Development of Colon Drug Delivery System for the Treatment of Inflammatory Bowel Disease

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Abstract - **Inflammatory bowel disease (IBD) is one of the most common chronic diseases that affect the entire gastrointestinal tract (GIT) especially the colon. Its symptoms extend from mild diarrhea, abdominal pain, and bloody diarrhea to severe conditions which affect the quality of life. Many treatments have been developed to treat and cure IBD and to improve patient's quality of life. The big challenge faces the newly developed treatments is the site of action as the colon presents at the distal end of the GIT and have a complex biological environment. Many technologies have been investigated to target the colon, load higher amounts of active ingredients, and decrease unwanted side effects resulted from upper GIT absorption. This review briefly discusses the IBD, treatment lines, physiological considerations, and all methods of colon targeting technologies starting from the traditional methods which based on pH, time, and microbial content of the colon. Also, we discussed in detail all new techniques based on Micro and Nanotechnology which improve the effectiveness of used therapeutics.**

Index Terms - **Inflammatory bowel disease, colon drug delivery systems, OROS-CT, pH-dependent carriers, CODESTM, novel colon approaches.**

INTRODUCTION

Newely designed pharmaceutical drug delivery systems focus on delivering existing drugs with improved safety and efficacy together with lower dose frequency. Also, the choice of the most appropriate administration route is very important in order to achieve the required therapeutic response.

In comparison with the alternative routes of drug delivery, oral route and oral deliver systems are considered to be most suitable and best to administer drugs. Oral route have maby advantages above other routes such as easiness in administration, low cost , and patient noncompliance. The main drawbacks and the moat serious problem in oral route and usimg conventional drug delivery system are alowing the amount of actibe substances. In addition, drug absorption from gastrointestinal tract (GIT) region depends mainly on physiochemical properties of the active ingredients.

Modified-release systems showed a controlled manner of the required plasma levels and steady-state concentration for a long period [4]. The advanced drug delivery systems planned to control drug release in the oral route also, planned to control the release of poorly water-soluble drugs and to target specific GIT sites [6]. Pharmaceutical researchers extensively studied and developed in the area of drug targeting and/or site-specific drug delivery. Delivery of drugs to specific sites or to treat specific diseases is very important and essential to improving therapeutic efficiency by increasing the dose of the desired drug at the site of action. Also, to reduce undesirable side effects and cost [7]. Colon drug delivery systems (CDDS) are an example of drug targeting which has promising developments in the area of local and systemic treatment. At the same time, CDDS have various challenges as reaching the distal part of GIT presents significant physiological difficulties and environmental barriers [8, 9]. Targeting drug to the colon is highly valuable for local treatment of numerous diseases such as ulcerative colitis, Crohn's disease and colonic cancer [10]. Also, for the systemic delivery of drugs such as proteins and

peptides which may be unstable in the stomach and small intestine due to many problems like hydrolysis and lower absorption from the lumen of upper GIT due to their relatively large molecular weight

ANATOMICAL AND PHYSIOLOGICAL RELATED TO THE COLON

The colon is the terminal part of the GIT. It is the part of large intestine and has the following anatomical features:

1. The length of the colon is about 1.5-1.66 m (5 ft).
2. Having an internal diameter of 2.5 cm and a surface area 3 m sq.
3. Starts from the ileun by a small junction called ileocecalsphincter and ends with the anus.
4. According to anatomical structure, tbe large intestine is divided into four anatomical position are cecum, colon, rectum, and anal canal.
5. The colon is divided into four regions are ascending colon, tranverse colon, descending colon, and sigmoid colon.

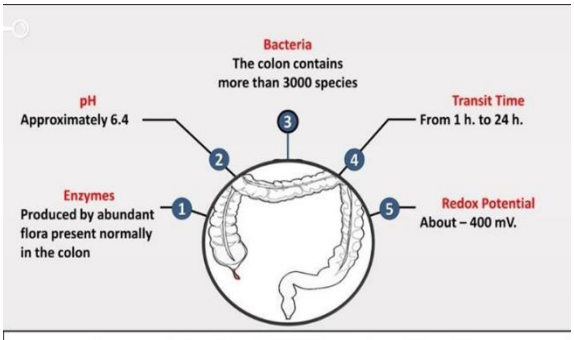
INFLAMMATORY BOWEL DISESASE(IBD)

Inflammatory bowel disease is relapsing and chronic inflammatory disease of bowel mucosa, more susceptible to the colon.IBD is a chronic, progressive, disabling disease [20], characterized by the unknown origin and both long-term and short-term inflammation [21]. IBD is a term used to describe both ulcerative colitis (UC) and Crohn's disease (CD) [22-24]. Both diseases are thought to be a result of dysregulated mucosal response in the bowel function [25]. Both UC and CD are usually extending over many years and sometimes impossible to differentiate between them [23]. Whatever both are characterized by similar symptoms, for example, severe diarrhea, bodyweight loss, bloody stool and abdominal pain [23]. Pathological lesions and the position of the inflammation can distinguish between UC and CD to some extent [26]. In the case of UC, inflammation mainly affects the innermost mucosa and not involve the deeper tissues like serosa and muscularis. The lesion mainly is confined to the colon and rectum. But in case of CD, inflammation is transmural, affects the entire wall of the intestine, and deeper to the serosal layer. The lesion occurs over the length of the large intestine and small intestine, sometimes even reach to the mouth [27, 28]. IBD characterized by alternative cycles of remission and relapse [22, 29]. Although IBD has been extensively studied for many years, its pathogenesis remains idiopathic and unknown [30]

DRUG MOLECULES FOR IBD TREATMENT

Pharmacological treatment of ulcerative colitis and crohn's disease is very difficult and depends mainly on the location and activity of the disease. The main goal of treatment is to prolong remission cycles and decrease relapsing cycles. IBD treatment is long-life treatment [45]. Wide range of medicinal agents used for the treatment of IBD as 5-aminosalicylates, glucocorticoids, antibiotics, thiopurines, methotrexate, and biological treatment as TNF-α antibodies [23]

5-aminosalicylates are the first line of the treatment for patients having mild to moderate UC and have a big role in induction and maintenance of remission periods at doses of 3000-4500 mg per day for sulfasalazine Aminosalicylates group include sulfasalazine [46], mesalazine [47], olsalazine [48, 49], and balsalazide [50, 51]. The action of aminosalicylates depends on the modulation of cytokines released from bowel mucosa [23]. Also, by decreasing the nuclear localization of nuclear factor-kappaB (NF-kB) through peroxisome proliferator-activated receptor gamma (PPAR-γ) mediation [24]. Aminosalicylates are the most common treatment of ulcerative colitis [24, 46], and have no proven role in the treatment of Crohn's disease [23]. Sulfasalazine having more side effects due to sulfapyridine-related intolerance in some patients [52], so the use of sulfasalazine is limited. Other agents as mesalazine, olsalazine, and balsalazide are more tolerated.



Most common colon drug delivery systems (CDDS) are based upon this five conditions.

Figure 1: The most important colon environment conditions

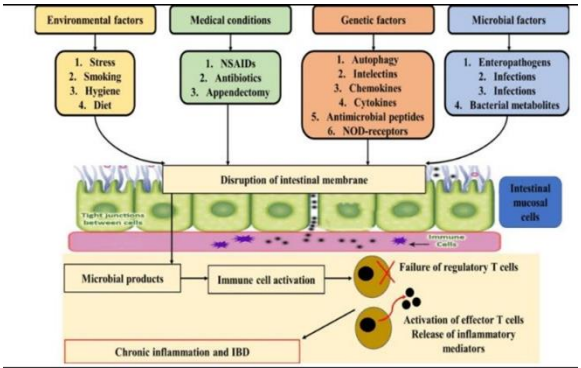


Figure 2: Pathogenesis of inflammatory bowel disease

DRUG DELIVERY STRATEGIES FOR IBD THERAPY

a) Colonic absorbtion

The colon has a different physiological environment and in the case of IBD, the colon environment becomes more complex due to the disease severity and location of the lesion in the distal part. Also, treatment becomes more difficult due to the previous conditions and due to colonic absorption, which hardly to be predicted as the small intestine. Irrespective of therapy required for local or systemic drug delivery, drug absorption from the colon mainly depends on three major factors include pH, transit time, and microbial flora of the colon [65]. The large intestine characterized by the small surface area 3 m2 [8]. The small surface area of the colon is overcompensated by the very long transit time (≤ 48 h.) [66] and the absence of digestive enzymes. Drugs which reached to the colon may be absorbed by two main mechanisms, the first one is the transcellular transport in which the drug passes through colonocytes, and the other is the paracellular transport in which drug passes through the junctions between adjacent colonocytes [67]. The paracellular pathway is highly difficult and more restricted in the colon due to very small gaps between colonocytes-very tight junctions only molecules of 60 molecular weight or lower can be absorbed paracellular. Absorption in the colon occurs by the second transcellular pathway (passive transcellular diffusion) in which lipophilic drugs pass through colonocytes but not similar to the small intestine as the colon having lower water volume and small surface area available for drug absorption [68]. Drug delivery strategies to the colon (Figure 3) include at the first rectal preparations like suppositories, enemas, and foams. Rectal preparations have been efficiently used for the treatment of lesions in the lower part of the colon, but not effective in some cases in which the inflammation was located in the upper part of the colon such as pancolitis [26]. The traditional oral route is considering an effective route for the treatment of IBD especially lesions that extend to the small intestine and ever to mouth. Oral route has many limitations as extensive first-pass metabolism, side effects due to drug absorption from upper GIT and only a small amount of the active drug reach to the inflamed areas of the colon.

b) Factors affecting drug absorption from colon

b1) Drug related factors

Drug absorption from the colon differs from other sites of GIT as the colon is distal part of yhe alimentary canal and having some different features. Also, drug properties affect drug absoprtionfrom the colon as

1. Drug solubility, drug log P, and permeability at the site of action
2. Physiochemical properties of drug as pKa and degree od ionization.
3. Drug degredationand stability in the colon.
4. The drug should be in solution before reaching the colon, where the water volume and fluids content is low.

b2) Colon related factors

The colon emvironment has a big role in drug absorption by different and various factors which affect the absorption rate as

1. Lumen pH level
2. Transit time of the colon which has higher values and big variations.
3. Bacterial enzymes activity against drugs.
4. Mucous binding and selectively to drugs.
5. Disease state of colon.
6. Local physiological action of drugs.

b3) Formulation related factors

Colon targeted drug delivery systems should be formulated in a manner which produces the highest

drug targeting and highest drug absorption from the colon. Many formulation factors can affect drug absorption as:-

1. Type of drug delivery system.
2. Polymer and exipients nature
3. Drug delivery system release manner, which should be able to control release in the stomach, upper gastrointestinal tract, and able to release the drug in the colon.
4. Particle size as microparticle or nanoparticle delivery systems.
5. Using of absorption enhancers.
6. Colon drug delivery systems (CDDS) should be able to delay drug release till reaching the colon in which formulationmay release the drug in burst manner or sustained- release.
7. Formulation factors, retention time, and retrograde spreading influence drug conc. Reaches the drug.

PHYSIOLOGICAL CONSIDERATION IN COLON DRUG DELIVERY SYSTEM DESIGN

c1) Transit time:

A big variation in physiological state occurs in IBD patients and becomes dynamic, more inter-related, and difficult to examine correctly in isolation. Transit time across the gastrointestinal tract (Orocecal transit time, OCTT) has been shown to be delayed in both ulcerative colitis and Crohn's disease [22] [78]. Patients with ulcerative colitis have colonic transit time twice faster than normal persons due to high secretions and diarrhea, leading to challenges in targeting the colon using conventional formulations. OCTT in the normal and IBD patients shown in (Table 1). Using the delayed-release conventional formulations is not effective in colon targeting and showing bidistribution phase as higher drug concentration in the proximal colon and lower drug concentration in the distal colon.

c2) Microbial contents:

Normal flora occupies our gastrointestinal tract from mouth to the colon and plays a big role in GIT physiology as digestion of carbohydrates, proteins, and fatty acids. In normal conditions, the GIT hosts over 500 distinct species [22], and many studies estimating the number of species to 2000 [80]. Gastrointestinal microbiota is a complex system includes bacteria, yeasts, archei, and fungi [14]. The colon contains at least about 1011 - 1012 CFU of microorganisms and the most common types in the colon are Bacteroids, Clostridium group IV, XIV, Bifidobacteria, and Enterobacteriace [22, 80]. Ulcerative colitis and Crohn's disease occur in the colon and distal ileum, which having the highest concentration of microbiota. Both composition and function of intestinal microorganisms in UC, CD, and pouchitis are abnormal [80]. Dysbiosis is the imbalance of the normal microbial flora and considered as one of the common theories of IBD pathogenesis, in which occur an increase in the concentration of anaerobic bacteria, particularly gram-negative (G -Ve) bacteria as Bacteroids, and reduction in beneficial bacteria as Bifidobacteria [81]. Also, dysbiosis of commensal microbiota includes decreased the ratio of protective/ aggressive bacteria, decreased the microorganisms which produce short-chain fatty acids (SCFA), and increased the concentration of aggressive bacterial species as hydrogen sulfide reducing bacteria, Bacteroids, Enterobacteriace, and Candida albicans [80]. Normal microbial flora and dysbiosis are presented in (Table 2)

c3) Colonic pH:

Gastrointestinal pH changes along different regions of alimentary canal as shown in (Table 3). The highly acidic stomach secretions and contents rapidly changed to slightly acidic pH in the duodenum and then rose to basic pH at the terminal ileum [22, 82]. The colon pH in normal individuals changes from cecal pH of 6 to the rectum pH of 6,7 [71, 83]. The slightly acidic pH of the colon is due to the production of short-chain fatty acids (SCFA) by the abundant bacterial microbiota of the colon [84]. The gastrointestinal pH controlled by many factors as the food and fluid intake, microbial digestion and fermentation process, and gastrointestinal secretions [85]. During the active phase of inflammatory bowel disease occurs disruption in three main mechanisms which control luminal pH level, microbial fermentation and digestion process especially SCFA production in the colon, bile acid metabolism of fatty acids, and bicarbonate/carbonate secretions mechanism [82]. Disruption of these mechanisms leads to alterations in the colon pH from 6,8 to 5,5 in active UC, [71] and 5,3 in CD [22, 83]. Alterations in

pH lead to a change in transit time and microbial flora contents, which significantly affects drug release from traditional formulations [86].

c4) Intestinal membrane integrity:-

Normal intestinal barrier composed of following three layer:

1. Thick mucus layer,which composed of two main layers, the outer mucus layer, and the inner mucus layer. Mucus produced by goblet cells consisting of a thick layer of about 150 µm and acts as a chemical barrier by protecting the intestinal epithelium by its viscosity. Mucus layer contains a high concentration of glycosylated mucins, and trefoil factors (TFFs), which acts as a defensive mechanism. Also, acting by entrapping bacteria.
2. A mono;ayer of epithelial cell, which mainly composed of colonocytes, and goblet cells. The epithelial cells regulate the intestinal permeability between the cells by junctions, the most common types of colonocytes junctions are desmosomes, adherent junctions (AJs), and tight junctions (TJs).
3. The lower barrier, which composed mainly group ofcells as macrophages mesenchymal cells, dendritic cells, and lymphocytes. Thes layer acts mainly as a protective layer.

Chronic inflammation of intestinal membrane as in both UC and CD leads to destructive changes in the intestinal barrier as:

1. Disruption of intestinal membrane characterized by mucosal surface changes and crypt distortion.

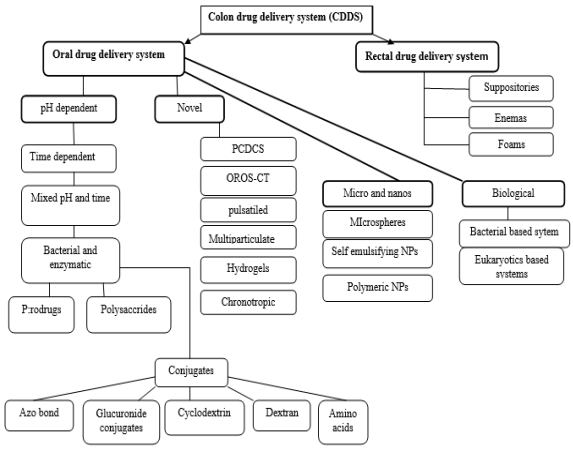


Figure 3: Colon-targeted drug delivery systems.

Table 1: OCCT in normal individuals and IBD patients

Transits time (hrs)	Normal	IBD
1. Stomach	1-2 hr	Increased 30%
2. Small intestine	3-4hr	
a. Duodenum	2 hr	Increased 30%
b. Jejunum	1.5 hr	
c. Ileum	1.5 hr	
1. Large intestine	6-70 hr	24 hr

Table 2: Commensal microbial content of gastrointestinal tract in healthy individuals and IBD.

GIT parts	Microorganism counts	Species in healthy	Species in IBD
1. Stomach	10^2	Clostridiales Streptococcus	Increased E.coli. Decrease Clostridium
2. Small intestine	10^4	BacteroidsActinomycinae Lactobacillus	
a. Duodenum	10^5	Corynebacteria	Increase bacteroids,
b. Jejunum	10^7		Eubacteria,Peptostreptococcus, and
c. Ileum		Firmicutis Bacteroids Proteobacteria	decrease Bifidobacteria and E.coli.
3. Colon	10^{11}	Actinobacteria	

2. Reduction in a number of goblet cells, reduction in mucus production, reduced mucus layer thickness, and altered mucus composition [90].

3. Infiltration of inflammatory immune cells as lymphocytes, neutrophils, and macrophages.

4. Changes in mucosal physiology and metabolism, as membrane trying to repair and limit damage of cells, the compensation mechanism leads to activation of a number of protective pathways as the oxygen-sensing transcription factor, and hypoxia-inducible factor (HIF) mediates increased expressions of mucus components as mucins, and TFs, subsequently leading to mucus viscosity changes, which may affect permeability of lipophilic drugs [91].

5. Changes in mucosal membrane transport mechanisms as downregulation of TJ complex, which associated with loss of intestinal integrity [22], and increased paracellular absorption in patients with IBD [92]. TJ complex is considered as an attractive target for drug absorption [93]. Also, HIF transcriptionally regulates multi-drug resistance gene 1 (MDR 1), which stimulate both xenobiotic drug efflux pump, and P-glycoprotein (P-gp), which actively acting in the transportation of the drug back

again to the lumen, and contributes to many drug resistance, For example, glucocorticoids

Primary approaches for colon drug delivery

Main strategies for the colon drug delivery systems include primary or traditional approaches such as tablets which mainly depends on three main mechanisms namely, enzymatic or microbial approach which mainly acts by the aid of colonic microbial enzymes, pH-dependent approach, and timedependent approach. In microbial or enzymatic approach, targeting depends mainly on drug activation by colonic microbial enzymes. The colon contains at least about 1011 - 1012 CFU of microorganisms and the most common types are Bacteroids, Clostridium group IV, XIV, Bifidobacteria, and Enterobacteriace. [22, 80] The main drawbacks of this system are its dependency on the enzymatic activity of colonic normal flora that may be totally disrupted in case of IBD. Dysbiosis, which is defined as the imbalance of the normal microbial flora and considered as one of the common theories of IBD pathogenesis, is not common in case of UC, but in CD many variations in microbial enzymes have been observed [96, 97]. The microbial-based approach includes using of prodrugs, the most common example is sulfasalazine and 5-ASA which cleaved microbially and activated to mesalazine and sulfonamide [98, 99]. Also, include the use of conjugates like azo-bond conjugates, glucuronide conjugates, cyclodextrin conjugates, dextran conjugates, and amino acids conjugates [69, 100-102]. Finally, this system is widely available using a variety of polysaccharides (Table 4). In the pH-dependent approach, a widely used approach and depends mainly on the retardation of drug release at lower pH values. Therefore, drug release occurs only at pH of distal ileum (pH > 6). Patients with IBD showed lower colonic pH ranging from 5 to 7 and in some cases drops to 2.3 which cause incomplete drug release at the site of treatment [71, 82]. Time-dependent systems or time-controlled systems are usually known as delayed-release systems or sigmoidal-release systems [103]. The system is designed mainly to resist the acidic medium of the stomach, prevent drug release in the upper GIT, and unaffected by the intestinal bacteria or enzymes [70, 104, 105]. The main drawbacks of time-dependent approach may be concluded in the following: the gastric emptying time is variable, inconsistent between individuals and depends mainly on food intake, type of food, size, shape, the density of the dosage form, disease conditions, and gastric motility associated with the physiological condition of the patient [105-111]. The release of the drug from time-dependent systems occurs by different mechanisms such as swelling mechanism, osmosis mechanism or combination of both [104, 112]. Erodible polymers (Table 5) are most common used for time-controlled systems as a lag time can be built in it to allow drug release from the dosage form after this time, such as Eudragit RS 100, Eudragit RL 100, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and hydroxyethyl cellulose (HEC).

Table 3: Gastrointestinal luminal pH in Healthy individuals and IBD patients.

GIT parts	Normal pH	IBD pH
1. Stomach	1.5	
a. fed state	3 – 5	
b. fasted state	1.5 – 2.0	
1. Stomach		7.4
a. Duodenum	6	
b. Jejunum	6.8-7	7
c. Ileum	7.4	
		7.4
3. Colon		
a. Ascending colon	6-8(6.4)	
b. Transverse colon	6.8(6)	2.3-6.5
c. Descending and sigmoid	6.7	2.3-6.5
		2.3-6.5

Table 4: Polysaccharides used for colon drug delivery

Polysacchrides	Properties	Bacteria species that degradethe polymers
Amylose	Unbranched ingredient of starch	Bacteroids
Arabinogalactan	Natural pectin	Fidobacterium
Chitosan	Deacetylated chitin	Bacteroids
Dextran	Plasma expanders	Bacteroids
Chondroitin sulfate	Mucopolysaccharide contains sulfate ester	Bacteroids
Cyclodextrin	Cyclic structure of 6,7, and 8 units	Bacteroids
Guar gum	Galactomannan, thickening agent	Bacteroids and Ruminococous
Pectin	Partial methyl ester, thickening agen	Bacteroids Bifidobacterium Eubacterium
Inulin	polysaccharide composed of a mixture of oligomers and polymers	Bifidobacterium

Xylan	Abundant hemicellulose	Bacteroids
Chitosan derivatives	Chitosan succinate and phthalate	Bacteroids
Locust bean gum	Mainly galactomannan units	Bacteroids

NOVEL DRUG DELIVERY SYSTEMS

a) Pressure controlled drug delivery systems (PCDCS)

The large intestine has more peristaltic movements than the small intestine producing a higher-pressure property. Taking into consideration this point, Takaya et al. [114] developed a new technique depends on the pressure difference between the small intestine and the colon. The new drug delivery system is based mainly upon the using of ethyl cellulose which is a waterinsoluble polymer. The system is composed mainly of a drug containing capsule covered with ethyl cellulose polymer. The drug release is controlled by the disintegration of the polymer due to the pressure inside the lumen of the colon. The main driving parameter controlling the drug release is the thickness of the capsule shell [10, 72, 108, 115, 116].

b) Osmotic controlled drug delivery systems (OROS-CT)

Generally, osmotic based drug delivery systems are very common drug carriers in the oral route. The system mainly designed upon the difference in the osmotic pressure generated between the system and the lumen of the colon. The colon has osmolarity of 81 mOsm/Kg, which is the main driving force affecting the drug release from the osmotic based systems. This system is designed to target and treat colon conditions like IBD or to attain drug release for many drugs that degraded in the small intestine. The OROS-CT may be composed of one unit or 5-6 push-pull units, encapsulated within a hard gelatin capsule. The main composition of osmotic based drug delivery carriers is the main unit which containing osmotic drug compartment and osmotic push compartment covered with a semipermeable membrane with a small orifice drilled through the drugcompartment. The entire unit is covered with an enteric impermeable membrane (Figure 4). The mechanism of drug release from osmotic based systems could follow the following cascade; first, the gelatin capsule dissolves immediately after the system is swallowed. The entire system is covered with an impermeable membrane which resists drug release at the acidic pH of the stomach. Secondly, at the higher pH of the intestine (pH > 7) the semipermeable membrane starts to dissolve, and the water enters to the central unit causing the osmotic push compartment to swell and creates a flowable gel in the drug unit. Finally, the swelled osmotic push unit forces the drug gel out of the orifice, and the drug release occurs at a controlled manner and over a precise time [10, 72, 108, 115, 116].

c) A novel colon targeted system (CODESTM)

A new technique was developed to overcome the drawbacks of the pH and time-dependent drug delivery systems. The CODESTM system (Figure 5) is mainly composed of a simple tablet core containing the active ingredient and coated with acid-soluble polymer and a degradable polysaccharide such as lactulose layer, then a new layer of the enteric polymer Eudragit L 100 or hydroxy methylcellulose (HPMC) polymeric coat is added and finally the tablet was coated with Eudragit E polymer. The enteric polymer protects the system inside the stomach and until the system delivered to the small intestine. At the higher pH of the small intestine, the enteric coat starts to dissolve with the presence of barrier layers such as HPMC or Eudragit L 100 to prevent the interaction between polymeric coats. At the colon, lactulose starts to dissolve by the aid of microflora producing a sufficient acid media capable for dissolving the acid layer surrounding the drug and affect the drug dissolution rate.

d) Other novel drug delivery systems

A wide range of newly designed colon drug delivery systems have been evaluated in the last decade to enhance colon-specific drug targeting. For example, bioadhesive-based systems using various polymers such as polycarbophils, and polyurethanes, redox-based systems, COLAL® tableting technology, MMX® technology, and PHLORAL® technology (Table 6).

Table 5: Enteric polymers investigated for colon-based drug delivery systems

Polymers	Properties	pH or time dissolution threshold
	A) pH sensitive polymers:-	
Eudragit L 30 D-55	30% aqueous dispersion	Above pH 5.5
	Powder	Above pH 5.5
Eudragit L 100-55	Powder	Above pH 6.0
	12.5 % organic solution	Above pH 6.0
Eudragit L 100	Powder	Above pH 7.5
Eudragit L 12.5	12.5 % organic solution	Above pH 7.0
Eudragit S 100	30 % aqueous dispersion	Above pH 7.0
Eudragit S 12.5	Powder	Above pH 5.0
Eudragit FS 30D		Above pH 7.0
PVAP	Dry flakes	Above pH 5.5
Shellac	Powder	Above pH 6.0
HPMCP-50 and 55	Powder	Above pH 5.5
	Powder	
HPMCAS		Sustained release
CAT	B. Time dependent	
Eudragit RS 100	polymer	Sustained release
Eudragit RS 100	Granules	
Eudragit RL 12.5	Granules	Sustained release
Eudragit NE 30 D	12.5 % organic solution	
	30 % aqueous dispersion	Sustained release

N.B: PVAP; Polyvinyl acetate phthalate, HPMCP; Hydroxypropyl methylcellulose phthalate, HPMCAS; Hydroxypropyl methylcellulose acetate succinate, CAT; Cellulose acetate trimelitate.

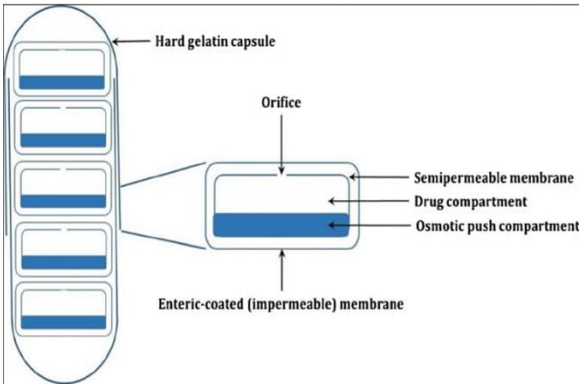


Figure 4: Schematic diagram of OROS-CT drug delivery system.

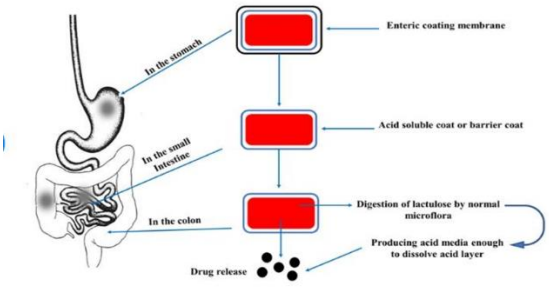


Figure 5:Schematic diagram of the new technology drug delivery system CODEST

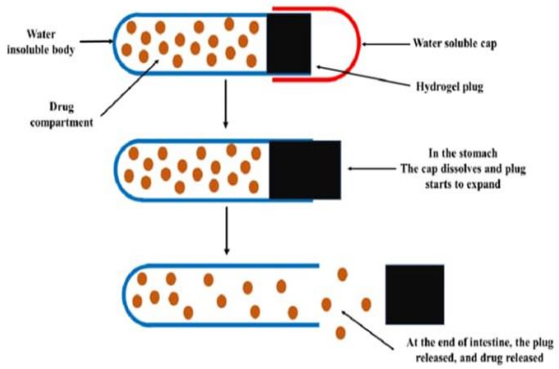


Figure 6: Schematic diagram of PulsinCap technology

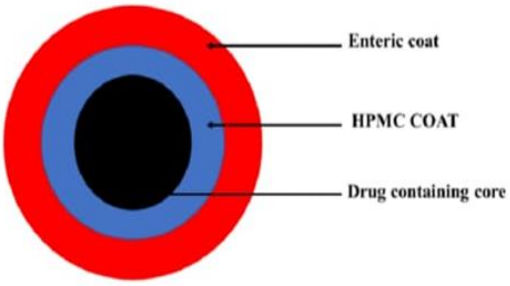


Figure 7:Schematic diagram of chronotropic drug delivery system

PREPARATION OF NANOPARTICLES FOR THE TREATMENT OF IBD

1.Methods of nanoparticles preparation.

The term nanoparticles are defined as solid, colloidal particles in the nanoscale range. The term nanoparticles are a collective term which includes any polymeric nanoparticles but specifically, describe both Nanospheres and Nanocapsules [166- 168]. One of the most fundamental characters of the nanoparticles is their size, which is generally taken to be in the range of 5-10 nm with an upper limit of 1000 nm, but the obtained size is generally around 100-500 nm [168, 169]. Nanospheres are known as a matrix particle in which the drug molecules may be dissolved, dispersed in the polymer matrix. On the other hand, Nanocapsules are defined as vesicular systems in which the drug molecules are confined in a cavity core consisting of a liquid lipid or water and surrounded by polymeric membrane coat.

a)Dispersion of preformed polymers (One-step methods):

The most common technique for the preparation of nanoparticles mainly used to manufacture

nanoparticles in onestep by the dispersion of preformed polymers. Many biodegradable and biocompatible polymers are used i.e. poly (D,L-Lactide-co-glycolic acid) (PLGA) [171, 172], poly (lactic acid) (PLA) [173], poly-epsilon-caprolactone (PCL) [174], poly (cyanoacrylate) (PCA) [175, 176] and methacrylate copolymers as Eudragit® [177-182].

Nanoprecipitation method is the most common and widely used method [183-186]. Simple, rapid, less energy-consuming, and timesaving. Nanoprecipitation is known as solvent displacement method or interfacial deposition method [187]. For the synthesis of nanoparticles, the method requires two main phases first, solvent phase (organic phase) consisting of solvent as acetone, polymer, surfactant, and drug. Oil is required in case of nanocapsules preparation. Secondly, the non-solvent phase (aqueous phase) consisting of water or buffer and stabilizer. The organic phase should be completely miscible with non-solvent phase [188]. The method is based mainly on spontaneousemulsification of organic phase into the non-solvent phase (aqueous phase) [189]. The rapid diffusion of solvent phase into the aqueous phase leads to precipitation and formation of nanoparticles.

b)Polymerization of monomers (two-step methods):

In this method, the drug could be encapsulated during the formation of polymers from starting monomers or by adsorption on the prepared nanoparticles [168, 216]. Three main techniques used for the polymerization of monomers are emulsionpolymerization method, mini-emulsion, and microemulsion polymerization method. Excess drug and surfactant used during the preparation of nanoparticles could be removed either by flow filtration techniques or by centrifugation. Many monomers used for the preparation of nanoparticles by polymerization methods.

PHYSICO-CHEMICAL CHARACTERIZATION OF PREPARED NANOPARTICLES

a)Behavior of nanoparticles as drug delivery systems:

Nanoparticles properties and characterization are based upon some physicochemical properties like particle size, surface charge and the particle morphology [189]. It is very important properties for the interactions between the nanoparticles and biological systems and control nanoparticles therapeutic activity and its toxicity. Many techniques used for determination of particle size and particle size distribution as photon correlation spectroscopy (PCS), atomic forced microscopy (AFM), electron microscopy (EM) and dynamic light scattering (DLS). The surface charge or zeta-potential is a very important parameter that determines the total surface charge and used to predict the stability of nanoparticle dispersion.

b)In-vitro drug release from loaded nanoparticles:

1. Barriers affecting oral drug delivery:-Oral drug delivery systems and especially delivery to the distal region of the GIT encountered many barriers like the harsh acidic environment of the stomach and intestine, gastric and bacterial enzymes, mucus layer especially thicker mucus layer in IBD, and tight junctions of the epithelium [139, 220]. The acidic environment of the GIT includes highly acidic pH of the stomach which ranged from 1.2 to 2.5 and the pH-value raised to 6.6-7.5 at the duodenum and the distal part of the intestine then pH drops again to 6.4 at the cecum which making the design of nanoparticles more difficult [221, 222]. Also, the mucus layer that becomes thicker in the case of IBD and rapid turnover of mucus leading to the rapid clearance of nanoparticles rather than the physical barrier.

2. In vitro drug modeling for nanoparticles:-In order to develop a successful drug delivery system to the colon, the drug release from loaded nanoparticles is one of the very important factors that control drug delivery designs. The Release rate from loaded nanoparticles especially nanocapsules depends on a great variety of factors including nanocapsulesrelated factors i.e. drug concentration, drug solubility and oil/water partitioning, Physico-chemical properties, molecular 418 J. Adv. Biomed. & Pharm. Sci. Qelliny et al. weight and concentration of the polymer matrix, the oil nature, and the size of the prepared nanocapsules. Release media conditions-related factors i.e. medium pH, medium temperature, release enhancers, and contact time. The method of the preparation-related factors i.e. method of the drug incorporation which includes adsorption and other incorporation techniques.

BIOPHARMACEUTICAL ASPECTS

Different studies have been introduced to study nanoparticles' cytotoxicity as human exposure to nanomedicines is inevitable. The most important tests for cell viability studies are LDH (lactate dehydrogenase) which is normally released by the destroyed and damaged cells, the amount of LDH is directly proportional to the number of dead cells. On the other hand, MTT (methyl thiazolyl tetrazolium) test is used to differentiate between dead and live cells. MTT is a pale yellow dye converted into dark blue farmazan product only in the viable cells and could be determined spectrophotometrically [238, 239]. In order to understand IBD and especially disease pathogenesis, animal models have been used and particularly mouse models. Experimental colitis could be induced by many techniques include chemically induced colitis, bacterial-induced colitis, and genetically induced colitis. Transgenic (Tg) and gene knockout (KO) strains have been developed as genetically-induced models [240, 241]. The most common chemical-induced models are dextran sodium sulfate (DSS) model [242-245], oxazolone model, TNBS model [246-249], and acetic acid model [250, 251]. Acetic acid-induced colitis was performed by many techniques including instillation of 3-6 % of acetic acid (2 mL) transrectally for 2 minutes in rats and animals were kept in a horizontal position to avoid leakage of the solution then the colon was rinsed with saline. In the case of mice, injection of 4- 5 % v/v of acetic acid (1 mL) in 0.9 saline solution in the colon lumen approximately about 4 cm from the anus [250, 251]. Successful colitis model was evaluated by the clinical scoring system depending on some criteria i.e. animal activity, bloody stool, diarrhea, animal weight, and histopathological examination of the colon. Clinical application of nanoparticles for the treatment of IBD in humans is limited due to human patients are more complex than the animal models. Passive targeting technique for the treatment of IBD may not be sufficient to obtain a therapeutic outcome. Therefore, active targeting techniques such as targeting cell receptors which extensively expressed in the case of inflammation and mucus targeting are a promising technique for colitis treatment with lower adverse effects and higher drug therapeutic concentration at the site of inflammation.

CONCLUSION

Site-specific drug delivery systems offer many advantages over other drug carriers especially in the oral route such as protection of the drug from the harsh environment of the gastrointestinal tract, loading high amount of the drug to the site of action, and decreasing unwanted side effects. Colon drug delivery systems are one of the most rapidly growing delivery technologies in the pharmaceutical field. The newly developed systems are directed to treat local diseases such as colon cancer, inflammatory bowel disease, and other colon conditions. Also, many colon drug delivery systems are used for the protection of drugs and biologically active ingredients such as peptides and antibodies which easily degraded in the upper gastrointestinal tract. All colon drug delivery systems even the newly developed technologies are based on three colon conditions: pH of the colon, transit time, and microbial content.

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