

## A RESEARCH PROJECT ON DESIGN AND EVALUATION OF COLON TARGETED MODIFIED PULSINCAP DELIVERY

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### ABSTRACT

This study aimed to create, design, and test a special kind of medicine capsule that releases drugs directly in the colon. The main goal was to make the medicine stay in the stomach and small intestine for a while before releasing it slowly and exactly in the colon. This would help the medicine work better and cause fewer side effects in the rest of the body. To do this, the outer part of the hard gelatin capsule was changed so it would not dissolve quickly. This was done by exposing it to formaldehyde vapor. The capsules that weren't treated stayed soluble. The medicine, which included metronidazole, was put into the treated capsules along with other ingredients that help control how fast the medicine is released. A special coating was added to stop the medicine from dissolving in the stomach and small intestine. The capsules were tested for several things like how they looked, their weight, how evenly the medicine was inside, how quickly they broke apart, how the medicine came

out in a test setup, how long it took before the medicine started to come out, and how the medicine was released over time. The results showed that the modified capsules worked well, with a delay before releasing the medicine, and then releasing it in the colon as planned. The study suggests that this new type of capsule is a good way to deliver medicine directly to the colon, especially for drugs like metronidazole. It can improve how well the medicine works and make it easier for patients to take.

**KEYWORDS:** Pulsincap, metronidazole, colon targeted drug delivery system, capsules.

## INTRODUCTION

A colon-targeted drug delivery system is made to send medicine directly to the colon. This can help treat diseases like ulcerative colitis, Crohn's disease, colon cancer, and amoebiasis locally, or help the body absorb drugs that work better when taken in the colon. The colon has some great features for drug delivery, such as a long time it takes for food to pass through, a pH that is almost neutral, and less enzyme activity than the stomach and small intestine. These factors make the colon a good place to release drugs that don't work well or break down quickly in the upper part of the digestive system. Taking medicine by mouth is the most common way to use a colon-targeted system because it's easier for patients, safer than injections, and usually causes fewer side effects. However, traditional ways of delivering medicine through the mouth often don't work well for treating colon diseases. That's because they don't release the drug in the right place in a strong enough form, which makes the treatment less effective. So, delivering drugs specifically to the colon is important for treating issues in the colon safely and effectively.<sup>[1]</sup> The colon also has a lot of immune-related tissue, which makes it good for giving vaccines. When antigens are taken in by the immune cells in the colon, they can quickly start an immune response. The colon is also useful for improving the absorption of medicines that are hard to take in because the environment is milder, and there are substances that help with absorption. Plus, the colon keeps things in for a longer time, which is good for slowly releasing medicine over time. This is especially helpful for drugs like peptides and proteins that are usually broken down in the upper part of the digestive system. Putting medicine directly into the colon brings several benefits.<sup>[2]</sup> It can help lower the amount of medicine needed, reduce side effects, and deliver the active drug closer to where it's needed. To do this well, the colon-targeted system needs to keep the medicine safe as it moves through the stomach and small intestine, so it doesn't break down or release too early. The colon's low enzyme activity and long time for food to stay in the colon—up to five days—makes it very suitable for taking in peptides and proteins, which would otherwise be broken down in the small intestine. These things help make sure that these kinds of drugs are available in the body when they're delivered through colon-targeted systems.

## Advantages

The benefits of using colon-specific drug delivery systems in treatment include the following points.<sup>[3]</sup> It helps reduce side effects when treating colonic diseases such as Crohn's disease, Ulcerative Colitis, and Colorectal Cancer. It avoids the first-pass metabolism of steroids. It

prevents the stomach and intestinal irritation that can happen when taking NSAIDs by mouth. Medicines used for conditions like Rheumatoid Arthritis, Asthma, and Angina are released slowly over time. It means patients don't have to take medicine as often, which improves their ability to follow the treatment plan. It provides a suitable environment for peptides and proteins that are damaged by the acidic environment and enzymes in the stomach. It improves the absorption of drugs that are not well absorbed in the body.

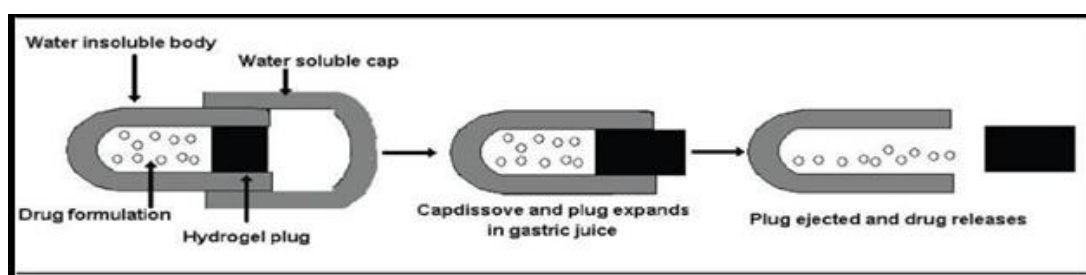
### **Limitations**

People have different pH levels in their colon and small intestine, which can cause the drug to release in the wrong place in the colon-targeted drug delivery system (CTDDS). These differences can lead to ineffective treatment. The caecum and small intestine have similar pH levels, which makes it harder for the formulation to target a specific site. Poor site targeting is the main problem with delivering medicine to the colon. The system requires a low dose of the drug and a lot of other ingredients. The bacteria in the colon can be affected by what someone eats and their health, which can make the drug less effective at targeting the colon. What people eat can also change how the drug works in the digestive system. If the enzymes break down the drug too slowly, it can change how the drug is released from the formulation. In a time-based colon drug delivery system, if the time the drug stays in the stomach varies a lot, the drug might release in the wrong place.

### **Pulsatile Drug Delivery System**

Time-controlled drug delivery systems aim to disperse medication according to both time and location, enhancing treatment success and encouraging better patient adherence. These systems are advantageous as they accurately deliver medicine to the right spot, at the right moment, and in the exact quantity, in harmony with the body's natural rhythm (circulating rhythm). Unlike systems that consistently release medicine, pulsatile systems are designed for drugs that do not require constant exposure. Rather, they offer a delayed phase, followed by a swift and complete release of the medicine, which makes them suitable for conditions where the timing of drug activity is crucial.<sup>[4]</sup> The Pulsincap system is a sophisticated drug delivery approach that employs capsules for delayed, pulsed drug discharge. It achieves this by utilizing a mix of physical obstacles, pH-sensitive substances, and hydrogel plugs. The design includes a specially treated, water-resistant hard gelatin capsule body, capped at one end with a hydrogel plug. This plug, often crafted from polymers like hydroxypropyl methylcellulose (HPMC), is designed to expand or degrade after a specific delay.<sup>[5]</sup> Upon reaching this delay,

meticulously adjusted to match the gastrointestinal travel time, the plug detaches or breaks down, triggering quick drug release from the capsule. This timing ensures the drug is discharged only when it reaches the colon, utilizing the colon's unique attributes, such as its near-neutral pH, longer travel time, and presence of microbial flora, to boost drug efficiency. This system is notably effective for addressing colon-related diseases like ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), and colorectal cancer. Additionally, it is suitable for distributing drugs that are unstable or poorly absorbed in the stomach and small intestine.<sup>[6]</sup> By providing site-specific, time-regulated drug discharge, the Pulsincap system enhances therapeutic effectiveness and minimizes undesirable systemic side effects.<sup>[7]</sup>



**Fig. 1: Capsule-Based System.**

### **Factor to be Considered in the Design of Colon-Specific Drug Delivery System**

The colon is often referred to as the body's "black box," making it difficult to target specific areas. Several factors can impact the development of a Colon Targeted Drug Delivery System (CTDDS) and how well the drugs are absorbed in the colon. A brief overview of some of these factors is provided below.<sup>[8]</sup>

**Intrinsic Factors** - Intestinal colonic transit time, pH of colon, Colonic microflora and enzymatic metabolism, Mucus barrier.

**Extrinsic factors** - Polymeric drug carrier, Drug candidate.

### **Time Controlled Pulsatile Release**

#### **Single Unit System**

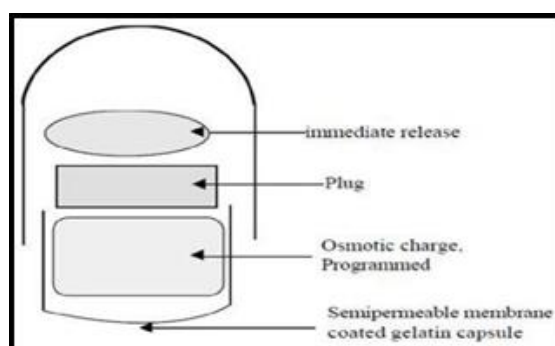
These are subdivided as capsule-based system, osmotic system, delivery system with soluble or erodible membranes, and delivery system with reparable coating.

### Capsule based system

The Pulsincap system uses a capsule made of an insoluble material that's sealed with a plug made from approved substances like hydrophilic polymers or lipids. This plug is designed to control how long the drug stays inside the capsule before it's released. When the capsule comes into contact with a liquid, the plug swells or breaks down over a set period, which then pushes it out of the capsule, allowing the drug to be released quickly in a single burst. The plug is often made from materials such as hydroxypropyl methylcellulose (HPMC), polyvinyl acetate, polyethylene oxide, polyvinyl alcohol, glyceryl monooleate, pectin, or polymethacrylates. The size and type of the plug determine how long it takes for the drug to be released after the capsule is taken.<sup>[9]</sup>

### Osmotic System

The osmotic drug delivery system uses a capsule that has a semipermeable membrane covering it. Inside the capsule, there's an insoluble plug made of an osmotically active substance along with the drug. Another version of this system uses an expandable orifice, where the liquid drug is attached to highly porous particles. Once the barrier layer dissolves, the drug is released through a small opening. In the Port System, a gelatin capsule with a semipermeable membrane, like cellulose acetate, holds an insoluble plug and an osmotically active agent along with the drug. When this capsule comes into contact with water, the water moves through the membrane, creating pressure inside. This pressure eventually pushes out the plug after a specific time delay. The length of this delay is controlled by the thickness of the membrane, which allows for accurate timing of when the drug is released.



### MATERIALS AND METHOD

The creation of oral formulations that release medication slowly and in a controlled way brings many benefits. These include better control over the dose given, keeping drug levels in the blood steady, fewer side effects, less frequent dosing, and better patient adherence. These

systems are especially helpful in chronotherapy, which targets diseases that get worse at certain times of day, like bronchial asthma, angina, and rheumatoid arthritis. Delivering drugs directly to the colon rather than the upper part of the digestive system has several advantages, especially for treating diseases that affect the colon, such as ulcerative colitis, Crohn's disease, colon cancer, and infections. Targeting the colon allows for high concentrations of the drug at the right place while reducing side effects from the drug being released too early in the upper digestive tract or being absorbed unnecessarily into the bloodstream. The colon has a milder environment compared to the stomach and small intestine—there's less enzyme activity and less harsh conditions—and it stays in the body longer, which improves the absorption of drugs that are hard to take in (10). This makes the colon a good target for both local and systemic treatment, including drugs like undigested and active peptides and proteins. Common methods to target the colon include using thicker coatings that slow down drug release or slow-release matrices. Overall, colon-targeted drug delivery systems are very valuable for treating various bowel diseases and for delivering sensitive drugs systemically, offering both local and systemic benefits, especially for conditions like inflammatory bowel disease (IBD).

**Table 1: Key ingredients used in formulation of pulsion cap.**

INGREDIENTS	EXAMPLES
Solubility modifier in gelatine capsule	Formalin
Polymer	HPMC K4M, Sodium alginate, Xanthan gum
Diluent	Lactose
Lubricant	Mg. stearate
Glidant	Talc
Sealing agent	Ethyl cellulose
Enteric coating agent	Cellulose acetate phthalate

## Formulation Development

### Preparation of Cross-Linked Gelatin Capsules

Formalin treatment is used to change how soluble gelatin capsules are. When gelatin is exposed to formalin vapors, it causes an unexpected reduction in its solubility. This happens because the amino groups in the gelatin molecules form bonds with the aldehyde groups in formaldehyde through a process called Schiff's base condensation, which creates cross-links in the molecular chain.<sup>[11]</sup>

### Method

Hard gelatin capsules of size 0 were used, and the body parts were separated from the caps.

To make formaldehyde vapors, 25 ml of a 15% (volume by volume) formaldehyde solution was put into a desiccator along with a small amount of potassium permanganate. The empty capsule bodies, placed on a wire mesh, were left in the desiccator to be exposed to the formaldehyde vapors, while the caps were not treated and stayed water-soluble. The desiccator was closed tightly, and the exposure lasted for 12 hours. After that, the capsule bodies were taken out and dried at 50°C for 30 minutes to finish the reaction between the gelatin and the formaldehyde vapors. Then, the bodies were dried at room temperature to get rid of any leftover formaldehyde, and finally, they were put back together with the untreated caps and stored in a polythene bag.<sup>[12]</sup>

### **Preparation of hydrogel plug**

The hydrogel plugs for pulsing cap 90mg and 100mg were made by compressing equal parts of various polymers and diluents, including lactose, using 6 mm punches and dies on a rotary tablet press, while adjusting the thickness and hardness of the resulting tablet plugs.<sup>[13]</sup>

### **Preparation of granules**

Granules were prepared by wet granulation method using different concentration of polymers.

### **Preparation of modified pulsing cap**

The same amount of drug granules, measured in milligrams, were placed into the capsule bodies and sealed with a hydrogel plug. Both the body and the cap of the capsules were then sealed using a small amount of 5% ethyl cellulose solution in ethanol. After sealing, the capsules were fully covered with an enteric coating made of 5% CAP to help control the time it takes for the capsules to empty in the stomach. This coating process was repeated until the weight of the capsules increased by 8 to 12% as expected.<sup>[14]</sup>

### **Preparation of metronidazole pellets and formaldehyde-exposed hard gelatin capsules**

Metronidazole pellets are made using the extrusion-spheronization method, which is a common way to create uniform, round multi-particulate dosage forms. In this process, metronidazole is combined with a filler called microcrystalline cellulose (Avicel PH102), which helps bind the mixture and makes it easier to form spheres. Hard gelatin capsule bodies (Size 0) were placed on a wire mesh. Formaldehyde (15%) was put into a dessicator, and potassium permanganate was added until vapors were formed. The wire mesh with the

capsule bodies was then exposed to these formaldehyde vapors. The reaction was allowed to continue for 12 hours after which the bodies were taken out and dried at 50°C for 30 minutes to make sure the reaction between gelatin and formaldehyde was complete. The bodies were then dried at room temperature to remove any leftover formaldehyde. The mixture was moistened and extruded to create cylindrical shapes, which were then processed in a spheronizer to form round pellets. This method produces pellets that are all the same size and shape, which is important for making sure the drug content is even and the release of the medicine is consistent every time.<sup>[15]</sup>

### Development of modified Pulsincap dosage form

Pellets containing an amount equal to 150 mg of metronidazole were carefully measured and manually placed into the treated bodies. Each of these pellets was then enclosed in capsules, and the capsules were sealed using different types of polymers such as guar gum, carboxymethylcellulose sodium, hydroxypropyl methylcellulose 10K, and sodium alginate, each at varying concentrations. After filling, the capsules were fully coated with a 5% solution of cellulose acetate phthalate in acetone, to help control how quickly they empty in the stomach. This coating process was done multiple times until the weight of the capsules increased by 8 to 12%. The percentage increase in weight before and after coating was measured.<sup>[16]</sup>

**Table 2: Composition of modified pulsing cap formulations.**

FC	Weight of drug pellets (mg)	Polymer used	Weight of polymer (mg)	Drug content (%)
F1	300.0	Guar gum	20.0	100.23
F2	300.0	Guar gum	30.0	100.13
F3	300.0	Guar gum	40.0	100.26
F4	300.0	SCMC	20.0	100.65
F5	300.0	SCMC	30.0	98.86
F6	300.0	SCMC	40.0	97.68
F7	300.0	HPMC	20.0	100.82
F8	300.0	HPMC	30.0	102.08
F9	300.0	HPMC	40.0	97.85
F10	300.0	Sod.alginate	20.0	100.32
F11	300.0	Sod.alginate	30.0	100.65
F12	300.0	Sod.alginate	40.0	96.66



**Table 3: Pellet analysis.**

Parameter	Observation
Appearance	Spherical with smooth surface
Average pellet size (mm)	0.95
Angle of repose ( $\Theta$ )	22.7°
Bulk density (g/cc)	0.790
Tapped density (g/cc)	0.832
% Carr's index	5.04

**Evaluation of Granules****Pre compression study****Angle of repose**

The powder will allow to flow through the funnel fixed to a stand at definite height (h). The angle of repose will then calculate by measuring the height and radius of the heap of granules will be form.

$$\tan \phi = h/r \quad \phi = \tan^{-1} h/r$$

Where,  $\phi$  = angle of repose, h = height of the cone, r = radius of the cone

h = 2.09cm, r = 5cm

$$\frac{h}{r} = \frac{2.09}{5} = 0.418$$

$$\phi = \tan^{-1}(0.418)$$

$$\phi \approx 22.7^\circ$$

The angle of repose is 22.7°.

**Bulk density**

Both loose bulk density (LBD) and tapped bulk density (TBD) will determine. A quantity of 10 g of powder from each formulation will introduce into a 10 ml measuring cylinder. Initial volume will observe, the cylinder will allow to tap. The tapping will continue until no further change in volume is noted. Bulk density is calculated by using formula:

$$\text{Bulk density } (\rho_b) = \text{Weight of the powder} / \text{Bulk volume of the powder}$$

Where, Weight of powder = 15.8g, Bulk volume = 20cm<sup>3</sup>

$$\rho_b = \frac{15.8g}{20cm^3} = 0.79g/cm^3$$

Bulk Density ( $\rho_b$ ) = 0.79 g/cm<sup>3</sup>

**Tapped density ( $\rho_t$ )** = Tapped volume of the powder/ Weight of the powder.

Where, Tapped volume = 13.15 cm<sup>3</sup>, Weight = 15.8 g

$$\rho_t = \frac{13.15}{15.8}$$

$$\rho_t = 0.832$$

Tapped density = 0.832 cm<sup>3</sup>/g

### Carr's index

The Carr's index of the powder will determine by using formula: Carr's index (%) = [(TBD -LBD) × 100]/TBD

Where,

LBD (loose bulk density) = weight of the powder/volume of the packing

LBD= 0.79 g/cm<sup>3</sup> (from above calculation)

TBD (Tapped bulk density) = weight of the powder/tapped volume of the packing

TBD = 0.832 cm<sup>3</sup>/g (from above calculation)

**Weight of powder** = 39.5 g

**Loose bulk density (LBD)** = 0.790 g/cm<sup>3</sup>

→ Loose bulk volume = 39.5/0.790=50.0 cm<sup>3</sup>

**Tapped bulk density (TBD)** = 0.832 g/cm<sup>3</sup>

→ Tapped bulk volume = 39.5/0.832=47.48 cm<sup>3</sup>

$$\text{Carr's index} = \frac{(0.832 - 0.790) \times 100}{0.832}$$

$$\text{Carr's index} = \frac{0.042 \times 100}{0.832}$$

Carr's index = 5.04%

### Pre-formulation Studies

FTIR and DSC tests showed there was no major chemical reaction between Metronidazole and the other ingredients like HPMC, Eudragit S100, Guar gum, and sodium alginate. The unique peaks of Metronidazole remained unchanged, which means the drug and the other

materials work well together. Metronidazole dissolves a little in water and acidic conditions, but not so much in alkaline conditions. This means it's better to deliver the drug to the colon, so it doesn't release too early in the digestive system.<sup>[17]</sup>

### **Evaluation of Capsule and Plug Systems**

Hard gelatin capsules of size 0 were made successfully and had consistent weight, varying by no more than  $\pm 5\%$ . The capsules had uniform size and were not cracked or brittle. Hydrogel plugs were made using HPMC K100M, sodium alginate, and guar gum, and the best formula was chosen. The time it took for the plug to start dissolving (lag time) was between 4 and 8 hours, depending on the type of polymer used and how much force was applied. The plug containing 30 mg of HPMC K100M had the most consistent lag time of about 6 hours, which is good for targeting the colon.<sup>[18]</sup>

### **Pre-compression Properties of the Drug Mixture**

The granules of Metronidazole that were going to be filled into capsules were tested for how well they flow and how easy they are to compress.

Angle of Repose:  $28.7^\circ \pm 0.45$ , which shows that the granules flow well.

Carr's Index: 14.6%, meaning they have good compressibility.

Hausner's Ratio: 1.17, which means they are suitable for making capsules.<sup>[19]</sup>

### **Post-compression and Capsule Testing**

Weight Variation: Within  $\pm 3\%$ , which meets the standards set by IP.

Uniformity of Drug Content: Between 97.5% and 101.2% of the expected amount.

Disintegration Test: The capsules stayed intact for 6 hours in simulated stomach and intestine fluids, showing that the plug inside works well.

Friability: Less than 0.4%, meaning the capsules are strong enough (20).

### ***In-vitro* Drug Release Studies**

#### **Release Behavior in Simulated Gastrointestinal Fluids**

The dissolution test was done in the following conditions:

- 0.1N HCl (for 2 hours),
- Phosphate buffer at pH 6.8 (for 3 hours), and
- Phosphate buffer at pH 7.4 with 4% rat caecal content (up to 24 hours).

In stomach pH (0–2 hours): Very little drug was released (<2%), showing that it resists acid.

In intestinal pH 6.8 (2–5 hours): Only a small amount was released (~6%), which shows that the plug controls the release.

In colonic pH 7.4 with enzymes: The drug released quickly and completely (~96% within 8 hours), proving the pulsatile burst effect.

## RESULTS AND DISCUSSIONS

This study focused to create a new type of colon-targeted drug delivery system called Pulsincap for Metronidazole, a medicine used to treat infections like amoebiasis and other diseases that affect the colon. The goal was to make sure the drug only releases in the colon and not earlier in the digestive system. This was done by making a capsule that has a body sealed with hydrogel plugs and then coated with materials that respond to changes in pH and enzymes. These coatings help delay the release of the drug until it reaches the colon. To test this, the researchers used simulated fluids that mimic the conditions in different parts of the stomach and intestines. They tested for 12 hours using three types of fluids: acidic fluid that mimics the stomach (pH 1.2) for 2 hours, a fluid that mimics the small intestine (pH 7.4) for 3 hours, and a fluid that mimics the colon (pH 6.8) for the rest of the time. The pH 7.4 and 6.8 fluids were only used to simulate the environments of the small intestine and colon and did not affect how the drug was released. The results showed that no drug was released in the acidic stomach fluid, which confirmed that the 5% cellulose acetate phthalate coating was effective in keeping the drug from releasing too early. The study also found that the release of Metronidazole from the modified Pulsincap system increased with higher concentrations of the hydrogel plug material. Among the different formulations tested, F2 (30 mg guar gum), F5 (30 mg sodium carboxymethyl cellulose or SCMC), F11 (30 mg sodium alginate), and F12 (40 mg sodium alginate) worked best for delivering the drug to the colon. These formulations kept the drug from releasing too much in the small intestine while allowing a significant release in the simulated colon fluid. This shows that these formulations could help deliver Metronidazole directly to the colon, improving how well the drug works for treatment. The study showed that using a time-dependent modified Pulsincap system can successfully target Metronidazole to the colon, offering better and more effective drug

delivery.

## CONCLUSION

The current study focused on creating a new colon-targeted drug delivery system called Pulsincap for Metronidazole, which is an antibiotic used to treat infections in the colon, like amoebiasis. This method was chosen to improve upon the usual ways of taking Metronidazole, which often lead to side effects all over the body, are not very effective in the upper part of the stomach, and don't work well at the exact location where the infection is. The main goal was to design a system that delays the release of the drug for a certain time and then releases it quickly and fully in the colon. This should improve how well the drug works and make it easier for patients to take. The study followed a detailed process that included analyzing the drug before making it, developing the formulation, improving the capsule and the plug made of hydrogel, checking the physical and chemical properties, and testing how the drug is released in a lab. Lab tests using liquids that mimic the stomach, small intestine, and colon showed that almost no drug was released in the stomach or small intestine, which means the hydrogel plug and the coating that reacts to pH kept the drug from being released too early. When the drug reached the colon, where there are a lot of enzymes, it released almost entirely, showing that the Pulsincap system works well with a combination of time-controlled, pH-sensitive, and enzyme-activated release. In total, the study showed that this new Pulsincap system is a good, effective, and easy-to-use way to deliver Metronidazole directly to the colon. It solves the problems with traditional methods by giving a reliable, repeatable way to release the drug exactly where it's needed. This delivery method has the potential to be used in treating amoebiasis and other colon infections, and its flexible design could be adapted for other drugs that need to be targeted specifically to the colon.

## Conflict of Interest

The authors state that there are no conflicts of interest related to publishing this research. The study was carried out on its own, without any connections to companies or money that might create a conflict of interest.

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