ASSORTED TRAITS OF VARIED TECHNOLOGIES USED IN MIDDLE OF COLONIC DELIVERY

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INTRODUCTION

The development of site-specific formulations for drug delivery to the colon has piqued interest in the previous decade. The colon is a location where these local and systemic delivery of drug approach can occur. Topical treatment of inflammatory bowel illness, such as ulcerative colitis or Crohn's disease, could be possible with a local medication delivery system.

Glucocorticoids and sulphasalazine are commonly used to treat inflammatory disorders. If the pharmacological compounds were targeted directly at the site of action in the colon, treatment may have been more effective. Lower doses may be sufficient, and systemic adverse effects may be decreased as a result. A variety of other significant colon disorders, such as colorectal cancer, may be treated more adequately if drugs were focused exclusively at the colon.

Oral dosing of peptide and protein medicines, which are generally inactivated in the upper gastrointestinal tract, could be possible with site-specific drug delivery [1]. Candidate hormones include insulin and growth hormone. The permeability of the colon epithelium to peptide and protein medicines, on the other hand, is fairly low, and bioavailability are relatively too low. In illnesses where a diurnal rhythm is present, such as asthma, rheumatoid arthritis, ulcer disease, and ischemic heart disease, colon-specific devices could be utilized. Asthmatic attacks, for example, are most common in the wee hours of the morning. Colon-specific formulations could be employed to prolong medication delivery because dose forms stay longer in the large bowel than in the small intestine [2].

The following are some of the medical reasons for developing orally delivered colonic medication platforms:

To ensure excellent local concentrations in the treatment of various ailments of the distal gut,

A. to minimise dosing frequency,

B. to postpone delivery to the colon.

C. To delay administration to a time appropriate for treating acute phases of disease (chronotherapy).

D. To administer at a less metabolically hostile region, e.g., to enhance absorption of acid and enzymatically labile materials, especially peptides. Drug absorption is improved in the colon rather than the small intestine [3].

TECHNOLOGIES AVAILABLE

1. Codes:

The Codes® system uses a succession of polymers to preserve the medication core until the formulation reaches the colon. An enteric outer coating with a cationic polymer coating for retarding release during transit along the small intestine is used in Codes, an oral tablet

technology. Lactulose, which is integrated in the drug core, is destroyed by the colonic microbiota once it reaches the colon, allowing the medication to be released.

2. Colon-Targeted Delivery Technique:

Shah and colleagues were the first to describe this system, which relies on lag time to ensure colon delivery. An outside enteric coat, an inner semipermeable polymer membrane, and a central core containing swelling excipients and an active component make up the system [4]. These components of the system work together to keep food from being released too soon in the upper gastrointestinal tract. A time-dependent rupturing mechanism in the dose form ensures consistent medication release in the colon.

Until the tablet enters the small intestine, the outer enteric coating blocks drug release. The enteric coating dissolves in the small intestine, allowing gastrointestinal fluids to pass past the semipermeable barrier into the core. The core expands until it bursts after 4–6 hours, releasing the active component into the colon. The core also contains a swelling agent, such as croscarmellose sodium or sodium starch glycolate, and an osmotic agent, such as mannitol, sucrose, or glucose, in percentages of 10–30 percent and 15–25 percent w/w, respectively, in addition to the active component.

3. Ethyl cellulose System with Time Control:

Niwa and colleagues described a unique four-compartment system based on an ethyl cellulose shell that releases medication in a time-controlled method [5].

The system's base is drilled to allow water access to a swellable component, which causes the system to rupture at a rate determined by the thickness of the cap. Because such systems work best at low pH, combining them with food may promote premature release in the upper gastrointestinal tract [6].

4. Oros-CT:

Oros-CT is an Alza Corporation technology that includes an enteric coating, a semipermeable membrane, a layer to delay medication release, and a core with two compartments. The active medicine is contained in an excipient layer close to an exit passageway in the first compartment, and the osmopolymer composition in the second compartment provides the osmotic push in the system [7]. In the stomach, the enteric coating does not erode, degrade, or change its structural composition. Phthalates, keratin, formalin-treated protein, oils, and anionic polymers make up the substance. The semipermeable wall is

made up of non-erodible, selectively permeable polymers that are insoluble in bodily fluids but permeable to fluid flow. Semipermeable membranes can be made from these polymers (cellulose acylate and cellulose acetates).

Polyethers, polyoxyethylene, and hydroxypropylmethylcellulose make up the layer beneath the semipermeable membrane, depending on the formulation. It takes roughly 2–4 hours for the medication to be released. The mechanism absorbs liquids and begins to dispense medication at a controlled rate as it passes through the small intestine.

The osmopolymer swells or expands at its centre, pushing the active drug-containing substance out of the delivery mechanism. Hydrophilic polymers such as poly (hydroxyalkylmethacrylate), poly(vinylpyrrolidone), and poly(vinylalcohol) or acidic carboxy-polymers are commonly used as osmopolymers. Wet or dry granulation is used to make the compartment containing the active medication and the osmopolymer, and a tablet press is used to make the dosage form. An air suspension process is used to create the wall and the delay coat. The enteric coating is placed to the delay layer's surface. A 6.35-m aperture is laser-drilled through the semipermeable membrane to the core components

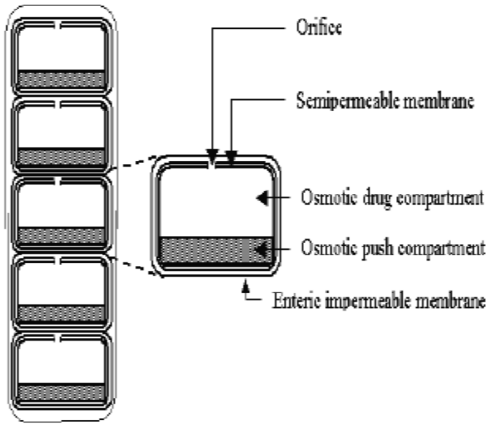

Figure 1: The OROS-CT colon targeted drug delivery device in cross section.

5. Drug Delivery System with Controlled Release:

An osmotic system with a solid core containing an active drug, a significantly soluble delay jacket, a semipermeable membrane, and an enteric coating is used as the delivery device. At least one component from the group consisting of a binder, an osmotic agent, and a lubricant is

included in the delay jacket. A releasing opening may be incorporated into the semipermeable membrane's construction [8].

6. Time Clock:

Pozzi and colleagues created the Time Clock delivery device, which is a pulsed administration system based on a coated solid dosage form. The coating is a hydrophobic-surfactant layer with the addition of a water-soluble polymer to promote coating adhesion to the core, which is applied via aqueous dispersion. Once in an aqueous environment, the dispersion rehydrates and redisperses in a time proportionate to the thickness of the film. The core is ready for disintegration after redispersion.

The presence of intestinal digestive enzymes or the mechanical activity of the stomach appear to have no effect on the hydrophobic film redispersion. As a result, the lag time interval can be considered independent of digestion condition. The Period Clock, on the other hand, releases its primary content at a predetermined lag time, independent of where the delivery mechanism is located in the gastrointestinal tract. If a positioned site-specific drug delivery is necessary, this is a disadvantage. Steed and colleagues presented product development work in 1997 that used a hydrophobic enteric coating to increase the specificity of medication release.

The Time-Controlled-Explosive Drug-Delivery System, which works on the same idea as the Time-Clock System, has also been developed. It has a four-layered spherical shape with a drug-filled core, a swelling agent, and an ethyl cellulose water-insoluble polymer membrane. Rapid medication release with a predetermined lag period characterises this technique. The swelling agent grows and eventually explodes when it comes into contact with water through the polymeric membrane, allowing the contained medicine to be released. The pH has no effect on drug release, but the lag time is determined by the thickness of the outer polymeric barrier. For the release of the medication isosorbide-5-nitrate, a similar technique based on ethylene–vinyl acetate polymers was tested [9].

7. Pulsincap: Pulsincap is a single-unit pulsatile dosage form with a capsular design. The majority of them are made up of an insoluble capsule body that holds the medicine and a stopper that blocks drug release during the lag phase. Dissolution, erosion, or forced pushing-out of the plug by swelling or osmotic pressure are all mechanisms for plug removal. A water-insoluble body (hard gelatin capsule coated with polyvinyl chloride) was filled with the drug formulation in the Pulsincap_ system. [10,11] A swellable hydrogel plug was used to shut the open end of the

capsule half. The plug inflated and pushed itself out of the capsule after a lag period when it came into touch with dissolution media or gastrointestinal fluids, followed by a fast release of the capsule content (Fig. 2). The size and position of the plug determined how long it took for the medicine to be released.

The Pulsincap method was coated with an enteric layer that dissolved once it reached the higher pH areas of the small intestine, overcoming the potential problem of varying stomach residence time of a single unit dose form. Because the transit time in the intestinal tract is less variable, this allowed for more exact medication release following stomach passage. [12-13] The complicated manufacturing process, reproducibility issues, and use of a plug material, a cross-linked polyethylene glycol based polymer that has not been approved in pharmaceutical products, were the major drawbacks of the Pulsincap system, which led to the discontinuation of commercial activities with this system.

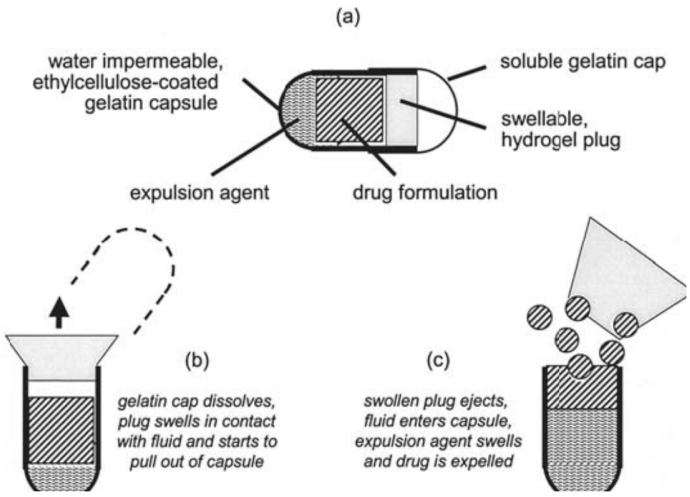

Figure 2 Pulsincap delivery system .

8. HS Capsules (Hydrophilic Sandwich Capsules):

Stevens et al. [14] designed a manually assembled delivery system based on a capsule-within-a-capsule, in which the intercapsular space was filled with a layer of hydrophilic polymer in an attempt to develop a simple, time-delayed probe capsule (HPMC). Between the two gelatin capsules, this effectively constructed a "hydrophilic sandwich." The sandwich of HPMC produced a gel barrier layer when the outer capsule dissolved, providing a time delay before fluid could enter the inner capsule and cause medication release. The time delay was regulated by the

polymer's molecular weight and could be further adjusted by including a soluble filler in the hydrophilic layer, such as lactose (Fig. 3).

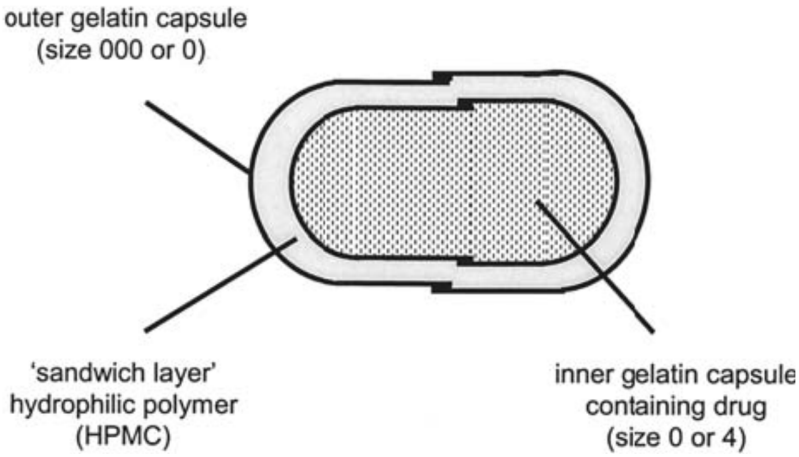

Figure 3 The lyophobic sandwich capsule.

9. Eroding systems (Egalet technology):

Figure 4 depicts the fundamental form of Egalet technology. The system comprises of an impermeable shell with two lag plugs enclosing an active drug plug in the middle of the unit, as shown in the diagram. The length and composition of the plugs can then be used to control the release time. Cetostearyl alcohol and ethylcellulose make up the shells, while polyethylene glycol monostearates and polyethylene oxides make up the plugs' matrix.

An injection moulding stage is included in the manufacturing process. The premixed powders, which are utilised to make either the active matrix or the plug, are injected into the mould, and the shell and core contents are moulded sequentially within the dies using a reciprocating injection moulding technique [15].

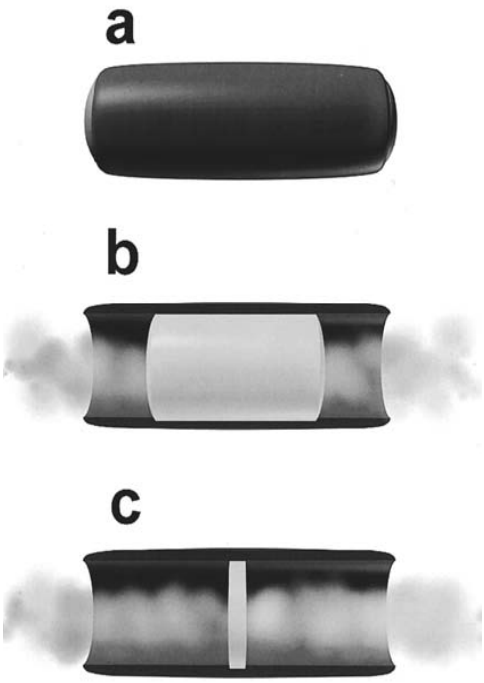

Figure 4 Egalet release displaying heterogeneous erosion and continual release: (a) entire Egalet, (b) Egalet during erosion, and (c) Egalet almost completely eroded.

10. Drug-delivery systems with pressure control:

The colon experiences higher pressures than the small intestine as a result of peristalsis. Takaya et al. created pressure-controlled colon-delivery capsules made of ethyl cellulose, which is water insoluble. In such devices, drug release occurs when a water-insoluble polymer capsule disintegrates due to pressure in the colon's lumen. The most essential aspect in the formulation's breakdown is the thickness of the ethyl cellulose membrane. The mechanism seems to be influenced by capsule size as well. When the salivary secretion of caffeine after oral administration of pressure-controlled capsules was tested in human volunteers, a link was discovered between the thickness of the ethyl cellulose membrane and the time when caffeine first appeared in the saliva. [16].

The viscosity of luminal material in the colon is higher than in the small intestine due to water reabsorption from the colon. As a result, medication breakdown in the colon has been suggested as a potential issue with colon-specific oral drug delivery systems [17]. The medicine is in a liquid in pressure-controlled ethyl cellulose single-unit capsules. When pressure-controlled capsules were given to human participants, lag durations of three to five hours were seen in

connection to medication absorption. The capsules crumbled in the colon due to increased pressure, according to the findings. The formulation tested was also shown to be favourable in that the drug release mechanism is pH independent [18].

MARKETED PRODUCTS:

Drugs	Brand Names	Name of Company
Sulfasalazine	Azulfidine®	MGI Pharma
Budesonide	Targit®	West Pharmaceutical Services
	Budenofalk®	Galenica Pharma
	Entrocort®	Astra-Zeneca Pharmaceuticals
Mesalazine	Pentasa®	Kyorin Pharma
	Mesazal®	Rohm Pharma
	Salofalk®	Axcan Pharma
	Asacolitin®	Tillotts Pharma AG
	Claversal®	Recordati Pharma

CASE STUDY:

Development of colon-specific metronidazole delivery methods [19]

Purpose: The ability of matrix, multilayer, and compression coated metronidazole tablets to reach the colon intact in vitro was examined utilising pectin as a carrier.

Methods: Wet granulation and direct compression procedures were used to make matrix tablets with varied pectin contents. Pectin was used as a release regulating layer on either side of metronidazole matrix tablets in multilayer tablets. Pectin compression coating was used to rapidly disintegrating metronidazole core pills. The impact of the coat:core ratio and the proportion of chitosan in the pectin coat on medication release was studied.

Results: Matrix and multilayer tablets failed to control drug release in the physiological milieu of the stomach and small intestine, according to in vitro release experiments. Compression coated formulations, on the other hand, were able to protect tablet cores from early drug release, but only at high pectin coat:core ratios of 4: 1 (F13) and 5: 1 (F15) (F14). Incorporating chitosan at 3% and 5% w/w (F12) in the pectin coat improved protection while lowering the coat:core ratio (3: 1). After 24 hours of dissolving in pH 6.8 PBS containing 1.5 percent w/v rat caecal contents, compression coated tablet formulations F13, F14, and F12 released around 70.25 percent 9.9 percent, 51.3 percent 5.45 percent, and 20 percent 5.01 percent medication, respectively. After a year of storage at room temperature (25°C), neither the physical appearance nor the dissolving pattern of these tablets changed.

Conclusion: A pectin or pectin chitosan mixture in the form of compression coated tablets could be used to deliver metronidazole to the colon selectively.

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