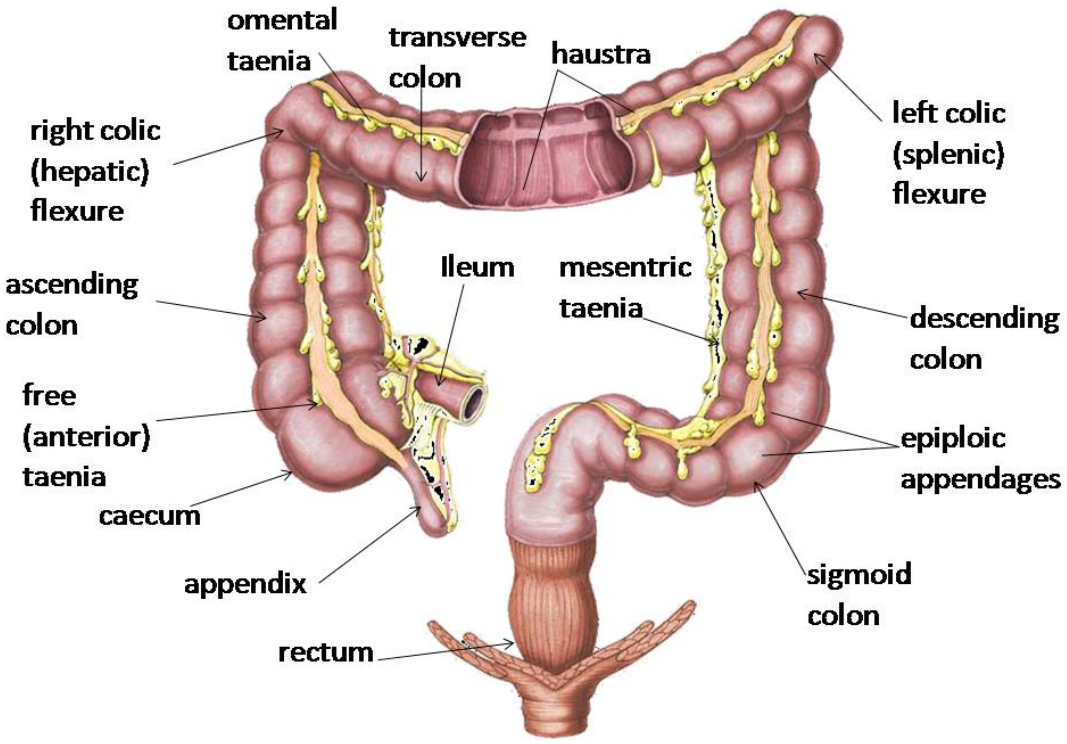

Figure 1 : Anatomy of colon

FACTORS AFFECTING COLON TARGETD DRUG DELIVERY

1. Physiological factors
2. Pharmaceutical factors

1. Physiological factors

a. Intestinal-Colonic Transit Time

The intestinal-colonic transit time plays a crucial role in the performance of CDDS and the colonic bioavailability of drugs. Drug delivery to the colon upon oral administration depends mainly on gastric emptying and bowel transit time. The transit of dosage forms generally depends on the time of administration, presence/absence of food, and the type of dosage form (Amidon et al., 2015).Smaller particles have more transit time compared to larger particles. Diarrhoea patients have shorter transit time whereas constipation patients have longer transit times (Malleswari and Ratna, 2016). Transit time of different parts of GIT is outlined in Table 1.

Table 1: Transit time of different parts of GIT (Sreelatha and Brahma, 2013).

Part of GIT	Transit time
Fasted state	10min – 2hr
Fed state	>2hr
Small intestine transit	3-4hr
Colon transit	20-35hr

b. Colonic pH

The pH varies significantly between different regions of the GIT and different individuals. The food intakes, diseased state influences the pH of the GIT (Prathap et al.).This change in the pH in different parts of GIT is the basis for the development of colon targeted drug delivery systems. Coating with different polymers is done to target the drug to the site (Sreelatha and Brahma, 2013).

Gastrointestinal pH profile: (Agarwala et al.)

- Stomach pH 1- 1.5
- Small intestine pH 5-7.5
- Ascending colon pH 6.3 ± 0.58
- Transverse colon pH 6.6 ± 0.83
- Descending colon pH 7.04± 0.67

c. Colonic micro flora and enzymes

The colon consists of over 400 different species of aerobic and anaerobic microorganisms like Escherichia coli and Clostridium species. These bacteria contain several hydrolytic and reductive metabolizing enzymes. These colonic enzymes catalyze a range of reactions, that include the metabolism of xenobiotics (e.g., drugs) and the biomolecules (e.g., bile acid), deactivation of harmful metabolites as well as carbohydrate and protein (Amidon et al., 2015).Various parts of the GIT use intestinal enzymes to trigger drug release. These enzymes are usually derived from gut micro flora that resides in high numbers in colon. These intestinal enzymes are used to degrade coatings/matrices as well as to break bonds between an active agent and its carrier (Friend, 2005). E.coli, Clostridia, Lactobacilli, Eubacteria, Streptococci are microorganisms that release various enzymes responsible for the different metabolic reactions that take place in the GIT (Malleswari and Ratna, 2016). Different micro-flora and their enzymes released are given in Table 2.

Table 2: Different micro-flora, enzymes released (Malleswari and Ratna, 2016)

Microorganism	Enzyme	Metabolic reaction catalyzed
E.coli, Bacteroids	Nitroreductase	Reduce aromatic and heterocyclic nitro compounds
Clostridia, Lactobacilli, E. coli	Azoreductase	Reductive cleavage of azo compounds
E. coli, P. vulgaris, B. subtilis, B. mycoides	Esterase and amidases	Cleavage of esters or amidases of carboxylic acids
Clostridia, Eubacterium	Glycosidase	Cleavage of β-glycosidase of alcohols and phenols
E. coli, A. aerogenes	Glucuronidase	Cleavage of β-glucuronidases of alcohols and phenols

2. Pharmaceutical factors

a. Drug candidates

The colon has a long residence time which is up to five days. Due to its high retention time colon causes an increase in the absorption of poorly absorbed agents like peptides, etc. and drugs used for treatment of Ulcerative colitis and Crohn's disease etc. making the organ an ideal site for drug delivery (Amidon et al., 2015). The best drug candidates for colon specific drug delivery are drugs which show poor absorption from the stomach or intestine including peptide drugs that are used in the treatment of IBD, ulcerative colitis, diarrhoea and colon cancer are ideal candidates for local colon targeted delivery (Philip and Philip, 2010).

b. Drug carriers

Selection of carrier for colon targeting depends on the physicochemical nature of the drug as well as the disease for which the system is to be used. There are various physicochemical factors of drug which affects the carrier selection such as chemical nature, stability, partition coefficient, type of the absorption enhancer etc (Prathap et al.). Choice of drug carrier depends on the functional groups of the drug molecule. Several ways have been attempted for colon specific drug delivery which includes prodrug formation,

coating with pH sensitive polymers, coating with biodegradable polymers, embedding in biodegradable matrices and hydrogel, timed-release systems, osmotic systems, and bioadhesive systems (Kumar et al., 2009).

POLYMERS USED FOR COLON SPECIFIC DRUG DELIVERY SYSTEM

Polymers are macromolecules, widely used in formulating various pharmaceutical products having a large number of structural units joined by same type linkage. Polymers have repeating units of monomers or co-monomers with various functional groups. Naturally found polymers as well as variety of synthetic polymers are used nowadays controlled drug delivery systems (Malleswari and Ratna, 2016). Before formulating a polymeric carrier system certain factors must be taken into consideration; the significant one is the drug/polymer ratio, which plays an important part in establishing the vital characteristics of polymeric vehicles such as particle size, entrapment efficiency and drug release characteristics. The particle size and entrapment efficiency of polymeric carriers are increased by increasing the drug/polymer ratio, while drug release can be enhanced by decreasing the ratio. Polymers, which are frequently used in the colon targeting belongs to the polysaccharides and polyesters family (Dar et al., 2017).

POLYSACCHARIDES IN COLON-SPECIFIC DRUG DELIVERY

Natural polysaccharides are now widely used for targeted delivery of drug to the colon. There is presence of large amounts of polysaccharides in the human colon as the colon is inhabited by a large number and variety of bacteria that makes the polysaccharides choice for polymer used for colon targeting (Sinha and Kumria, 2001). Polysaccharides are the polymers of monosaccharide's (sugars) and are found in abundance and are inexpensive. Polysaccharides can be modified chemically and biochemically with ease and have property such as highly stable, safe, nontoxic, hydrophilic and gel forming and biodegradable, which suggest their use in colon targeted drug delivery systems. Problem encountered with the use of polysaccharides is their high water solubility. A huge number of polysaccharides have already been tried for their potential as colon-specific drug carrier systems, such as pectin, chitosan, cyclodextrins, dextrans, guar gum, insulin etc (Sinha and Kumria, 2001). Some of the commonly used polysaccharides and their characteristics for colon targeted drug delivery are discussed in this article.

Pectin

Pectin is one of the most abundant carbohydrates, non-starch, linear polysaccharides extracted from the plant cell walls. Generally, it consists α-1, 4 D-galacturonic acid and 1, 2 D-rhamnose with D-galactose and D-arabinose side chains having average molecular weights that ranges from 50,000 to 150,000 Daltons(Khandelwal et al., 2012).Pectin is very good as a thickening agent, gelling agent, and a colloidal stabilizer polysaccharide in food industry. It has high solubility in water. In contact with GIT fluids it swells and the entrapped drug is released through diffusion (Agarwala et al.). The problem of not able to shield its drug load effectively during its passage through the stomach and small intestine pectin was manipulated with chemical modification without affecting favourable biodegradability properties. Chemical modification of pectin can be done by saponification catalysed by acids, bases, enzymes and salts of weak acids (Reddy et al., 2011). It was found that a coat of a considerable thickness was required to protect the drug core in simulated in vivo conditions for colon targeting. So, focus shifted towards development of such derivatives of pectin that were less water soluble but were degradable by the colonic micro-flora (Sinha and Kumria, 2001). A novel colon targeted tablet formulation using diltiazem hydrochloride and indomethacin as model drugs and pectin as a carrier was developed (Ravi and Kumar, 2008). In-vitro study from this dosage form reveals the release of drug is limited in stomach and small intestine and maximum release is in colon. This shows that pectin can be used for targeting both water soluble and insoluble drugs (Kumar et al.). Strategies used to protect the pectin based formulations from upper GIT environment are by coating it with a pH sensitive polymer like Eudragit® or by using low methoxylated pectin

(Dar et al., 2017). In a study, 5- fluorouracil (5-FU) was loaded into pectin microspheres and coated with Eudragit® S100. These coated microspheres were able to release the drug in a controlled manner at the colon as revealed by in vitro drug release study in the simulated gastric fluid and in vivo organ distribution studies in the rats (Paharia et al., 2007). Pectin shows a great potential in colon specific drug delivery systems for systemic action or a topical treatment of diseases such as ulcerative colitis, Crohn's disease (Reddy et al., 2011).

Chitosan

Chitosan is a polycationic polysaccharide of high molecular weight derived by hydrolysis and partial deacetylation of the chitin, which is the second most abundant polysaccharide present in nature after cellulose. Chemically it is poly (N-gluocosamine) and shows resistance to enzymes of upper GI tract. It is nontoxic, biocompatible and biodegradable. Chitosan has favourable biological properties as it is nontoxic, biocompatible and biodegradable (Khandelwal et al., 2012). Chitosan consists repeated units of β-1/4-linked D-glucosamine units (deacetylated entities) and N-acetyl-D-glucosamine units (acetylated entities) (Dar et al., 2017). The average molecular weight of chitosan is ranging between 3800 and 20,000 Daltons (Agarwala et al.). Chitosan is a novel drug carrier material used as a coating agent, gel former and to induce properties such as muco-adhesion and permeation enhancement for improvement of drug oral bioavailability (Kumar et al.). Chitosan microspheres provides controlled release of many drugs and are used to improve the bioavailability of degradable substances such as protein, as well as it improves the uptake of hydrophilic substances across the epithelial layers. These chitosan microspheres are being investigated both for the parenteral and oral drug delivery (Akanksha and Kumar, 2009). A colon specific drug delivery system composed of drug reservoir and the outer drug release regulating layer by dispersing chitosan powder in a hydrophobic polymer was developed in which chitosan was dissolved in aqueous solutions containing aspartic, glutamic, hydrochloric, lactic and citric acids to obtain different chitosan salts. It was observed that the thickness of the outer layer control the release rate of drug since the dispersed chitosan dissolves easily under acidic conditions. Additional outer enteric coating was also provided to prevent the release of drug from chitosan dispersed system in the stomach (Orienti et al., 2002). Chitosan is a well-accepted and a promising polymer for drug delivery in colon, as it can be biodegraded by the micro flora present in the human colon (Agarwala et al.).

Dextran

Dextrans are an important class of polysaccharides mainly consisting α-1,6D-glucose and side chain of α-1,3 D-glucose units (Sinha and Kumria, 2001). Dextran gets degraded by the microbial enzyme Dextranase, found inside the colon which encourages its use as a colon specific drug delivery carrier (Sery and Hehre, 1956). Dextrans are colloidal, hydrophilic and water-soluble substances, which are inert in biological systems and do not affect cell viability which makes it among the main promising candidates for the preparation of networks capable of giving a sustained release of proteins (Sonia and Sharma, 2011). Glycosidic bonds of dextran are hydrolyzed by Dextranase to give shorter prodrug oligomers. These oligomers are further split by the colonic esterase to release the drug free in the lumen of the colon. Prodrug approach of dextran can be used for colon-specific delivery of drugs containing a carboxylic acid function (−COOH) (Sonia and Sharma, 2011). Pharmacodynamically, conjugation with dextran has shown prolongation of the effect of drug and alteration of its toxicity profile (Rajpurohit et al., 2010). Novel hydrogels of dextran based on dextran cross-linked with diisocynate were prepared for colon specific drug delivery. These hydrogels were characterized by equilibrium degree of swelling and mechanical strength. It was found that it is possible to control the equilibrium degree of swelling, mechanical strength and degradability by changing the chemical composition of the hydrogels. Release of the hydrocorticosone from the hydrogels was evaluated. It was found that hydrocorticosone release was dependent on the presence of dextranases in the release medium. The results

suggest that the dextran hydrogels are potential candidates as carriers for colon specific drug delivery (Hovgaard and Brøndsted, 1995).

Guar-gum

Guar gum is a naturally occurring galactomannan polysaccharide derived from the seeds of *Cyamopsistetragonolobus*. It consists of mainly high molecular weight hydro-colloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and degrades in the large intestine due the presence of microbial enzymes (Minakshi et al.). The molecular weight of guar gum is estimated to be in the range of 200,000 to 300,000 Daltons (Agarwala et al.). It is hydrophilic in nature and swells in cold water resulting in viscous colloidal dispersions or sols. This gelling property retards the release of the drug from the dosage form, making it more likely that degradation will occur in the colon. Due to its drug release retarding property and susceptibility to microbial degradation in the large intestine, guar gum is preferably used to deliver drug to the colon (Sinha and Kumria, 2001). In convectional dosage form guar gum is used as a protective colloid, binder and disintegrating agent. It is also used as bulk-forming laxative, appetite depressant and in peptic ulcer therapy. Guar gum find its use as an ideal thickening agent in medicated tooth paste, lotions, creams, and ointments. It is widely used as emulsifying agent and stabilizing agent (Agarwala et al.). Guar gum matrix tablets of water-soluble diltiazem hydrochloride were developed for oral controlled release. From the results of in vitro and in vivo studies it was concluded that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride (Al-Saidan et al., 2005). Colon-specific delivery system for 5-aminosalicylic acid (5-ASA) using guar gum as a carrier was developed. From the study it was concluded that selective delivery of 5-ASA to the colon can be achieved using guar gum as a carrier in the form of a compression coating over the drug core (Krishnaiah et al., 1999).

Xanthan gum

Xanthan gum is extracellular polysaccharide of high molecular weight that is produced by the fermentation of the gram negative bacterium *Xanthomonascampestral*. In comparison to the other polysaccharide solution itis a very effective thickener and stabilizer as it gives highly viscous solutions even at low concentration. The solution of xanthan gum offer very good stability(Thakur et al., 2016). The anionic character of this polymer is due to the presence of both glucoronic acid and pyruvic acid groups in the side chain(Evans, 2009). Xanthan gum and hydroxypropylmethyl cellulose were used as hydrophilic matrixing agent for preparing modified release tablets of diazepam HCl. The hydroxy propyl methyl cellulose and Xanthan gum exihibited significant effect on drug release from the tablets prepared by direct compression technique. It was concluded that by using a stable blend of hydroxyl propyl methyl cellulose and xanthan gum desired modified drug release could be achieved (Kumar et al.).

Inulin

It is a naturally occurring polysaccharide found in many plants, such as onion, garlic, artichoke and chicory. Chemically, inulin belongs to the gluco-fructans and consists of a mixture of oligomers and polymers containing 2 to 60 (or more) β-2-1 linked D-fructose molecules having a glucosyl unit at the reducing end. Inulin is not hydrolysed by the endogenous secretions of the human digestive tract. It can resist the hydrolysis and digestion in the upper gastrointestinal tract. This polysaccharide gets degraded by colonic bacteria, especially *bifidobacteria*, which constitute up to 25% of the normal gut flora in man are able to ferment inulin (Sinha and Kumria, 2001). Inulin hydrogels were developed as potential new carriers for colonic drug targeting for colonic delivery of drugs and swelling property of these hydrogels was investigated. The influence of various parameters on the swelling property of hydrogels such as the degree of substitution, feed concentration of methacrylated inulin, varying concentrations of the initiators of the polymerisation reaction, the effect of pH, ionic strength were studied (Vervoort et al., 1998). Inulin serves as a biodegradable compound with eudragit. Inulin have been incorporated into Eudragit RS films for preparation of mixed films

that resisted degradation in the upper gastrointestinal tract but digested in human faecal medium by the action of Bifido bacteria and Bacteroids (Agarwala et al.).

Alginate

Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate form is mostly used. They are linear polymer that consist D-mannuronic acid and L-guluronic acid residues arranged in blocks in polymer chain. The alginates present various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering applications (Akanksha and Kumar, 2009).In a comparative study for improving the bioavailability of two clinically important antifungal drugs clotrimazole and econazole alginate formulation appeared to be better than the poly-lactide-co-glycoside (PLG) formulation. The nanoparticles were prepared by using the emulsion-solvent-evaporation technique in case of PLG and by using the cation-induced controlled gelling in case of alginate. Calcium alginate beads as cores were developed with a spray coat of 5-ASA on them. The in vitro evaluation of this formulation was done for colon specific drug targeting (Agarwala et al.).

Amylose

Amylose is a polysaccharide that is obtained from plant extract and is a component of starch. Amylose is unbranched linear polymer of glucopyranose units (α-1, 4-D-glucose) that is linked through α–D-(1-4) linkage. Amylose shows resistance to pancreatic amylases in its glassy amorphous form but it degrades by the bacteroids, bifidobacterium. The amylose possesses the ability to form films. Such formed films are water swellable and are potentially resistant to pancreatic-amylase but these are degraded by bacterial enzymes or micro flora of colon (Thakur et al., 2016).They are easily available, safe and nontoxic. With application of dried amylose films to pharmaceutical formulations colon-specific drug delivery may be possible. Though, under simulated gastrointestinal conditions, coatings made only of amylose will become porous and allow drug release. Incorporation of insoluble polymers into the amylose film provides a solution to this problem (Kumar et al., 2009). Organic solvent based amylose–ethylcellulose films were evaluated as potential coatings for colonic drug delivery. Varying the concentration of amylose and ethylcellulose in the films could vary the drug release rate from these films. The films were found to be susceptible to digestion by bacterial enzymes in a simulated colonic environment. On the whole, the results implied that such amylase-ethylcellulose films could be used as coatings for drug delivery to the colon (Siew et al., 2000).

SYNTHETIC POLYMERS

The polymers used for targeting the colon should be capable to withstand the lower pH or acidic medium of stomach and of the proximal part of the small intestine and should also be able to disintegrate at slightly alkaline pH of the terminal ileum and moderately at the ileocecal junction. Such properties of a polymer help to distribute the drug throughout the large intestine and thus improve the potential of colon targeted delivery systems. There are a variety of synthetic polymers which are use for colon targeted drug delivery. These can also be called as pH dependent polymers (Neha and Harikumar, 2013). Synthetic polymers generally offer greater advantages over natural materials as they can be modified to give a wider range of properties and have more expected uniformity than materials from natural sources (Minakshi et al.).

Eudragit:-

Eudragit and its derivatives are pH-dependent methacrylic acid polymers that contain carboxyl groups. The pH level at which dissolution takes place is affected by the number of esterified carboxyl groups. There are three types of Eudragit: Eudragit L, Eudragit S, and Eudragit RS. Eudragit S coatings protect well against drug release in the upper parts of the gastrointestinal tract and thus have been used frequently in preparing colon-specific formulations (Neha and Harikumar, 2013).Eudragit S is soluble above the pH 7 and Eudragit L is soluble above pH 6. Eudragit are non-biodegradable, non-absorbable,

and nontoxic. A number of marketed drug products currently used for the treatment of colon specific diseases like IBD use the pH sensitive approach of these polymers (Thakral et al., 2013).

Eudragit L

Eudragit L is an anionic polymer that is synthesized from methacrylic acid and methyl methacrylate and has a pH dependent solubility. Eudragit® L 100 would release the drug at pH of range 6-6.5 i.e. ileum and large intestine. It is a white powder and has a faint characteristic odour. It is capable of providing an effective and stable enteric coating with a fast dissolution in the upper bowel. It also finds its use to form a site specific drug delivery system to the intestine by combination with Eudragit® S100 (Thakur et al., 2016).

Eudragit S

Eudragit S is an anionic copolymer that is synthesized from methacrylic acid and methyl methacrylate. It is available only in the form of organic solution i.e. isopropanol and solid. Eudragit® S 100 releases the drug at pH above 7.0. In order to form a controlled release drug delivery system it is used in powder form for granulation of drug substance. It is also used for the delivery of drug in the intestine with the combination of drug with other grades of Eudragit S such as Eudragit® S12.5 Eudragit® FS 30 D. In colon specific drug delivery Eudragit S has also been used in combination with Eudragit L 100-55(Thakur et al., 2016). When the sites of disintegration of Eudragit S-coated single-unit tablets were investigated using a gamma camera they were found to be positioned between the ileum and splenic flexure. Site specificity of Eudragit S formulations, both single- and multiple-unit, is generally poor. Eudragit S coatings have been used to target 5-aminosalicylicacid (anti-inflammatory drug) in single-unit formulations on the large intestine (Neha and Harikumar, 2013).

Shellac

Shellac is the purified product of the natural resin lac, a hardened secretion of the small, parasitic insect Kerria Lacca which is commonly known as the lac insect. Shellac is the only known commercial resin of animal origin. It is a hard, brittle and resinous solid. It is practically odourless in the cold but on heating and melting evolves a characteristic smell. It is water insoluble. The coatings of shellac for food applications are commonly applied from ethanolic solutions. It is inappropriate for a conventional enteric coating. It is relevant for colon targeting formulations (Neha and Harikumar, 2013).The shellac coating layer remains integral during the passage of the stomach and the small intestine until it reaches the colon with which allows the transport of drugs into the colon for topical treatment of colonic diseases. Additionally, the peptidase activity in the colon is lower than in the upper GI tract that allows oral delivery of peptide drugs such as insulin (Thakur et al., 2016).

Poly Lactic-co-Glycolic acid

PLGA is a synthetic polymer that is prepared by the co-polymerization of the glycolic acid (GA) and lactic acid (LA) cyclic dimers. It is non-toxic, biocompatible and biodegradable as the hydrolytic products are easily metabolized through Krebs cycle inside the body(Dar et al., 2017). It is synthesized by means of random ring-opening co-polymerization of two different monomers, the cyclic dimers (1,4-dioxane-2,5-diones) of glycolic acid and lactic acid. Common catalysts that are used in the preparation of this polymer include tin (II) 2-ethylhexanoate, tin(II) alkoxides, or aluminium isopropoxide. During polymerization, these monomeric units (of glycolic or lactic acid) are linked together in PLGA by ester linkages that yield linear aliphatic polyester as a product (Minakshi et al.). In the presence of water PLGA degrades through hydrolysis of its ester linkages. It has been revealed that the time required for the degradation of PLGA is related to the ratio of monomers used in its production, higher the content of glycolide units, lower the time required for degradation. An exception to this is copolymer with 50:50 ratio of monomers which undergoes faster degradation (about two months) in both in vitro and in vivo conditions (Lodhi et al., 2014). PLGA has been successful as a biodegradable polymer as it undergoes hydrolysis in the body and produces lactic acid and glycolic acid. Under normal physiological conditions, these monomers are by-products of various metabolic pathways in

the body. Because the body efficiently deals with these monomers, there is very minimal systemic toxicity associated with using PLGA for drug delivery (Minakshi et al.).

Poly lactic acid

PLA is a synthetic polymer and belongs to the aliphatic linear polyester family. It is manufactured both by chemically linking the LA monomers and by carbohydrate fermentation. The FDA (Federal Drug Administration, USA) has approved the PLA safe and non-toxic for use in the food and drug delivery applications (Dar et al., 2017). PLA possess several advantages. It is biocompatible, biodegradable, and can be readily broken down thermally by hydrolysis. It is available from renewable agricultural resources. The most important ability of PLA is that one can modify its physical properties by material modifications. The polymer is relatively hard, with the glass transition temperature in the range 60-70 °C and melting at 170-180 °C. PLA has been approved by the FDA (Federal Drug Administration, USA) for use as a suture material because of features that offer fundamental advantages (Gupta et al., 2007). Poly (lactic acid) in both L and DL forms has proved valuable as implants and supports in the human body. The material characteristics of the polymer may be altered controlling the molecular weight and the L/DL composition. The polymer may take 10 months to 4 years to degrade that depends on the micro-structural factors such as chemical composition, porosity and crystallinity that may influence tensile strength for specific uses (Vainionpää et al., 1989).

APPROACHES USED FOR COLON SPECIFIC DRUG DELIVERY SYSTEM

Several approaches are used for colon specific drug delivery. These include:

1. Primary approaches for colon targeted drug delivery
    a. pH sensitive polymer coated drug delivery system
    b. Delayed or time controlled release drug delivery system
    c. Microbially triggered drug delivery
        i. Prodrug approach
        ii. Polysaccharide based system
2. New approaches for colon targeted drug delivery
    a. Pressure controlled drug delivery system (PCDDDS)
    b. Novel Colon Targeted Delivery System (CODES^{TM})
    c. Osmotic controlled drug delivery system (OROS-CT)
    d. Pulsatile
        i. Pulsincap system
        ii. Port system
    e. Azo hydrogels
    f. Multiparticulate system based drug delivery

1. Primary approaches for colon targeted drug delivery

a. pH sensitive polymer coated drug delivery system

The pH-dependent drug delivery system uses the generally accepted view that pH of the human git increases progressively from the stomach (pH 1-2 which increases to 4 during digestion) to small intestine (pH 6-7) and it increases to 7-8 in the distal ileum (Neeraj et al., 2017). This change in the pH along the gastrointestinal tract has been used as a mean for colon targeted drug delivery. This can be achieved by means of intact coating at lower pH of the stomach but that will dissolved at neutral pH of the colon. These polymer coats are intractable to the acidic condition of the stomach but ionize and get dissolved above a certain threshold alkaline pH found in small intestine (Mahajan et al.). Thus it is possible to apply same concept to deliver drugs to the terminal of ileum or colon by use of enteric polymers with a relatively high threshold pH for dissolution and subsequent drug release. The most commonly used polymer for this purpose is a copolymer of methacrylic acid, methyl methacrylate and ethyl methacrylate (Eudragit FS), which dissolve at a slower rate and at a higher threshold pH (7.0- 7.5) have been investigated (Anuj and Amit, 2010). This approach is based on the fact that the gastrointestinal pH increases progressively from small intestine to colon. But the pH of the distal is 6. This delivery system thus has an inclination to release the drug load prior to reaching the colon. To overcome the problem of premature drug

release, a copolymer of methacrylic acid, methyl methacrylate and ethyl acrylate (Eudragit FS) which dissolves at slower rate and at higher threshold pH 7 to 7.5 is used (Neeraj et al., 2017). The lists of drugs delivered to colon based upon this approach along with pH sensitive polymers are given in Table 3.

Table3. Examples of colon targeted formulations based on various approaches.

Approach employed	**Polymer (s) used**	**Drug used**	**Reference**
pH dependent	Eudragit L100 and S100	Mesalazine	(Khan et al., 1999)
	Eudragit L100 and S100	Diclofenac sodium and 5-ASA	(Cheng et al., 2004)
	Eudragit S, Eudragit FS, Eudragit P4135 F	Prednisolone	(Ibekwe et al., 2006)
	Eudragit L 30 D-55 and Eudragit FS 30 D	Paracetamol	(Cole et al., 2002)
Time dependent	Hydroxy propyl methyl cellulose	Pseudo ephedrine HCl	(Halsas et al., 2001)
	Hydroxy ethyl cellulose, ethyl cellulose, microcrystalline cellulose	Theophylline	(Alvarez-Fuentes et al., 2004)
	Lactose/ behinic acid	Indomethacin	(Peerapattana et al., 2004)
	Hydroxy propyl methyl cellulose acetate succinate	Diltiazem HCl	(Fukui et al., 2001)
Bacteria dependent Polysaccharide based	Chitosan	Diclofenac sodium	(Lorenzo-Lamosa et al., 1998)
	Pectin	Indomethacin	(Rubinstein et al., 1993)
	Guar gum	Dexamethasone	(Wong et al., 1997)
	Chondroitin sulphate	Indomethacin	(Rubinstein et al., 1992)
	Amylose	5-Acetyl salicylic acid	(Milojevic et al., 1996)
	Alginates	5- Acetyl salicylic acid	(Lin and Ayres, 1992)

b. Delayed or time controlled release drug delivery system:

This system is also known as pulsatile release, delayed or sigmoidal release system. Time controlled formulations for colonic delivery are also delayed-release formulations in which the delay in drug delivery is time-based (Mahajan et al.).Time controlled release system delayed release dosage forms are very promising drug release systems. Due to a large variations of gastric emptying time of dosage forms in human's colon arrival time of dosage forms cannot be accurately predicted in these approaches, that results in poor colonic availability. Such dosage forms may be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h (Philip and Philip, 2010). The strategy for designing delayed or timed-released systems is to resist the acidic pH of stomach and to undergo a lag time of predetermined span of time after which drug release takes place. The lag time is the

time required to transit from the mouth to the colon. The first formulation based on this principle was Pulsincap® (Chourasia and Jain, 2003). The device consists of anon disintegrating half capsule body that is sealed at the open end with a hydrogel plug which is covered by a water-soluble cap. To avoid the problem of variable gastric emptying the whole unit is coated with an enteric polymer. The enteric coating dissolves when the capsule enters the small intestine, and the hydrogel plug starts to swell. The hydrogel amount is adjusted so that it pops out only after the stipulated period of time to release the contents (Singh and Khanna, 2012). Enteric coated timed release press tablets (ETP Tablets)(Fig 2),a new oral drug delivery system for colon targeting were developed by coating enteric polymer on timed -release press coated tablets. These (ETP) tablets, are composed of three components, a drug containing core tablet(rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer, time release function) and an enteric coating layer (acid resistance function) (Chourasia and Jain, 2003). ETP tablets do not release the drug in the stomach due to the acid resistance of the outer enteric coating layer. The enteric coating layer rapidly dissolves after gastric emptying and the intestinal fluid begins to slowly erode the press coated polymer (HPC) layer. Rapid drug release occurs when the erosion front reaches the core tablet, since the erosion process takes a long time as there is no drug release period (lag phase) after gastric emptying. The lag phase duration is controlled either by the weight or composition of the polymer layer (Philip and Philip, 2010).

Figure 2: Design of enteric coated timed-release press coated tablet (ETP Tablet)

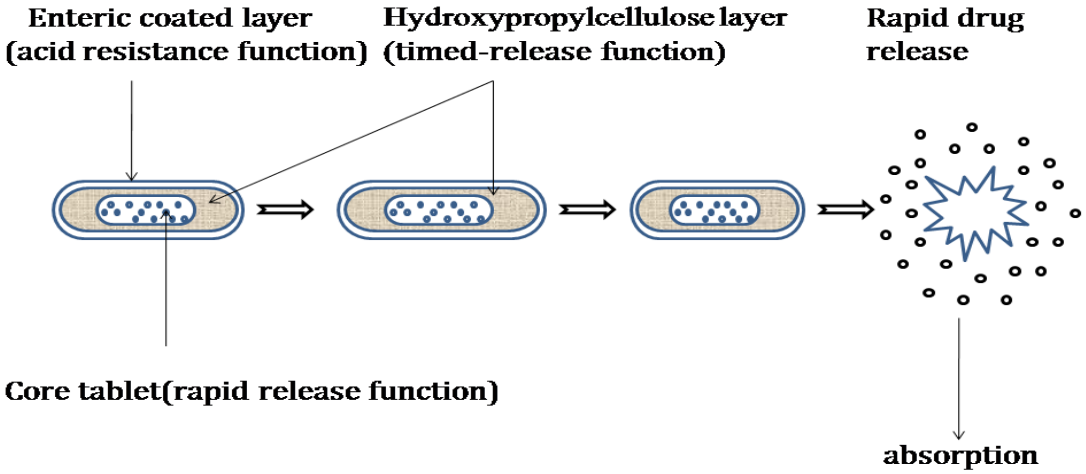

Figure 2: Design of enteric coated timed-release press coated tablet (ETP Tablet)

c. Microbially triggered dug delivery

Microbially controlled delivery system is the most tempting among the various approaches used for colon targeting, as it relies on the unique enzymatic ability of the colonic micro flora and enables a more specific targeting, independent of pH variations along the GI tract (Asghar and Chandran, 2006). Both anaerobic and aerobic micro-organisms are present in the human gastrointestinal tract. Even though bacteria are distributed all over the gastrointestinal tract, the immense majority are present in the distal gut. Bacteria present in colon are predominantly anaerobic in nature and are capable of metabolizing endogenous and exogenous substrates, such as carbohydrates and proteins,

which escape digestion in the upper gastrointestinal tract (Anuj and Amit, 2010). Bacteroides, Bifidobacteria, Clostridia, Enterococci, Enterobacteria, Eubacteria, and Ruminococcus, etc are various inhabitant microflora of the colon. For the energy requirements the microflora of gut depends on fermentation of undigested materials in the small intestine. The microflora performs fermentation by producing a huge number of biodegradable enzymes that are capable of degrading the polymers used for targeting the drug delivery to colon (Sreelatha and Brahma, 2013).

The enzymes present in the colon are-

- Reducing enzymes: Nitroreductase, Azoreductase, N-oxide reductase, sulfoxide reductase, Hydrogenase etc.
- Hydrolytic enzymes: Esterases, Amidases, Glycosidases, Glucuronidase, Sulfatase etc
- (Malleswari and Ratna, 2016).

i. Prodrug approach

The main approach of microbial triggered drug delivery system is prodrug. In this approach the drug release from the formulation is triggered by gut microflora. Prodrug is a pharmacologically inactive derivative of the parent molecule which requires enzymatic transformation in the biological environment for releasing the active drug at the targeted site (Neeraj et al., 2017). Prodrugs are prepared by linkage of the drug with hydrophobic moieties such as amino acids, glucoronic acids, glucose, galactose, cellulose, etc. In the presence of the enzymes released by the microflora these prodrug molecules get hydrolysed. The approach involves covalent linkage between the drug and its carrier so that the moiety remains intact in the stomach and small intestine upon oral administration (Sreelatha and Brahma, 2013). Generally, a prodrug is successful as a colon drug carrier if it is hydrophilic and bulky to minimize absorption from the upper GIT, and if once in the colon, it is converted into a more lipophilic drug molecule, which is then available for absorption. Limitation of the prodrug approach is that it is a less versatile approach because its formulation depends upon the functional group presented on the drug moiety for chemical linkage (Philip and Philip, 2010). New chemical entities known as prodrugs formed upon linkage need a lot of evaluation before using them as carriers. The metabolism of azo compounds by intestinal bacteria is the most widely used prodrug approach (Sreelatha and Brahma, 2013). A number of prodrugs have been outlined in Table 4..

Table 4: Examples of Prodrug system for CDDS(Sreelatha and Brahma, 2013)

Drug	Carrier	Linkage hydrolysed
5-ASA	Azo conjugates	Azo linkage
Dexamethasone	Saccharide carriers	Glycosidic linkage
Prednisolone, hydrocortisone, fludrocortisone	Glucose, galactose	Glycosidic linkage
Salicylic acid	Amino acid conjugates, glycine	Amide linkage

ii. Polysaccharide based delivery

The naturally occurring polysaccharides are attracting a lot of attention for drug targeting to the colon as these polymers of monosaccharide are found in abundance, have extensive availability, are inexpensive and are offered in a verity of structures with varied properties. They

can be modified chemically and biochemically with ease. They are highly stable, safe, nontoxic, hydrophilic, gel forming and are biodegradable also. These include naturally occurring polysaccharides that are obtained from plant (guar gum, inulin), animal (chitosan, chondrotin sulphate), algal (alginates) and microbial (dextran) origin. The polysaccharides can be easily broken down to simple saccharides by the microflora present in the colon. Thus, they fall in the category of "generally regarded as safe" (GRAS) (Philip and Philip, 2010). Polysaccharides retain their integrity as they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain integral in the physiological environment of stomach and small intestine but if they are once acted upon by the bacterial polysaccharides, it results in the degradation of the matrices (Mahajan et al.). Uses of a combination of polysaccharides in colon targeting have been found to be more effective for achieving colon specific delivery compared to the use of a single polysaccharide. Cellulose derivatives are often used in combination to develop such delivery systems because cellulose is not absorbed systemically when it is administered orally. Two groups of cellulose esters can be used in drug formulations. Non-enteric cellulose esters such as cellulose acetate those are insoluble in water having solubility independent of pH and can be used in insoluble, permeable coatings. The enteric cellulose esters such as cellulose acetate phthalate (CAP) and hydroxypropyl methylcellulose phthalate (HPMCP) have pH-dependent solubility and are insoluble in highly acidic conditions, but they dissolve as the pH reaches a certain range (Amidon et al., 2015).

2. New approaches for colon targeted drug delivery

a. Pressure controlled drug delivery system

The digestive processes in the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from the ascending to the transverse colon by forcible peristaltic movements frequently termed as mass peristalsis. These strong peristaltic waves are of short duration within the colon, occurring only three to four times a day. They temporarily increase the luminal pressure within the colon that forms the basis for design of the pressure-controlled systems (Sreelatha and Brahma, 2013). As resulting from peristaltic motion, the luminal pressure is higher in the colon as compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic due to abundant water in digestive juices. But the viscosity of the content is significantly increased in the colon because of reabsorption of water from the lumen and formation of faeces. Thus it has been concluded that drug dissolution in the colon possibly will present a problem in relation to colon-specific oral drug delivery systems (Disha et al., 2013).The peristaltic movements of the intestine results increase in luminal pressure. This increase in luminal pressure is the key point in the development of pressure controlled drug delivery system (Yang et al., 2002). The pressure controlled drug delivery system consists of a capsular shaped suppository that is coated with a water-insoluble polymer like ethyl cellulose. These gelatin capsules are coated with these polymers on their inner side. The drug is introduced into the capsule along with suppository base. The disintegration capacity of the capsule is determined by the thickness of ethyl cellulose coating (Takaya et al., 1998). After administration, suppository base dissolves at body temperature. The water from intestine contents is absorbed that result in increased viscosity which leads toan increase in the pressure in the capsule. This increased pressure in the capsule expels the drug into the colon. The developed intestinal pressure varies with the circadian rhythms, state of body and food administration, etc (Sreelatha and Brahma, 2013). In pressure-controlled ethyl cellulose single-unit capsules the drug is in a liquid. When pressure-controlled capsules were

administered to human lag times of three to five hours were noted in relation to drug absorption (Philip and Philip, 2010).

b. Novel Colon Targeted Delivery System (CODES™)

CODES™ is a distinctive colon specific drug delivery technology which was designed to avoid the intrinsic problems associated with pH or time dependent systems. This technology is a combined approach of pH dependent and microbially triggered colon targeted drug delivery. The advantages of certain polysaccharides are exploited by the design of CODES™ that are only degraded by bacteria available in the colon (Yang et al., 2002). CODES™ has been developed by utilization of a unique mechanism that involves lactulose, which acts as a trigger for the site specific drug release in the colon, (Fig 3.). The CODES™ system consists of a traditional tablet core containing lactulose, which is over coated with an acid soluble material, Eudragit E, and later overcoated with an enteric material, Eudragit L. The basis of the technology is that the enteric coating will protect the tablet while it is located in the stomach and will dissolve quickly following gastric emptying. Then the acid soluble material coating will protect the preparation as it will pass through the alkaline pH of the small intestine (Disha et al., 2013). Upon the entry of tablet into the colon, the polysaccharide inside the core tablet will dissolve and diffuse through the coating. The bacteria will degrade the polysaccharide (lactulose) enzymatically into organic acid. This lowers the pH surrounding the system sufficient to effect the dissolution of the acid-soluble coating and subsequent drug release (Yang et al., 2002).

Figure 3: Schematics of the conceptual design of CODES™

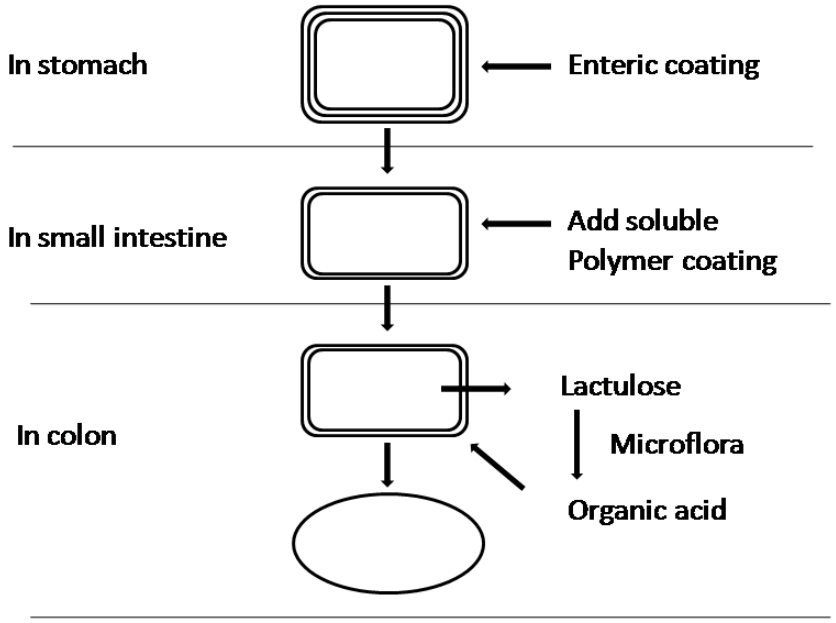

Figure 3: Schematics of the conceptual design of CODES™

c. Osmotic controlled drug delivery system (OROS-CT)

Even though the concept of osmotic controlled drug delivery has been around for several years but its applications in the design of colon-specific oral dosage forms have gained popularity only in the 10–15 years. An example of the system regulated by osmotic pressure is the OROS-CT. It consists of a hard gelatin capsule that dissolves in the pH of small intestine and allows water to enter the unit which causes it to swell and the drug is forced out (Amidon et al., 2015). OROS-CT can be used for the treatment of disease or to achieve systemic absorption by targeting the drug locally to the colon that is otherwise unachievable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter that are encapsulated in a hard gelatin capsule.(Fig 4.) (Philip and Philip, 2010). There can be as many as 5–6 units within each capsule and each unit is surrounded by a drug impermeable enteric coating which prevents water from entering in the acidic environment of the stomach. Yet, this coating dissolves once the capsule enters the higher pH of the small intestine and the water enters. There is a semi-permeable membrane within the enteric coating that has an osmotic push compartment as well as a drug compartment. The water causes the push compartment to swell and forms a gel in the drug compartment which is forced out of an orifice through the membrane next to the drug compartment. The rate of outflow of drug depends on the rate at which water enters. These systems can also be designed such that there is a lag time between when the enteric coating dissolves and the drug is released to prevent drug release in the small intestine (Amidon et al., 2015). For treatment of ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay that prevents drug delivery in the small intestine. Drug release begins when the unit reaches the colon. The OROS-CT units can uphold a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours (Chourasia and Jain, 2003).

Figure 4: Cross-Section of the OROS-CT colon targeted drug delivery system

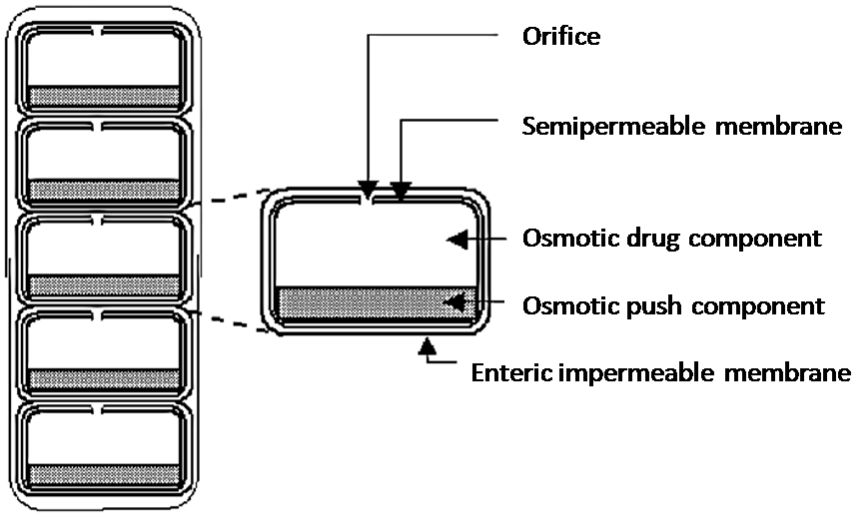

Figure 4: Cross-Section of the OROS-CT colon targeted drug delivery system

d. Pulsatile colon targeted drug delivery

i. Pulsincap systems

Time-dependent systems are not always absolute for delivery of drugs to the colon due to unpredictability in the gastric emptying time and the changes in gastrointestinal transit due to peristalsis or disorders such as IBS. For that reason, the integration of a timed-release system with pH-sensitive properties can be beneficial in achieving colon-targeted delivery (Amidon et al., 2015).Pulsincap system is one example of a formulation that utilizes both these techniques. On the basis of time-release principle Pulsincap was the first formulation developed. It was alike in appearance to hard gelatin capsule. It consists of water insoluble body and water soluble enteric coated cap. The contents are placed inside the body which is plugged with hydrogel plug (Fig 5). The enteric coat dissolves and the hydrogel plug starts to swell after predetermined time of administration (Kolte, 2012).The release of the drug is controlled by the plug placed in the capsule. For sealing the drug contents swellable hydrogels are used. Insoluble but permeable and swellable polymers used as hydrogel plugs are such as different grades of hydroxyl propyl methyl cellulose (HPMC), poly methyl methacrylate and polyvinyl acetate. The length and point of intersection of the plug in the capsule body controls the lag time(Singh and Sharma, 2014).

Figure 5: Schematic representation of the mechanism of the pulsincap colon-targeted drug delivery system

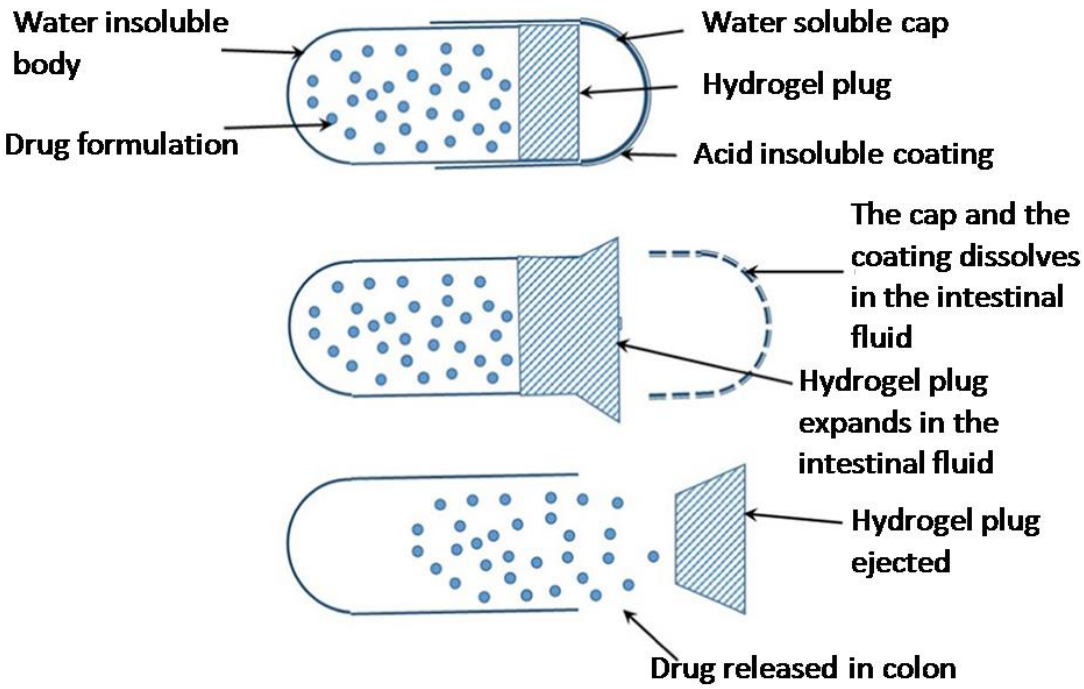

Figure 5: Schematic representation of the mechanism of the pulsincap colon-targeted drug delivery system

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ii. Port system

Port system consists a gelatin capsule body coated with a semi-permeable membrane (e.g., cellulose acetate). The capsule body consists of an insoluble plug consisting of osmotically active agent along with the drug formulation (Fig 6) (Kolte, 2012).When the capsule comes in contact with the aqueous medium (dissolution fluid) the semi permeable membrane permits the fluid flow into the capsule resulting in increased inner pressure in

the capsule body which leads to release of drug due to expelling of the plug after a lag time. The drug is released at regular intervals with time gap between the successive intervals (Sreelatha and Brahma, 2013). Coating thickness controls the lag time. Port system is the system that avoids the second time dosing (Satpute et al., 2012).

Figure 6: Drug release mechanism of port system.

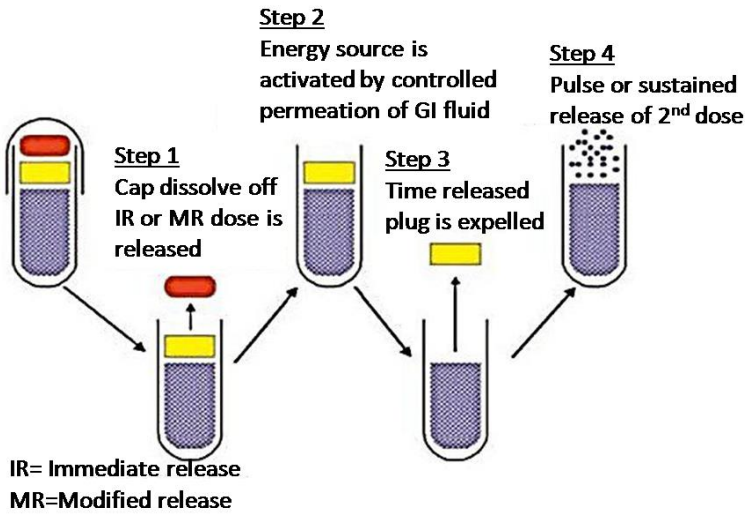

FIGURE 6 : Drug release mechanism of port system

e. Azo hydrogels

The presence of pH-sensitive monomers and azo cross-linking agents in the hydrogel structure produces the colon-specificity to the formulation. As the hydrogel travel through the GIT the swelling capacity of these hydrogel increases as the pH increases, being highest around pH 7.4. Upon entrance in the colon, these hydrogels attain a degree of swelling that makes the cross-links accessible to the enzymes (azo-reductase) or mediators. Later, the hydrogel network is progressively degraded via the cleavage of the cross-links and the drug
entrapped in hydrogel is released. By incorporating the hydrolyzable moieties in the hydrogel structure the swelling characteristics of the hydrogels can be controlled further (Yang et al., 2002). Different synthetic approaches were developed for preparation of the hydrogel systems. They can be obtained by cross-linking polymerization of N-substituted (meth) acryl amides, N-tert-butylacrylamide and acrylic acid with 4,4'-di (methacryloylamino) azobenzene, 4,4'-di (N-methacryloyl-6- aminohexanoylamino) or 3,3',5,5'-tetrabromo-4,4, 4',4'-tetrakis (methacryloylamino) azobenzene as cross linkers. The hydrogels were also prepared by polymer–polymer reaction using the same polymeric precursor with the subsequent copolymer containing side chains terminating in NH_2 groups. The rate of degradation of hydrogel was largely associated with the equilibrium degree of swelling, being inversely proportional to the cross-linking density (Satpute et al., 2012).

f. Multiparticulate based drug delivery system

Multiparticulate dosage forms are the pharmaceutical formulations in which the active ingredient is present as a number of minute independent subunits. These subunits are filled into a capsule or compressed with additional excipients to form a tablet for delivering the recommended total dose. The various

multiparticulate approaches for colonic delivery includes formulations such as of pellets, granules, micro particles, nanoparticles and beads (Satpute et al., 2012). Multiparticulate systems have several advantages over the conventional single unit as the multiparticulate systems enable the drug to reach the colon quickly and retained in colon for long period of time. Due to their smaller size these systems easily pass through the GIT. The various advantages of multiparticulate systems include increased bioavailability, reduced risk of local irritation and reduced risk of systemic toxicity (Choudhury et al., 2012). Multiparticulate drug delivery system is developed by time controlled explosion system (TES) for colon targeting. In time controlled explosion system drug release is caused by explosion of a membrane after a particular time period (i.e. lag times), which is programmed precisely. A multiparticulate system contains a core drug, an inert osmotic agent and suitable disintegrants. There are various reasons for designing and delivering drug as a multiparticulate system.

- Multiparticulate dosage forms shows improved reproducible pharmacokinetic behaviour than conventional formulations.
- By using multiparticulate dosage forms drug safety may also be increased (Satpute et al., 2012).

CONCLUSION

Colon-specific drug delivery system provides significant therapeutic benefits to the patients in terms of safety, efficacy, and patient compliance. The major benefit of CSDDS is that the colon offers near neutral pH, a long transit time, reduced enzymatic activity and increased responsiveness to absorption enhancers. The new approaches used for the colon targeting are more specific as compared to the primary approaches. All the approaches provide means for treatment of local diseases associated with the colon and for systemic absorption of poorly absorbable drugs through colon. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro-intestinal pH, but gives improved results with combination of time dependent system, microbially activated system and others. Various natural as well as synthetic polymers are used to prepare colon specific drug delivery by various approaches.

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