

Expert Opinion

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Cutting-edge technologies in colon-targeted drug delivery systems

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Oral colon-targeted drug delivery systems have gained enormous attention among researchers in the last two decades. The significance of this site-specific drug delivery system can be measured by its usefulness for delivering a variety of therapeutic agents, both for the treatment of local diseases or for systemic therapies. With the arrival of newer innovations, a large number of breakthrough technologies have emerged for targeting a drug molecule to the colon. Researchers have attempted various approaches in the development of these formulation technologies, such as pH-dependent, time-dependent and microflora-activated systems. Recently, a number of approaches have been proposed that utilize a novel concept of di-dependent drug delivery systems, that is, the systems in which the drug release is controlled by two factors: pH and time, and pH and microflora of the colon. This *Editorial* article is not intended to offer a comprehensive review on drug delivery, but shall familiarize the readers with the formulation technologies that have been developed for attaining colon-specific drug delivery.

Keywords: colon cancer, colon targeting, inflammatory bowel disease, irritable bowel syndrome, local delivery, microflora, systemic therapy and technologies

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1. Introduction

Colonic delivery refers to the targeted delivery of drugs into the lower part of the gastrointestinal tract (GIT), that is, the large intestine. Colonic drug delivery can be achieved by either oral or rectal administration. The rectal routes (suppositories and enemas) are not always effective because of high variability in the distribution of the drugs administered by this route. On the other hand, the major drawbacks of administering the drugs by oral route are absorption and degradation of drug in the upper part of the GIT. Hence, in the design of per-oral controlled release drug products, colon-targeted drug delivery systems (CoDDS) have gained a tremendous interest for delivering a variety of drugs [1].

CoDDS are mainly used for localized treatment of certain diseased conditions such as inflammatory bowel disease (IBD), colon cancer, irritable bowel syndrome (IBS) and so on. Recently, much attention has been focused on the colon as a potential site for the absorption of proteins, peptides (such as insulin, calcitonin and vasopressin) and vaccines (since it is rich in lymphoid tissues). Oral pulsatile/delayed systems intended for chronotherapy (of diseases such as arthritis, asthma, cardiac arrhythmias, hypertension or inflammation), when provided with an external enteric film, can offer interesting possibilities for colonic drug delivery. Since onset of these diseases is at night time or early in the morning, it is desirable to have a delayed release delivery system that can provide nocturnal release of a drug, which in turn provides a considerable relief to the patient while resting [1,2].

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Over the last few years, various approaches have been used for oral delivery of drugs to the colon, which include a pH-dependent, time-dependent, pressure-controlled system and systems that use bacteria that colonize in the colon or produce enzymes to modulate the drug release [1]. It has been reported that the system coated with pH-dependent polymers lacks site specificity for drug release in the colon and may either lead to a premature release of drug in the small intestine or no drug release in the colon [2-4]. For time-dependent systems, the location of initial drug release predominantly depends on the transit times of the GIT. Although the transit time of small intestine is relatively constant (3–4 h), a large variation in the gastric emptying time may lead to either a premature release of drug in small intestine or a delayed release far down in the colon [5-8]. A more precise and accurate strategy for targeting drugs to the colon uses the ecosystem of the specific microflora present in the large intestine, that is, microbially triggered CoDDS. Natural polysaccharides are the most promising and commonly explored carriers for CoDDS, which are specifically hydrolyzed by the colonic microflora. Unfortunately, as most of the natural polysaccharides are highly hydrophilic, there is difficulty in controlling release of drug from these materials [9,10]. Hence in order to overcome the drawback of each individual approach, recently, newer approaches have been proposed that utilizes a novel concept of di-dependent drug delivery systems, that is, the systems in which the drug release is controlled by two factors viz., pH and time, and pH and microflora of the colon. This *Editorial* article is not intended to offer a comprehensive review on drug delivery, but to highlight the breakthrough technologies that emerged as a milestone in the field of CoDDS. Additionally, an attempt has been made to give a brief about how colon can be exploited for delivering drugs for local and systemic applications.

2. Colon as a potential site for local and systemic delivery of drugs

CoDDS has major advantages in the direct treatment of the local diseases as well as for systemic therapy. In order to achieve a successful colonic delivery, the drug molecule must reach intact to the desired site by overcoming all the barriers of the upper GIT.

2.1 Local delivery of drugs

CoDDS for local treatment is usually undertaken for various diseased conditions such as IBD, IBS, colon cancer and so on.

IBD is a localized inflammation of the small and large intestines. It mainly comprises two types of specific conditions, that is, ulcerative colitis and Crohn's disease. Use of site-specific drug delivery to the colon can reduce the total amount of drug administered, thereby reducing side effects. Drug therapies for these disorders include aminosaliclates, corticosteroids, immunosuppressive agents, nicotine, cationized antioxidant enzymes and genetically engineered bacteria to produce cytokines [1].

In addition to IBD, IBS is another common chronic gastrointestinal disorder in which the interaction of psychological, luminal and enteric factors results in disorders of the gut functions. The anticholinergics (e.g., dicyclomine, propantheline), anxiolytics, tricyclic antidepressants (e.g., desipramine and trimipramine), 5-hydroxytryptamine antagonists, calcium channel blockers (nifedipine, nicardipine) and calcium antagonist (pinaverium bromide) have been used for IBS treatment [1].

The treatment of colonic cancer using intravenous administration produces severe systemic side effects due to their cytotoxic effect on normal cells. Researchers have reported the use of various lectins and neoglycoconjugates for targeting drugs to cancer cells. They have shown improved specific targeting to the colon on oral administration, with avoidance of the degradation associated with the hepatic first-pass metabolism [11,12]. Recently, ligand-mediated targeted delivery is being explored for improving the selective toxicity of anticancer therapeutics. The delivery systems used for targeting anticancer drugs to tumor cells or tissues can be improved by a combination of binding drugs with molecules that bind to antigens or receptors that are specific on the target cells as compared with normal cells or tissues [13].

Laxatives such as sennosides and related compounds, when targeted to the colon, show improved efficacy because they act specifically in the large intestine. The prodrug laxative sodium sulisatin, an anionic drug, is poorly absorbed and arrives intact to the colon on oral administration. It is then hydrolyzed in the colon by the bacterial arylsulfate sulfohydrolase to a diphenolic derivative, which is an active laxative [14]. Bisacodyl is also cleaved by the esterases in the small intestine to its active metabolite. This causes stimulation of water and secretion of electrolytes and causes a laxative effect [15].

2.2 Systemic delivery of protein/peptide and non-peptide drugs

The colon is also a potential site for delivering therapeutic proteins and peptides. The advantages of colonic delivery of peptide and protein drugs include low metabolic activity, longer residence time, responsiveness to absorption enhancers, good targeting opportunities due to the presence of colonic bacterial enzymes, improved absorption for ionizable/ionized drugs due to transmucosal and membrane potential differences, and scope for solvent drag due to bulk water absorption in this region. If the problems of limited bioavailability and successful targeting to the colon are resolved, the colon could be a potential site for proteins and peptides. Protein and peptide drug candidates exploited for CoDDS are insulin, calcitonin, met-enkephalins, vasopressin, interferons, glucagon and so on [1].

CoDDS are also advantageous to deliver non-peptide drugs when a delay in the absorption is required. They are also useful for the treatment of diseases that have peak symptoms in the early morning and exhibit circadian rhythms, such as arthritis, asthma, cardiac arrhythmias, hypertension or inflammation. These drugs include diclofenac sodium, ibuprofen, pseudoephedrine and others. The colon has also been proven to be a potential site for the absorption of various beta-blockers such

as alprenolol hydrochloride, atenolol, bunolol hydrochloride, penbutolol sulfate, pronethalol hydrochloride, metoprolol, oxprenolol, bevantolol, bufuralol, propranolol hydrochloride and timolol maleate, as reported by Vila *et al.* [16]. These researchers have reported the good penetrability of the drugs through the colonic membrane. Another series of references cited by Godbillon [17] and his research team has demonstrated the colonic absorption of metoprolol. Theophylline, acetaminophen and phenylpropanolamine hydrochloride have also been delivered to the colon with high relative bioavailability of these drugs, which suggests that the colonic absorbability of these drugs is quite good [18].

3. Cutting-edge technologies developed for CoDDS

With the advancements in the ongoing research in CoDDS, large numbers of formulation technologies have been reported. These technologies may be broadly classified based on the formulation approaches that have been exploited for the development of CoDDS, *viz.* pH-dependent, time-dependent, microflora-activated, pH- and time-dependent, and pH- and microflora-activated systems. Among them, pH-dependent systems are most widely used as far as commercial availability of CoDDS is concerned [2]. Furthermore, in early 2007, the first and only FDA-approved once daily oral formulation of mesalamine, MMX (Multi-Matrix System™, Shire Pharmaceuticals Inc., Pennsylvania, USA) was developed for the induction of remission of mild to moderate ulcerative colitis. In Europe, MMX mesalazine (Mezavant XL in the UK; Mezavant elsewhere in the EU) has been approved for the induction and maintenance of clinical and endoscopic remission in patients with active, mild to moderate ulcerative colitis. In order to understand the execution of some of the time-dependent systems, the readers are requested to have thorough knowledge regarding the maneuver of osmotic drug delivery systems. The breakthrough technologies that have been developed for CoDDS are summarized in Table 1 (a detailed schematic diagram of some of the technologies and their functioning is shown in Figure 1 and Figure 2).

The use of nanoparticles for targeted oral drug delivery to the inflamed gut tissue in IBD appears to be a promising approach. Such a strategy of local drug delivery would be a distinct improvement compared with the existing colon delivery devices for this disease. For colonic pathologies, it was shown that nanoparticles tend to accumulate at the site of inflammation in IBD. This is because in the case of colitis, a strong cellular immune response occurs in the inflamed regions due to increased presence of neutrophils, natural killer cells, macrophages and so on. It has been reported that microspheres and nanoparticles could be efficiently taken up by these macrophages. This results in the accumulation of the particulate carrier system resulting in prolonged residence time in the desired area. Lamprecht *et al.* proved an increased nanoparticle deposition in the inflamed tissue of the colon compared with

the healthy control [19,20]. Recently, researchers at the Georgia Institute of Technology and Emory University have designed and fabricated nanoparticles, which could be ingested orally, encapsulate anti-inflammatory drugs and dissolve only in the presence of inflamed tissue. The nanoparticles are composed of thioketals, organic molecules containing sulfur, which have the property that they remain stable in the presence of acids and bases, such as that occur in different regions of the digestive tract. But they break down in the presence of reactive oxygen molecules, which are secreted by macrophages and other white cells that cause inflammation. Thioketal nanoparticles containing anti-inflammatory drugs could be consumed orally and would remain intact as they pass through the digestive tract but would release the drugs as they encounter inflamed tissue. Such a drug delivery system would be ideal for treating Crohn's disease or ulcerative colitis [21].

4. Expert opinion

CoDDS have gained remarkable importance for the treatment of local disease as well as for systemic therapies. For the development of a successful CoDDS, the triggering mechanism in the delivery system must respond only to the physiological conditions particular to the colon. Due to the lack of continuity in physiological parameters along the GIT, few mechanisms can be incorporated into a delivery system to affect colon-specific drug release. Of the three principal approaches used for the development of colon-targeted technologies, microflora- or enzyme-activated systems appear more promising since the abrupt increase in the bacterial population and associated enzyme activity in the colon represent a non-continuous event independent of GI transit time. In this regard, formulations that employ di-dependent system based on the combination of dual approaches also represent a significant technological advancement. Taking into consideration the above-mentioned merits of the microflora- or enzyme-activated systems, among the two di-dependent approaches proposed, the combination of pH and microflora appears to be the most promising. The proposed advantages delivered by the technologies discussed in this article include commonly used pharmaceutical excipients and feasible processing, site specificity of drug release and versatile drug release kinetics.

In the past 20 years, the pharmaceutical literatures have been flooded with numerous experimental techniques for targeting the large bowel via the oral route. Unfortunately, very few of them succeeded in reaching the doors of clinical phase. The main reasons for the failure to move from promise to reality are i) the lack of appealing medical opportunities (excluding IBD, which employs old technologies, old drugs and large doses for topical colonic treatment) to justify complicated developments; ii) nonrealistic assumptions regarding the therapeutic advantage of targeting the colon with molecules that probably would have worked after systemic administration (in other words: the lack of accompanying in-depth pharmacological research) and iii) the ongoing difficulty to launch oral protein

Table 1. Breakthrough technologies developed for achieving colon-targeted drug delivery systems.

Technology/trade name	Description	Lag time determining factor	Drug candidate evaluated	Inventor/Ref.
<i>pH-dependent systems</i>				
Lialda [®]	MMX [™] technology (pH-dependent gastro-resistant coating with a tablet core containing drug with hydrophilic and lipophilic excipients)	Thickness of enteric coat applied	Mesalamine	Shire Pharmaceuticals Inc., Wayne, Pennsylvania, USA
Asacol [®]	Eudragit [®] -S 100 coated tablets	Thickness of enteric coat applied	Mesalamine	Tillots Pharma AG, Rheinfelden, Switzerland
Claversal [®]	Eudragit [®] -L 100 coated tablets	Thickness of enteric coat applied	Mesalamine	Merckle Recordati GmbH, Germany
Salofalk [®]	Eudragit-L coated tablets	Thickness of enteric coat applied	Mesalamine	Dr. Falk Pharma GmbH, Freiburg, Germany
Mesasal [®]	Eudragit-L 100 coated tablets	Thickness of enteric coat applied	Mesalamine	GlaxoSmithKline Inc., Ontario, Canada
Calitoflak [®]	Eudragit-L 100 coated tablets	Thickness of enteric coat applied	Mesalamine	GlaxoSmithKline Inc., Ontario, Canada
<i>Time-dependent systems</i>				
Pulsatile Hydrogel Capsule	The capsule body is prepared from a water-permeable and swellable hydrogel cross linked polyethylene glycol polymer. Hydrogel polymer swells when it comes in contact with aqueous fluid, which causes the plug to expel out of capsular body and drug is released in pulsatile manner	The rate of water ingress depends on hydrogel composition and wall thickness of the capsule. The lag time is defined by the time taken for fluid to diffuse through the wall	Salbutamol sulfate	[23]
Erodible plug, time-delayed capsule	A simple erodible compressed tablet is used in place of the swelling hydrogel plug	Thickness and composition of the erodible tablet	Chlorpheniramine	[24]
Hydrophilic sandwich capsule	A capsule-within-a-capsule system in which the inter-capsular space was filled with a layer of hydrophilic polymer (HPMC)	Thickness and molecular weight of HPMC layer between capsules	Paracetamol	[25]
Pentasa [®]	Ethyl cellulose-coated microgranules slowly dissolve throughout the small intestine and colon in time-dependent fashion	Thickness of ethyl cellulose coat	Mesalamine	Ferring Pharmaceuticals, Saint-Prex, Switzerland

GI: Gastrointestinal tract; HPMC: Hydroxypropyl methylcellulose; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; L-HPC: Low-substituted hydroxypropylcellulose.

Table 1. Breakthrough technologies developed for achieving colon-targeted drug delivery systems (continued).

Technology/trade name	Description	Lag time determining factor	Drug candidate evaluated	Inventor/Ref.
Time-controlled explosion system	Expansion of the swelling agent (L-HPC) by water penetrating through the outer membrane causes destruction of the membrane by stress due to swelling force and subsequent rapid drug release	Thickness of the outer ethyl cellulose membrane	Metoprolol tartrate	[26]
PORT [®] system	Consists of a hard gelatin capsule, film coated with semi-permeable membrane (capsule body), an insoluble plug and an osmotic agent along with drug molecule. On hydration, the internal pressure increases inside the capsule, which forces the plug to slide out of the shell to release the drug	Length of the insoluble plug The rate of influx of water through the semi-permeable membrane Type and amount of osmogen used	Captopril	Therapeutic System Research Laboratory Ann Arbor, MI, USA
Egalet [®]	The 3K form of the Egalet technology consists of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. The shells are made of ethyl cellulose and cetostearyl alcohol, while the matrix of the plugs comprises a mixture of polyethylene glycol monostearates and polyethylene oxides	Time of drug release can be modulated by adjusting the length and composition of the plugs	Quinine	Egalet Ltd., Vaerlose, Denmark
<i>Microflora-activated systems</i>				
Colazal [®]	Azo-bonded prodrug	Microflora-activated system	Balsalazide	Salix Pharmaceuticals Inc., North Carolina, USA
Dipentum [®]	5-ASA dimmer	Microflora-activated system	Olsalazine	Pharmacia AB Stockholm, Sweden
Salazopyrin [®]	5-ASA linked to sulfapyridine	Microflora-activated system	Sulfasalazine	Pfizer Australia Pty Ltd, West Ryde NSW, Australia
Azulfidine [®]	5-ASA linked to sulfapyridine	Microflora-activated system	Sulfasalazine	Pfizer, Inc., New York, USA

GI: Gastrointestinal tract; HPVC: Hydroxypropyl methylcellulose; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; L-HPC: Low-substituted hydroxypropylcellulose.

Table 1. Breakthrough technologies developed for achieving colon-targeted drug delivery systems (continued).

Technology/trade name	Description	Lag time determining factor	Drug candidate evaluated	Inventor/Ref.
Colal-Pred®	It has arisen from combining Alizyme's proprietary colonic drug delivery system, COLAL®, with an approved generic steroid. COLAL involves a coating for drug pellets, tablets or capsules, which is composed of ethyl cellulose and a form of starch called 'glassy amylose'	Thickness of the film applied, and the ratio of amylose and ethyl cellulose polymers used Degradation time of amylose by the colonic microflora	Prednisolone sodium metasulfobenzoate (has achieved successful Phase III clinical trial results for the treatment of moderate to severe ulcerative colitis)	Alizyme plc, Cambridge, UK
<i>pH and Time-dependent systems</i>				
Time Clock®	The inner coating consists of hydrophobic surfactant layer to which a water-soluble polymer is added to improve adhesion to the core	Thickness of enteric coat Thickness of the hydrophobic layer	Salbutamol	[27]
Chronotopic®	Composed of a drug-containing core and hydrophilic swellable polymeric coating capable of delaying drug release through slow interaction with aqueous fluids	Thickness of enteric coat Thickness and viscosity grade of HPMC layer	Antipyrine	[28]
Pulsincap®	Comprises an impermeable capsule body containing a drug formulation sealed in the capsule with a hydrogel polymer plug. The plug expands in water or GIT fluid and slowly exits the capsule body, releasing the capsule contents after a defined time delay. The entire capsule is enteric coated to overcome the problem of gastric emptying	Thickness of enteric coat, and the size of the hydrogel plug and its point of insertion into the capsule	Salbutamol sulfate	R.P. Scherer International Corp., Michigan, USA
OROS®-CT	It consists of as many as five push-pull units encapsulated within a hard gelatin capsule. Each push-pull unit is a bilayered laminated structure containing a drug layer and an osmotic push layer, both surrounded by a semi-permeable membrane (allow water or gastrointestinal fluid to pass but is impermeable to drug) and enteric impermeable membrane	Thickness of enteric coat The rate of influx of water through the semi-permeable membrane Type and amount of osmogen used	Aminosaliclates, Corticosteroids, Salicylazosulfapyridine	Alza Corp., Palo Alto, California, USA

GIT: Gastrointestinal tract; HPMC: Hydroxypropyl methylcellulose; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; L-HPC: Low-substituted hydroxypropylcellulose.

Table 1. Breakthrough technologies developed for achieving colon-targeted drug delivery systems (continued).

Technology/trade name	Description	Lag time determining factor	Drug candidate evaluated	Inventor/Ref.
Osmet TM	A miniature osmotic pump that can be swallowed, which will pass through the stomach and small intestine and then deliver its contents (240 µl) more than 8 h in the large bowel	Thickness of enteric coat The rate of influx of water through the semi-permeable membrane Type and amount of osmogen used	Anti-inflammatory agents, anti-hypertensive agents and receptor blocking agents	Alza Corp., Palo Alto, California, USA
Chronset TM	A proprietary OROS [®] delivery system that reproducibly delivers a bolus drug dose (> 80% drug release within 15 min). The drug formulation remains protected from chemical and enzymatic degradation in GIT	Thickness of enteric coat The rate of influx of water through the semi-permeable membrane Type and amount of osmogen used	Acetaminophen	Alza Corp., Palo Alto, California, USA
Eudracol [®]	It is a multiparticulate, multilayer system that uses aqueous polymethacrylate dispersion in the design of the release profile	Thickness of outer enteric coat and inner Eudragit [®] RS+RL layer	Caffeine (as a pharmacokinetic marker). Could be used for both local and systemic therapies	Evonik Röhm GmbH Pharma Polymers, Darmstadt, Germany
Entocort [®] EC	Contains granules that are coated to protect dissolution in gastric juice, but which dissolve at pH > 5.5, i.e., normally when the granules reach the duodenum. Thereafter, a matrix of ethyl cellulose controls the release of the drug into the intestinal lumen in a time-dependent manner	Thickness of enteric coat applied.	Budesonide	AstraZeneca, Sodertälje, Sweden

GIT: Gastrointestinal tract; HPMC: Hydroxypropyl methylcellulose; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; L-HPC: Low-substituted hydroxypropylcellulose.

Table 1. Breakthrough technologies developed for achieving colon-targeted drug delivery systems (continued).

Technology/trade name	Description	Lag time determining factor	Drug candidate evaluated	Inventor/Ref.
<i>pH and Microflora-activated systems</i> CODES TM	The design of CODES exploited the advantages of certain polysaccharides that are only degraded by bacteria available in the colon. This is coupled with a pH-sensitive polymer coating. On entry into the colon, the polysaccharide inside the core tablet dissolves and diffuses through the coating. The bacteria enzymatically degrade the polysaccharides into organic acids. This lowers the pH surrounding the system enough to affect the dissolution of the acid-soluble coating and subsequent drug release	Thickness of enteric coat Degradation time of lactulose by the colonic microflora	5-aminosalicylic acid, insulin, salmon calcitonin	Yamanouchi Pharmaceuticals Co. Ltd., Japan
TARGIT [®]	An enteric-coated injection-moulded starch capsule system designed for targeting specific sites within the colonic region. The coating consists of a mixture of Eudragit L and S, chosen to provide a coating that starts dissolving when the capsule enters the small intestine after leaving the stomach	The choice and thickness of the coating determines the site of release within the GIT Degradation time of starch by the colonic microflora	TARGIT-based products are in active clinical development for the topical treatment of diseases such as IBD, IBS and bacterial infections	West Pharmaceutical Services Drug Delivery & Clinical Research Centre Ltd., Nottingham, UK

GIT: Gastrointestinal tract; HPMC: Hydroxypropyl methylcellulose; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; L-HPC: Low-substituted hydroxypropylcellulose.

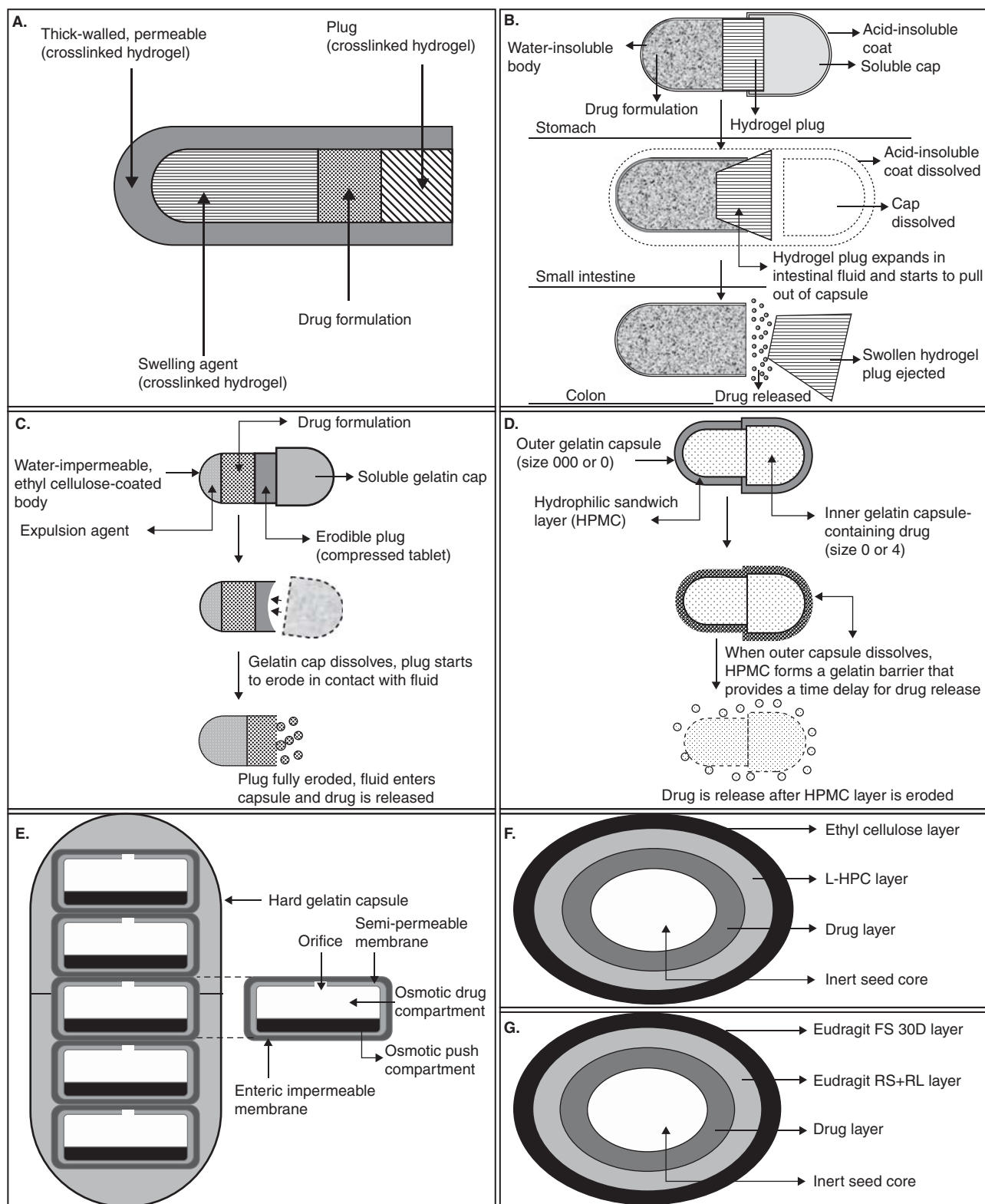


Figure 1. Schematic diagram of (A) pulsatile hydrogel capsule, (B) Pulsincap®, (C) erodible plug time-delayed capsule, (D) hydrophilic sandwich capsule, (E) OROS®-CT, (F) time controlled explosion system and (G) Eudracol®.

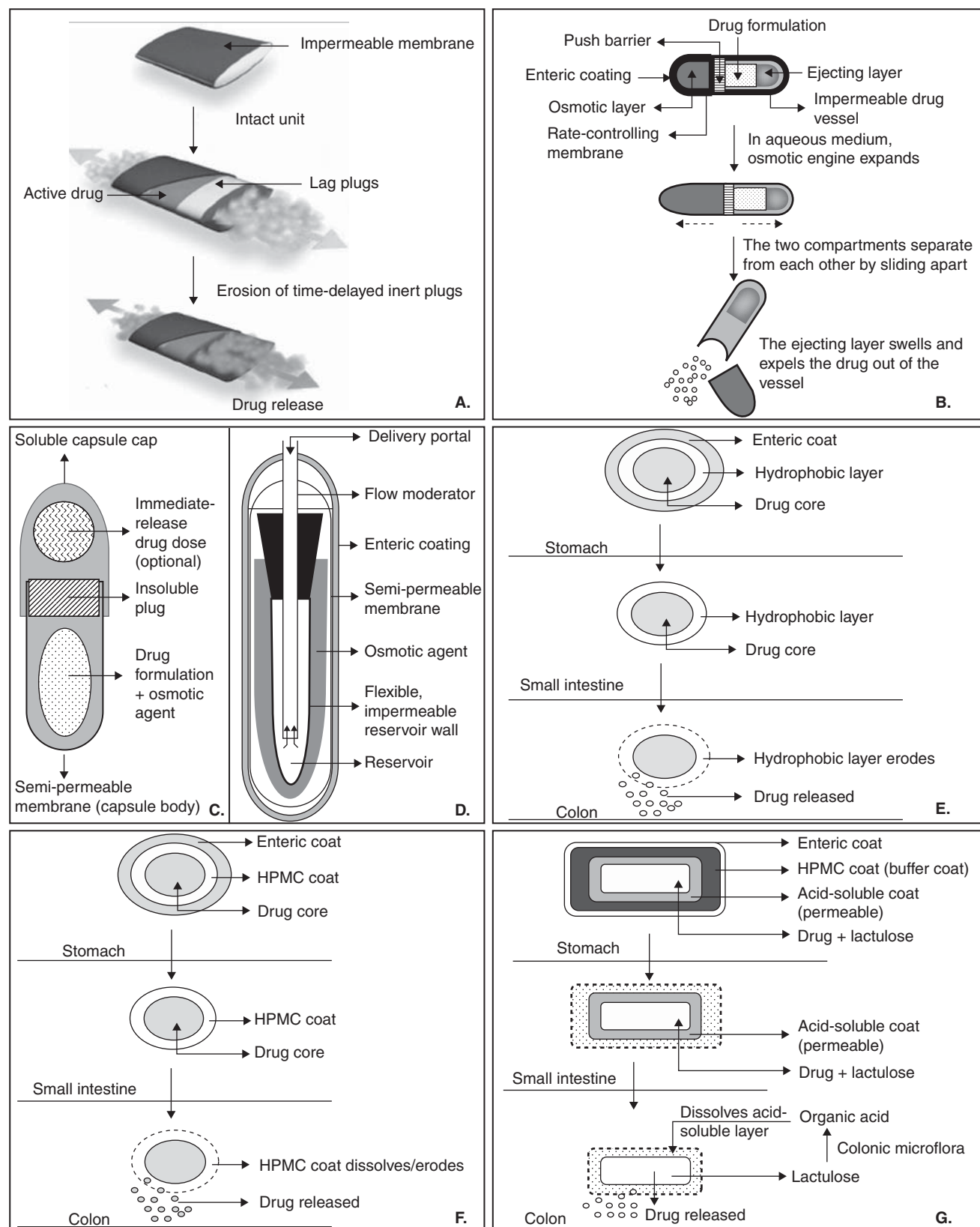


Figure 2. Schematic diagram of (A) Egalet®, (B) Chronset™, (C) PORT® System, (D) Osmet™, (E) Time Clock® system, (F) Chronotopic® system (G) CODES™.

products (biologics), which impacts on the development of colonic platforms for this complicated group of molecules [22].

The future direction in achieving effective colonic delivery for the treatment of diseases associated with the colon may involve the use of various receptors present on the surfaces of diseased cells and drugs may be taken up via receptor-mediated endocytosis after reaching the colon. The success for such approaches will require the drug carrier to be stable in the lumen while capable of releasing the active agent in

close proximity to, or within, the target cells. Thus, it is about time to explore realistic, efficient and safe modes of targeted drug delivery to colon. The search for colon-specific drug carriers has just begun.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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