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Recent Approaches and Patent Survey on Colon Targeted Drug Delivery System

Sahilhusen I Jethara[1, 2]* and Mukesh R Patel[1, 2]

[1]Research scholar, Gujarat Technological University, Gujarat, India

[2]Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education & Research, Modasa-383315, Gujarat, India

Abstract

Targeting drugs to the colon is one of the modern research areas in pharmaceutical sciences at the deciding time, place and exact amount, and improving patient flexibility, compliance and bioavailability. To reach doing well colon targeted drug delivery, a drug necessitate to be protected from degradation, release and absorption in the upper part of the GI tract and then to be ensure abrupt or controlled release in the proximal colon. The colon is a site wherever both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory disease like constipation, chronic pancreatitis, pacreatactomy and colonic cancer etc. However, treatment can be made useful if the drugs be able to target directly into the colon; thereby reducing the systemic side effect and improve drug therapy or bioavailability in the upper GI tract. This article also discuss different country patent and approach like prodrugs, pH dependent, time dependent, azo-hydrogels, pressure controlled, pulsatile and microbially triggered drug delivery system, and evaluation for site specific drug delivery to colon. This overview focused on more than 100 patents available in different colonic drug delivery on current days. It is demanding areas for future investigate and hold plenty of promise for novel and efficient approach for targeted drug delivery system.

Keywords: CTDDS Patents; Colon Targeted Drug Delivery System (CTDDS); Drug targeting; Novel approaches.

Abbreviations: CTDDS: Colon targeted drug delivery system; US: United States Patent; WO: World Intellectual Property Organization (WIPO) Patent; CN: China Patent; EP: European Patent; JP: Japan Patent; AU: Australian Patent; CA: Canadian Patent; IN: India Patent; BR: Brazil Patent; DK: Denmark Patent; RS: Serbia Patent; ES: Spain Patent; PT: Portugal Patent; HK: Hong-Kong Patent; SI: Slovenia Patent; PL: Poland Patent; KR: South Korea Patent; MX: Mexico Patent; FI: Finland Patent; IL: Israel Patent; TW: Taiwan Patent; DE: Germany Patent; AT: Austria Patent; SK: Slovakia Patent; RU: Russia Patent; HPMC: Hydroxypropyl methylcellulose; EC: Ethyl Cellulose.

***Corresponding Author: Sahilhusen I Jethara,** Department of Pharmaceutics, Shri B. M. Shah College of Pharmaceutical Education and Research, College Campus, Modasa-383315, Gujarat, India; Tel: +918460378336; E-mail: sahil.pharm4@gmail.com

Introduction

The oral route is by far the most common and preferred route for ingesting drugs into the patient body [1]. Mainly focused on

the targeted delivery, the drug targeted to specific organ (i.e. lower GI tract). For orally administered drugs, gastrointestinal tract is crucial for optimizing the bioavailability of orally administered drugs [2]. Colon is a site specific and offers benefits including much closed to neutral pH, decrease enzymatic activity and good response to drug absorption enhancer works better in the colon as compare to small intestine [3]. Drugs are absorbed passively by either paracellular (passing through colonocytes) or trans-cellular (passing between adjacent colonocytes) route. Absorption enhancers (e.g. ethylacetoacetate) facilitate effective absorption through different mechanisms. Trans-cellular absorption is constant through the small intestine and this is the route most lipophilic drugs takes but paracellular absorption appears to be limited to the small intestine and this is the route most hydrophilic drug takes, with negligible colonic absorption by this route. Ideally suited for absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours. The epithelial cell junctions are very tight which may leads to poor paracellular absorption of many drugs in the colon. The colon may not be the best site for drug absorption since the colonic mucosa lacks well defined villi as found in the small intestine. The slower rate if transit in colon lets the surface area of the colon is much lower compared to small intestine and is compensated by absence of endogenous digestive enzymes and longer period of colon (10-24 hours). The colon contents become more viscous with progressive absorption of water as content travels further through the colon. These cause a rate dissolution reduced and slow diffusion of drug through the mucosa. Theoretically, drug absorption can occur along the entire GI tract, while in actuality, most drugs are absorbed in the duodenum and proximal jejunum because of the small extent of paracellular transport. Recent study have been show some reported drugs continue to be well absorbed through colon contain glibenclamide, theophylline, diclofenac sodium, metoprolol, oxyprenolol, ibuprofen etc. Drugs have less absorbed like piretanide, buftomedil, atenolol and ciprofloxacin etc. The systemic drug absorption from the GI tract depends on the physicochemical properties of the drug, the dosage form used and the anatomy and physiology of the absorption site [4]. Oral colonic delivery is protects the targated drug release in the stomach, small intestine and colon [5]. The main aim of designing drug delivery contain targeted drug to the colon beneficial for local as well as topical treatments of numerous inflammatory or colonic diseases (IBD) mostly, diversional colitis, ischemic colitis, regional enteritis, diverticular Inflammatory Bowel Disease, chronic pancreatitis, pacreatactomy, colonic cancer and constipation, the localized treatments of solid systemic delivery of peptide and protein drugs into the lower GIT [5-7]. Particularly, few peptide and non-peptide drugs like interferon (INF), Interleukins (IL), erythropoietin Growth Hormone (GH) and insulin because of high hostile condition prevailing in the stomach and small intestine compare to colon [8, 9]. Targeted drug to the colon improving patient safety and reduced side effect when treatment of chronic disease [10]. They study by the use of possible method to improve oral bioavailability of peptide and non-peptide drugs [11]. They protect against enzymatic degradation in GI tract and drugs to facilitate good absorption property because of the colon contain theophylline, glibenclamide [12] and oxprenolol [13] (Figure 1).

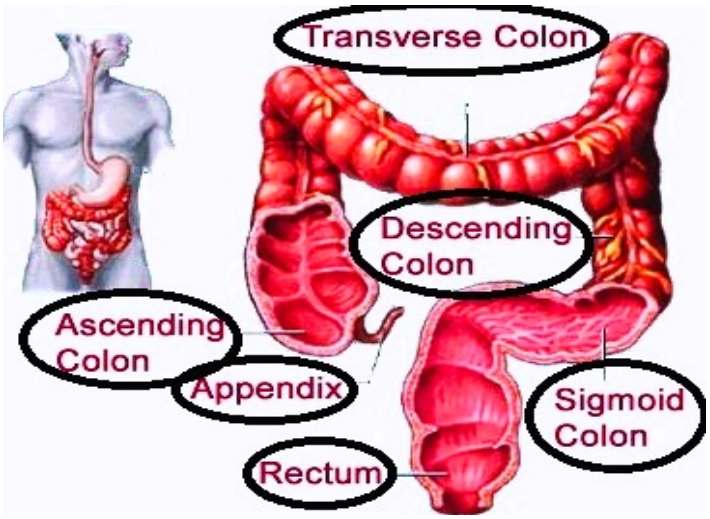

Figure 1: Anatomy of Colon

1. Pharmaceutical Approaches

In current years several approaches for CTDDS include;

1.1. Covalent linkage of drug with carrier: For prodrug systems [14-16]

Prodrugs are inert drug that become vital only after altered otherwise metabolized by the body. Drug and carrier formed covalent bond which upon orally administer that reach to colon lacking being absorbed from upper part of GI tract (Table 1).

- Azo bond conjugates or Azo-Polymeric Prodrugs
- Glycoside conjugation
- Glucoronide conjugates
- Cyclodextrin conjugate
- Dextran conjugates
- Amino acid conjugates
- Polymeric prodrug

1.2. New pharmaceutical approaches to deliver the intact molecules to the colon

Several approaches to deliver the drug to the colon include;

- pH dependent approach
  - Drug core coat with pH sensitive polymer
    - Eudracol™
    - DanBioSyst (Targit™) technology
  - Embedding in pH sensitive matrices
- Time dependent approach
  - Time clock® system
  - For capsule: pH sensitive and time release principles
  - Time controlled Explosive® system
  - Chronotropic® system
  - Pulsatile colon targeted drug delivery
    - Pulsincap™ system
    - Port® system
- Microbially triggerd (Enzymes controlled release) drug delivery to colon
  - Polysaccharide based delivery systems
    - Coating with biodegradable polymers
      - Colal-Pred™ system
      - CODES™ technologies (A Novel colon targeted delivery system)
    - Embedding in biodegradable polysaccharides
    - Hydrogel approach
  - Prodrug approach
- Bioadhesive system
- GEDD (Gas Empowered Drug Delivery System) system
- Probiotic approach
- Pressure dependent systems
  - Pressure Controlled Drug Delivery System (PCDDS)
  - Osmotic delivery
    - OROS-CT delivery
    - Osmet pump
- Multiparticulate (Nanoparticulate) system based drug delivery
  - Pellets
  - Granular matrix
  - Beads
  - Microspheres
  - Nano particle

Table 1: Pharmaceuticals approaches to deliver the intact molecules to colon

Sr. No.	Description	Polymers	Drug used	Ref.
pH dependent polymers				
1.	a) Drug core coat with pH sensitive polymer: Formulation coated with enteric polymers release drug when pH moves towards alkaline range. b) Embedding in pH sensitive matrices Degradation of pH sensitive polymer in the GIT and releases the embedded drug.	Eudragit L100 and S100	Mesalazine	[17]
2.		Eudragit L100 and S100	Flurbiprofen	[18]
3.		Eudragit L100 and S100	Tegaserod maleate	[19]
4.		Eudragit L100 and S100	Diclofenac sodium and 5-Acetyl Salicylic Acid (5-ASA)	[20]
5.		Eudragit S, Eudragit FS, And Eudragit P4135F	Prednisolone	[21]
6.		Eudragit L30D-55 and Eudragit FS 30D	Paracetamol	[22]
7.		Eudragit RS 100	5-Fluorouracil	[23]
8.		Eudragit RS 100	Paracetamol	[24]
9.		Eudragit L100	Ibuprofen	[25]
10.		Eudragit RS 100	Dicyclomine	[26]
11.		Eudragit S 100 and Eudragit L100	Indomethacin	[27]
Time dependent polymers				
1.	The release of drug from dosage form should be after a predetermined lag time to deliver the drug at the right site of action at right time and in the right amount. Colon targeting could be achieved by incorporating a lag time (3-5 hrs) into formulation equivalent to the mouth to colon transit time.	HPMC	Pseudoephedrine HCl	[28]
2.		Hydroxyethyl cellulose, EC	Theophylline	[29]
3.		Microcrystalline cellulose, Lactose/behinic acid	Indomethacin	[30]
4.		HPMC and Acetate succinate	Diltiazem HCl	[31]
Time and pH dependent systems polymers (Multiparticulate DDS)				
1.	The transit time through the small intestine is independent of the formulation. But, the time taken by the formulation to leave the stomach varies greatly and the time of arrival of a formulation in the colon cannot be accurately predicted.	Eudragit S-100 and Poly (dl-lactide-co-glycolide) (PLGA)	Budesonide	[32]
2.		Eudragit RS 30D and Eudragit L 55 30D	Indomethacin	[33]
3.		Eudragit L-100 and S-100 (1:2)	Theophylline	[34]
Microbial triggered (Polysaccharide/microflora activated) based polymer				
1.	The degradation of polymers coated on the drug delivery system by microflora	Chitosan	Diclofenac Sodium	[35]

	present in colon and there by release of drug load in colonic region because the bio- environment inside the human GIT is characterized by presence of complex microflora, especially the colon is rich in microorganisms. In this method, drugs and/or dosage forms are coated with the biodegradable polymers. When the dosage form passes through the GIT, it remains intact in the stomach and small intestine where very little microbial degradable activity is present which is insufficient for cleavage of the polymer coating. In case, multiple unit chitosan and drug formulations depend for delivery of drug on both variation in GI pH and the presence of colonic microflora. Limitations are that most ofpolysaccharides are hydrophilic and gel forming. GI transit time depends on drug delivery and transit time through the small intestine is independents on type of formulation. Finally, it has been found both large single-unit formulations and small multiple-unit formulations take 3-4 hours to pass through small intestine.			
2.		Chitosan	Budesonide	[36]
3.		Pectin	Indomethacin	[37]
4.		Guar gum	5- Fluorouracil	[38]
5.		Guargum	Dexamethasone	[39]
6.		Chondroitin Sulphate	Indomethacin	[40]
7.		Amylose	5- Acetyl Salicylic Acid (5-ASA)	[41]
8.		Sesbania gum	Metronidazole	[42]
9.		Guar gum	5- Amino Salicylic acid (5-ASA)	[43]
10.		Guar gum and Sodium Starch Glycholate (SSG)	Valdecoxib	[44]
11.		Pectin	5- fluorouracil	[45]
12.		Chitosan	Insulin	[46]
13.		Pectin	Radioactive tracer	[47]

14.		Pectin	Resveratrol	[48]
Microspheres based polymer (Multiparticulate DDS)				
1.	A multi-particulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties, which is depended on the polymer concentration in the preparation. Ideally having a particle size less than 200 μm.	Ca-pectinate, Eudragit S100	Theophylline	[49]
2.		Eudragit L-100, Eudragit S-100	Indomethacine	[50]
3.		Guar gum	Aceclofenac	[51]
4.		Guar gum	Methotrexate	[52]
5.		Cellulose acetate butyrate (CAB), Eudragit S	Budesonide	[53]
6.		Alginate, Eudragit S-100,	5- fluorouracil	[54]
Novel nanoparticles based polymer (Multiparticulate DDS)				
1.	The drug moiety can be dissolved, entrapped, or encapsulated in the nanoparticle matrix. They are better than the Conventional dosage forms in many aspects. They may result in more efficacy, reduced toxicity, better bio-distribution and improved patient compliance.	Soya lecithin, Dynasan and Dynasin	5- Fluorouracil	[55]
2.		Alginate and Chitosan	Tripeptide, Lys-Pro-Val	[55]
Pressure triggered (Pressure controlled) delivery based polymer				
1.	Higher pressures are encountered in the colon than in the small intestine. In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon.	EC film	Caffeine	[56]
2.		EC	Caffeine	[57]
3.		Zinc-pectinate	Theophylline	[58]
4.		Pregelatinized starch and wax	Pentoxifylline and behenic acid	[59]
Hydrogel based polymer				
1.	It contains acidic co-monomers and enzymatic degradable azo aromatic cross links.	Amydated pectin	Indomethacin	[60]
2.		Amydated pectin	Sulfamethoxazole	[60]
3.		Cross-linked HPMC	5- Acetyl Salicylic Acid (5-ASA)	[61]
Probiotic approach based polymer				

1.	Mainly three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature.	Guar gum	Diclofencac sodium	[62]
Microbial-triggered colon targeted osmotic pump (MTCT-OP)				
1.	MTCT-OP is a combination of osmotic technology and microbial-triggered mechanism had a high potential to deliver to drug load in colonic region.	Chitosan, Eudragit L-100-55	Budesonide	[63]
Bioadhesive approach based polymer				
1.	Drug coated with bioadhesive polymer that selectively provides adhesion to colonic mucosa.	Hydroxyl propyl methacrylamide (HPMA)	5- Acetyl Salicylic Acid (5-ASA)	[64]

2. Recent Advance Marketed Platform Approaches for CTDDS

Nowadays designing of dosage form is becoming complex because there is a vast use of technology in the dosage forms for controlling various aspects. Following examples are mentioned in case of colon targeted drug delivery given in Table 2.

Table 2: Recent marketed drug delivery technology

Sr. No.	Drug Delivery Technology	Dosage Form	Principle Mechanism	Description	Ref.
1.	MMX™ (Multimatrix technology)	Tablet	pH dependent and microbial activated	It has diffusion-based release mechanism to achieve sustained release, but this system does not give quicker therapeutic action. The technology has been designed in such a way that the drug gets release throughout the colon.	[65]
2.	PHLORAL™	Tablet	pH and microflora activated	This novel system comprises a mixture of pH-responsive polymer (EUDRAGIT S) and biodegradable polysaccharide (resistant starch) as a coat. In this PHLORAL™ technology, the EUDRAGIT S coating prevents the disintegration of the film in the upper gastrointestinal tract and controls swelling of starch.	[65]
3.	CODES™	Tablet	pH and microflora	It is comprises a series of polymers that are	[65,

			activated	combined to protect the drug core until the formulation arrives in the colon.	66]
4.	COLALPRED™	Tablet	Microflora activated	It has arisen from combining Alizyme's properitary colonic DDS, COLAL, with an approved generic steroid (Prednisolone sodium metasulfobenzoate).	[65]
5.	Diffucaps	Beads & Capsule	Multiparticulate system	In this multiparticulate system, drug profiles are created by layering an active drug onto a neutral core such as sugar spheres, crystals or granules followed by the application of a rate-controlling, functional membrane	[67]
6.	IPDAS (Intestinal protective drug absorption system)	Tablet	Multiparticulate system	It has been developed to enhance the gastric tolerability of potentially irritant or ulcerogenic drugs such as the NSAIDs. It consists of high density controlled release beads that are compressed into a tablet form.	[67]
7.	PRODAS (Programmable oral drug absorption system)	Capsule	Multiparticulate system	It is presented as a number of mini tablets contained in hard gelatin capsule and their size ranges is 1.5 – 4 mm in diameter	[67]
8.	PDS (Pelletized delivery system)	Pellets, Beads	Multiparticulate system	It is a sustained release system using pellets or beads manufactured using marumerization or pheronization or pelletization techniques or by layering powders or solutions on nonpareil seeds.	[67]
9.	Peltab® (Pelletised tablet)	Tablet	Multiparticulate system	Pelletised tablet system utilizes polymer-coated drug pellets or drug crystals, which are compressed into tablets.	[67]
10.	Multipart® (Multiparticle drug dispersing shuttle)	Tablet	Multiparticulate system	It consists of a tablet carrier for the delivery of controlled release beads or pellets through the GIT which preserves the integrity and release properties of the beads.	[67]
11.	Flashtab	Tablet	Multiparticulate system	It is a fast dissolving or disintegrating oral tablet formulation. It is a combination of taste masked multiparticulate active drug substances with specific excipients compressed into tablets.	[67]
12.	Minitabs	Tablet	Multiparticulate system	Eurand MINITABS means that they can be filled into capsules as a final dosage form and they are tiny (2mm x 2mm) tablets containing gel- forming excipients that control drug release rate. Additional	[67]

				membranes may be added to further control release rate.	
13.	TARGIT™	Capsule	pH dependent	It is mainly used in the delivery of drug to the lower GIT for local treatment of disorders. In this technique pH sensitive coating is done on the moulded starch capsules. The in vivo studies, about 90% of drug delivered to the target site	[68,69]
14.	OROS-CT (Osmotic controlled system)	Capsule	Pressure dependent	OROS-CT systems can be single osmotic unit or many incorporate as many as 5-6 puss-pull units, each 4mm in diameter and encapsulated with hard gelatin capsule (HGC).	[70, 71]
15.	Osmet pump	Capsule	Pressure dependent	It consists of an enteric coated semi-permeable shell which enclosed an osmotic layer along with a central impermeable and collapsible reservoir filled with drug.	[65]
16.	ETP Tablet (Enteric coated timed release press coated tablet)	Tablet	Time control/ dependent system	They are composed of three components, a drug containing core tablet (rapid release function), the press coated swellable hydrophobic polymer layer (Hydroxy propyl cellulose layer (HPC), time release function) and an enteric coating layer (acid resistance function).	[72, 73]
17.	Pulsincap®	Capsule	Time dependent Containing pulsatile system	It consists of non disintegrating half capsule body filled with drug content sealed at the opened end with the hydrogel plug, which is covered by water soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying.	[65, 74]

3. Quality Control Parameters

The successful CTDDS is one of that remains intact in the physiological environment of small intestine and stomach, but drug releases in the colonic region. It can be evaluate and characterize by means of different parameters including in-vitro, ex-vivo and in-vivo (Clinical) measures. A number of techniques have been used to characterize by CTDDS as well find out the various feasibility or flexibility of their formulation process.

➢ In-vitro evaluation

Different in vitro methods are used to assess the colonic drug delivery systems.

- In vitro dissolution testing method [75, 76]
  Following system including dissolution test via caecal contents, fresh human fecal slurries and studies using enzymes
- In vitro enzymatic degradation test [77]

- Drug delivery index [78, 79]
  - Relative Colonic tissue Exposure (RCE)
  - Relative Systemic Exposure to drugs (RSE)
- Clinical (In-vivo/ Pharmacokinetic studies) evaluation
  - High frequency capsule [80]
  - Animal model study [80-84]

  A variety of techniques which are used for monitoring the in vivo behavior;
    - Gamma scintigraphy imaging
    - String technique
    - Endoscopy
    - Radiotelemetry
    - Roentegenography
    - Colonoscopy and Intubation

  Note: The preferable animals to evaluate CTDDS including rats, guinea pigs and dogs.
- Magnetic moment imaging study
- Statistical analysis [85]

  It is used in find new formulation for applying statistical model and design new formula.
  - Factorial design
- Micromeritic properties [86-88]
  - Density measurements, Angle of repose, Carr's index (%), Hausner ratio, Preformulation study: Drug polymer compatibility studies, Loss on drying.
- Additional physicochemical parameters [86-87]
  - Thickness
  - Diameter
  - Hardness
  - Friability
  - Uniformity of drug content
  - Weight variation
    - Weight Variation before coating
    - Weight Variation after coating
  - Stability studies

4. Patents on Colon Targeted Drug Delivery System (CTDDS)

In Figure 2 summarize publication of recent patent related toward CTDDS (source: Patent Analysis Software CobaltIP, 2012 and Patentlense and Google Patent). Now a day, more than 100 patent on hand in current market on CTDDS in different country like WO, EP, CN, CA, US, KR, DE, BR, AT, HK, AU, JP, IL, RU, DK, SK, TW, MX, IN, ES, FI, PL, SI, PT, RS.

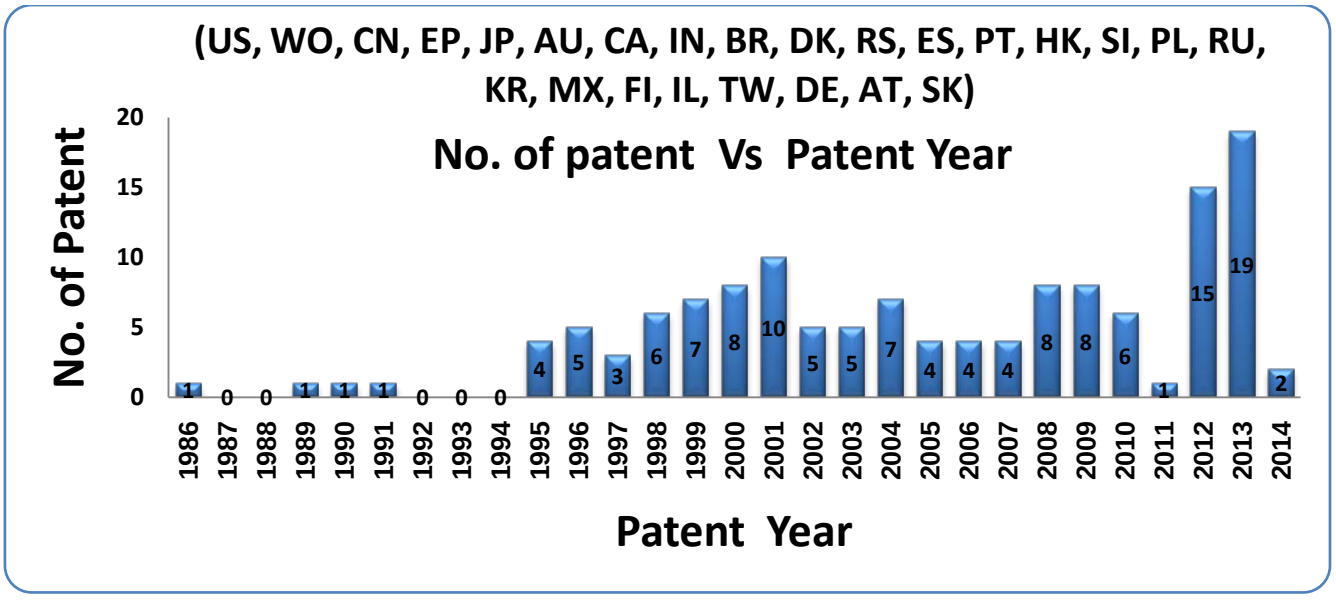

Figure 2: Graphically illustration of the patents on CTDDS

Table 3: Patents set-up on CTDDS formulations

Summary of granted or published patents based on colon targeted drug delivery system given in Table **3** [113-247].

Title	Patent No.	First author	Year	Ref.
Colon delivery system	AU1985/048886 A	Wong PSL et al.	1986	[88]
Colon delivery system	CA1255562 A1	Patrick SLW et al.	1989	[89]
Delivery of drug to colon by oral disage form	US4904474 A	George VG et al.	1990	[90]
Colonic drug delivery system	AU1991/080877 A	Sintov A et al.	1991	[91]
Colonic drug delivery composition	WO1995035100 A1	Peter W	1995	[92]
Colon-specific drug release system	AU1995/022668 A	Watanabe S et al.	1995	[93]
Colonic drug delivery system	AU660147 B2	Sintov A et al.	1995	[94]
Slowly releasable drug delivery device	JPH072648 A	Ruisu S et al.	1995	[95]
Colonic drug delivery system	IL98087 A	Sintov A et al.	1996	[96]
Colon-targeted delivery system	US5482718 A	Wantanee P et al.	1996	[97]
Pharmaceutical dosage form with multiple enteric polymer coatings for colonic delivery	WO1996036322 A1	Gary RK et al.	1996	[98]
Colonic drug delivery composition	AU1995/027460 A	Watts P	1996	[99]
Colonic drug delivery composition	US5525634 A	Abraham R et al.	1996	[100]
Colonic delivery of nicotine to treat inflammatory bowel disease	WO1997028801 A1	Rhodes J et al.	1997	[101]
Composition for enhanced uptake of polar drugs from the colon	AU1996/067059 A	Watts PJ et al.	1997	[102]
Colonic delivery of drugs	US5656294A	David RF et al.	1997	[103]
Pharmaceutical form for drug administration in colon, method of drug administration and a method of preparing matrices for this form	RU2113221C1	Sintov A et al.	1998	[104]
Site-specific controlled release dosage formulation for mesalamine	WO1998026767 A2	Busetti C et al.	1998	[105]
Colonic delivery of weak acid drugs	AU1997/045655 A	Watts P	1998	[106]
Pharmaceutical dosage form for colonic delivery	AU1996/077324 A	Kelm GR et al.	1998	[107]
Colon-specific drug release system	AU689250 B2	Watanabe S et al.	1998	[108]
Colonic drug delivery composition	AU688060 B2	Watts P	1998	[109]
Colonic drug delivery system	US5866619 A	Abraham R et al.	1999	[110]

Preparation for the drug delivery to alpha-adrenoceptor blocking agents	DK0700285 T3	Farraj N et al.	1999	[111]
Composition for colonic drug delivery	KR100212432B1	Lee SS et al.	1999	[112]
Composition for colon specific drug delivery	KR100219918B1	Lee SS et al.	1999	[113]
Colon selective drug delivery composition	AU1997/044007 A	Lee SS et al.	1999	[114]
Delayed total release gastrointestinal drug delivery system	WO1999018938 A1	Moshe F et al.	1999	[115]
Composition for enhanced uptake of polar drugs from the colon	AU707587 B2	Watts PJ et al.	1999	[116]
Colonic delivery of weak acid drugs	KR20000048939 A	Watts PJ	2000	[117]
Colonic delivery of weak acid drugs	SK44299 A3	Watts PJ	2000	[118]
Oral drug delivery system for enhancing the bioavailability of active form of glycyrrhizin	CA2344306 A1	Kanji T	2000	[119]
Enteric and colonic delivery using HPMC capsules	AU1999/062613A	Cole ET et al.	2000	[120]
Water-insoluble drug delivery system	AU2000/031278 A	Tabibi SE et al.	2000	[121]
Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	AU1999/040627 A	Lee SS et al.	2000	[122]
Colon targeted delivery system	US6039975 A	Wantanee P et al.	2000	[123]
Delayed total release two pulse gastrointestinal drug delivery system	WO2000074655 A2	Adel P et al.	2000	[124]
Topical delivery of drugs to the lower gastrointestinal track	TW442299 B	Berliner DL et al.	2001	[125]
Composition for rapid release of corticoid drugs after delay period, useful for drug delivery during the night, e.g. for preventing asthma, or for delivery to colon for treating inflammatory bowel disease	DE10012555 A1	Zobel HP et al.	2001	[126]
Colonic drug delivery composition	DK0810857 T3	Watts P	2001	[127]
Pharmaceutical preparation for submission of drugs in colon	DK0673645 T3	Phuapradit W et al.	2001	[128]
Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	KR20010074641 A	Bae CM et al.	2001	[129]
Colonic drug delivery composition	US6228396 B1	Peter W	2001	[130]
Colonic drug delivery composition	US20010026807 A1	Peter W	2001	[131]
Pharmaceutical dosage form for colonic delivery	AU739031 B2	Kelm G et al.	2001	[132]

Colonic delivery of weak acid drugs	AU732210 B2	Watts PJ	2001	[133]
Colon selective drug delivery composition	US6319518 B1	Seung-SL et al.	2001	[134]
Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	MXPA01000768 A	Lee SS	2002	[135]
Hyaluronic acid containing bioconjugates : Targeted delivery of anti-cancer drugs to cancer cells	WO2002090390 A1	Jindrich K et al.	2002	[136]
Therapeutic azo-compounds for drug delivery	WO2002009769 A2	Kathryn EU	2002	[137]
Active agent delivery systems and methods for protecting and administering active agents	WO2002034237 A1	Thomas P et al.	2002	[138]
Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharides	AU744183 B2	Lee SS et al.	2002	[139]
Composition for enhanced recording of polar drugs from colon	DK0843558 T3	Watts PJ et al.	2003	[140]
A process for the preparation of a composition useful for colonic drug delivery	IN190800 A1	Dwivedi AK et al.	2003	[141]
Colonic release composition	WO2003068196 A1	Richard MJP et al.	2003	[142]
Enteric and colonic delivery using HPMC capsules	AU757343 B2	Cole ET et al.	2003	[143]
Targeted drug delivery methods	WO2003066066 A1	Ling G et al.	2003	[144]
Enteric and colonic delivery using HPMC capsules	MXPA01003197 A	Scott RA	2004	[145]
A pharmaceutical formulation and dosage consisting of polysaccharides to controlled drug release in the colon	AT260649 T	Lee SS et al.	2004	[146]
Composition and pharmaceutical dosage form for a supply of a drug colonico using polysaccharides.	ES2214813 T3	Lee SS et al.	2004	[147]
Gene therapy for solid tumors, papillomas and warts	AT279525 T	Woo SLC et al.	2004	[148]
A pharmaceutical formulation and dosage consisting of polysaccharides to controlled drug release in the colon	DE69915184 D1	Lee SS et al.	2004	[149]
Gene therapy for solid tumors, papillomas and warts	DE69434069 D1	Woo SLC et al.	2004	[150]
Compositions and methods for diagnosing and treating colon cancers	AU2004/203749 A1	Martinez RV et al.	2004	[151]
Ingestible device platform for the colon	WO2005112895 A2	Yoel Z et al.	2005	[152]

Formulations and methods of treating inflammatory bowel disease	WO2005021009 A2	Jackie B et al.	2005	[153]
Oral controlled release system for targeted drug delivery into the cell and its nucleus for gene therapy, DNA vaccination and administration of gene based drugs	WO2005084644 A1	Adi S et al.	2005	[154]
Oral drug delivery system for enhancing the bioavailability of activated glycyrrhetin	EP1116489 B1	Kanji T	2005	[155]
Controlled release drug delivery device	JP2006342187 A	Savastano L et al.	2006	[156]
Composite rodenticide	EP1639893 A1	William D	2006	[157]
Oral controlled release system for targeted drug delivery into the cell and its nucleus for gene therapy, DNA vaccination and administration of gene based drugs	EP1720522 A1	Adi S et al.	2006	[158]
Specific time-delayed burst profile delivery system	EP1731142 A1	Adel P et al.	2006	[159]
Gene therapy for solid tumors, papillomas and warts	AT360697 T	Woo SLC et al.	2007	[160]
Site-specific intestinal delivery of adsorbents, alone or in combination with degrading molecules	WO2007132022 A2	Helene H et al.	2007	[161]
Colonic drug delivery formulation	AU2007/242648 A1	Basit A et al.	2007	[162]
Sustained release pharmaceutical formulation comprising phenylephrine	WO2007143158 A2	David M	2007	[163]
Colon-targeted oral formulations of cytidine analogs	WO2008028193 A2	Etter J	2008	[164]
Gene therapy for solid tumors, papillomas and warts	DE69434960 T2	Woo SLC et al.	2008	[165]
Give colonic drug composition	FI118626 B	Watts P	2008	[166]
Composition or drug delivery device for localized drug release in the colon and use thereof for local treatment of colonic diseases	IL142929 A	Flashner M et al.	2008	[167]
Colonic drug delivery formulation	TW200848091 A	Basit AW et al.	2008	[168]
Colon-targeted oral formulations of cytidine analogs	US20080057086 A1	Jeffrey BE	2008	[169]
Colonic delivery using Zn/pectin beads with a eudragit coating.	AU2007/321111 A1	Andremont A et al.	2008	[170]
Colonic delivery using Zn/pectin beads with a	WO2008059062 A1	Antoine A et al.	2008	[171]

eudragit coating				
Pharmaceutical composition containing naphthoquinone-based compound for intestine delivery system	EP2094261 A1	In GJ et al.	2009	[172]
Colonic delivery using Zn/pectin beads with a eudragit coating	EP2081557 A1	Antoine A et al.	2009	[173]
Galenic pectinate formulation for colon-targeted delivery of antibiotic-inactivating enzymes and method of use thereof	US7485294 B2	Sandrine B et al.	2009	[174]
Galenic formulation for colon targeted delivery of active principles	AU2003/274229 B2	Fattal E et al.	2009	[175]
In colon delivery of active agents	BRPI0606943 A2	Fattal E et al.	2009	[176]
Oral pharmaceutical preparation for colon-specific delivery	KR20090122489 A	Kubo H	2009	[177]
Colonic drug delivery formulation	KR20090032029 A	Basit AW et al.	2009	[178]
Colonic drug delivery formulation	MX2008013036 A	Basit AW et al.	2009	[179]
Water insoluble polymer: modified starch derivative-based film coatings for colon targeting	EP2179727 A1	Olaf H et al.	2010	[180]
Targeting prodrugs and compositions for the treatment of gastrointestinal diseases	WO2010072734 A2	John FG et al.	2010	[181]
Compositions and methods for elimination of gram-negative bacteria	WO2010103119 A1	Antoine A et al.	2010	[182]
Galenic formulation for colon-targeted delivery of active ingredients	US7833765 B2	Sandrine B et al.	2010	[183]
Development of mastic indicated for imflammatory bowel disease (IBD) applied with colon targeting drug delivery system (DDS)	KR20100022200 A	Moon YI et al.	2010	[184]
Pharmaceutical composition for drug delivery to the colon and method for preparing the same	BR9912075 A2	Lee SS et al.	2010	[185]
Colon drug delivery system preparation	JP2011105654 A	Imamura N et al.	2011	[186]
Colonic delivery of adsorbents	AU2006/249100 B2	Andremont A et al.	2012	[187]
Improved oral targetted drug delivery system	WO2012035561 A2	Sanjiv D et al.	2012	[188]
Compositions and methods for elimination of gram-negative bacteria	EP2405909 A1	Antoine A et al.	2012	[189]
Pharmaceutical cyclosporin compositions	EP2409691 A1	Ivan C	2012	[190]
Process to produce a diclofenac cyclodextrin	EP2422818 A2	Rocha GAMA et al.	2012	[191]

conjugate				
Method for preparing starch-base carrier material for controlling slow-release through high-pressure retrogradation, prepared material and application	CN102824642 A	Chen L et al.	2012	[192]
Drug delivery system	WO2012158030 A2	Johannes MMB et al.	2012	[193]
Polymer conjugate of taxane	US8323669 B2	Masayuki K et al.	2012	[194]
Sustained release pharmaceutical formulation comprising phenylephrine	EP2034970 B1	David M	2012	[195]
Compounds	US8283371 B2	Sjoerd NW	2012	[196]
Coating composition containing starch	RU2440104 C2	Podzhek GF et al.	2012	[197]
Colonic drug delivery formulation	PL2018159 T3	Basit AW et al.	2012	[198]
Colonic drug delivery formulation	SI2018159 T1	Basit AW et al.	2012	[199]
Colonic drug delivery formulation	PT2018159 E	Basit AW et al.	2012	[200]
Colonic drug delivery formulation	HK1128627 A1	Basit AW et al.	2012	[201]
Improved oral targetted drug delivery system	EP2632902 A2	Monica G et al.	2013	[202]
Colonic delivery of adsorbents	PT1883396 E	Fattal E et al.	2013	[203]
Contribution of colonic adsorbent	ES2429095 T3	Huguet HC et al.	2013	[204]
Submission of adsorbers for colon	DK1883396 T3	Huguet HC et al.	2013	[205]
Colonic drug delivery formulation	RS52434 B	Basit AW et al.	2013	[206]
Indigestible polymer: starch acetate-based film coatings for colon targeting	CN102883714 A	Xi P et al.	2013	[207]
A colon-targeted prodrug and its preparation method based on nano-cellulose carrier translated from chinese	CN103405778 A	Tang L et al.	2013	[208]
Site-specific intestinal delivery of adsorbents, alone or in combination with degrading molecules	US8388984 B2	Helene CH et al.	2013	[209]
Composition and method for treatment of diabetes	US8470885 B2	Jerzy RS	2013	[210]
Pharmaceutical cyclosporin compositions	US20130330411 A1	Ivan C	2013	[211]
Intestine-protecting and detoxifying micro pellets and use thereof	CN102406869 B	Li Y et al.	2013	[212]
Oral pharmaceutical composition	CN103120653A	Kurt	2013	[213]
Pharmaceutical dosage form with multiple coatings for reduced impact of coating fractures	US8580302 B2	Gregory PD	2013	[214]

Active agent delivery systems and methods for protecting and administering active agents	US8394813 B2	Travis M	2013	[215]
Methods and system for ultrasound-mediated drug delivery	US20130261442 A1	Feng YY	2013	[216]
Compositions for the oral delivery of corticosteroids	CN102088962 B	Peter W et al.	2013	[217]
Nanoparticle formulations with enhanced mucosal penetration	WO2013110028 A1	Laura E et al.	2013	[218]
Gastroresistant pharmaceutical formulations containing rifaximin	US8568782 B2	Giuseppe CV et al.	2013	[219]
Small peptides specifically bind to colorectal cancers	US8435490 B2	John MA et al.	2013	[220]
Compositions and methods of treatment for inflammatory diseases	US8629127 B2	Richard FH	2014	[221]
Colonic release bills using Zn/ pectin with a coating of eudragit	BRPI0719319 A2	Andremont A et al.	2014	[222]

Conclusion

The present overview focused on recent patent, current marketed status and future directions of targeted drug delivery to colon. As of the past few decades, exciting innovation into colon specific drug delivery contain exposed unique potential for growing the efficacy of drugs for colonic diseases. This short patent summary might provide a rough summarize of the present work and provide a people in general vision of the field. We believe that a young investigator field in oral targeted drug delivery to the colon have achieved tremendous growth and claim a good set of therapeutic application. In-depth research is still needed on several critical issues so that the field might be long lasting and deep impact in colon targeted applications. Growing information of multi-particulate drug delivery would possibly turn into commercially accessible to patients in the near future. In future, it is used in oral site specific or control drug delivery and improved number of international patent. The management of disorders of the large intestine, such as Irritable Bowel Syndrome (IBS), IBD, ulcerative colitis, Crohn's disease and additional colon diseases, where it is needed to accomplish a high concentration of the drug, might be capably achieved by colon-specific delivery. I hope that my effort is going to find new application in near future.

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