International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 4 July-Aug 2024, pp: 1272-1280 www.ijprajournal.com ISSN: 2456-4494

# A Review on Formulation and Evaluation of Colon Targeted Extended Release Capsule of Mesalamine

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Date of Submission: 10-08-2024 Date of Acceptance: 20-08-2024

**ABSTRACT**: Drugs can be given locally or systemically via colon. For example, local distribution can help in the treatment of inflammatory bowel disease topically. The effectiveness of the treatment could be increased if medications could be administered specifically to the colon. Also, systemic side effects may be reduced. Using colon-specific methods, oral delivery of peptide and protein medicines, which are frequently inactivated in the upper gastrointestinal tract, may also be possible.Prodrugs, pH and time dependent systems, and microbially triggered drug delivery systems are some of the primary techniques for CDDS (Colon Specific Drug Delivery), which have had little success and have several limitations. CDDS is a newly established drug delivery system that includes osmotic controlled drug delivery and a novel colon targeted delivery system.Pharmaceuticals with extended release have shown to be a highly helpful tool in medicine, providing patients with a variety of actual and expected advantages. Therefore, oral extended release drug delivery systems become a very useful option for oral medications with high dosage frequency and a shorter half-life. Colon targeted route ispreferable because to less pain, a lower risk of cross-infection, needle stick injuries, patient acceptance, and convenience of administration. The fluidized bed processor is especially useful for creating controlled release formulations.

**KEYWORDS:** Colon Targeted Drug Delivery, colon, Hard Gelatin Capsule, pellets, Ulcerative Colitis.

## I. INTRODUCTION:

**Extended Release Dosage Form:**Pharmaceuticals with extended release have shown to be a highly helpful tool in medicine, providing patients with a variety of real and perceived benefits. Of all the drug delivery channels, oral drug delivery is the most chosen for different drug molecules due to its ease of administration, which improves patient compliance. As a result, oral extended release drug delivery systems represent a very attractive treatment option for oral medications with short half-lives and frequent dosage schedules. By keeping the therapeutic concentration of the drug from fluctuating throughout the body, extended release is also offering a viable means of reducing the adverse effects of the medication. The majority of drug delivery medications will still be oral extended release formulations.

Advantages of Extended Release Delivery System:

- By using these formulations, elevated blood concentrations are prevented.
- Formulations with extended release may increase patient convenience and compliance.
- Reduce the adverse effects, both systemic and local.
- An increase in the effectiveness of treatment.
- Reduce medication build up by using continuous dosage.

Disadvantages of Extended Release Delivery System:

- Extended release product's bigger size may make them harder to swallow or pass through the stomach.
- The rate of transit through the gut and the presence of food are two elements that influence the release rates.
- High preparation costs.
- Drug tolerance may develop when the target tissue is exposed to a continuous dose of the medication for a prolonged period of time. [1]

**Capsule:**

Among all dosage forms, capsules are one of the most widely used because they are simply formulated, convenient to administer, and have a stable chemical and physical composition. They are easily customizable to meet the requirements of

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specific patients in terms of ingredients, dose, etc. Additionally, many medications can be included in each capsule to reduce the number of dosage forms the patient needs to take. It is possible to construct unique capsules that don't just include powders. The most preferred dosing form is a capsule.Gelatin is currently widely used as the shell material for capsules, both soft and hard. However, because of its animal origin and cross-linking properties, other capsule materials that satisfy vegetarian patients' dietary and cultural requirements as well as the regulations governing gelatin must be developed. As a result, various materials without an animal origin, such as starch, poly vinyl alcohol copolymer, hydroxyl propyl methyl cellulose, and others, have been developed and tested as shell materials for capsules.

Advantages:

- The pill can be given in an odourless and tasteless manner by being enclosed in a capsule shell.
- Manufactured, packaged, and shipped at a reduced cost with less breakage than liquid forms.
- The capsules are readily ingested due to their smooth and slippery texture.
- Patient compliance.
- Capsule manufacturing is simple.
- Used to encapsulate semisolids or lipids.
- Fast breakdown and fast bioavailability.

Disadvantages:

- Liquids that dissolve gelatine, such as aqueous or hydroalcoholic solutions, are not appropriate for use with capsules.
- Concentrated solutions that need to be diluted beforehand are inappropriate for usage in capsule form because they can irritate the stomach when taken that way.
- Not applicable to deliquescent or efflorescent materials. Capsules become softer due to efflorescence, and the capsule shell may become brittle due to deliquescent. [5]

**Gelatin:**

About half of the world's gelatin is made from pig skin, primarily from collagen that has been removed from the skin using heat and acidic solutions. A variety of goods, including hard gelatin capsules (HGC) with variable water solubility, are made from gelatin. This problem has been known for a long time and is still being researched and discussed.slow gelatin dissolution rates are primarily caused by the protein's propensity to create cross-links in denatured collagen chains under particular circumstances, which stabilise the gel network and inhibit dissolution. As gelatin is taken out of animal tissues, it could also contain other molecules (such as carbohydrates, lipids, and other proteins) that interact with the collagen chains to create covalent connections.Despite being the focus of several articles, the structure and composition of this biopolymer remain unclear. There are, in fact, a lot of variations between articles. As such, the reasons behind HGC collapse are poorly understood and managed. [6]

Types of Capsule:

a) Hard Gelatin Capsule
b) Soft Gelatin Capsule

a) Hard Gelatin Capsule:

Hard gelatine capsules have traditionally been used as an over-the-counter (OTC) and prescription dose type. Medications and herbal goods that are made into pellets or powder form. This has significantly increased the number of formulations that can be made using hard gelatine capsules as a straightforward dose form for oral medication delivery. It is made up of two cylinder-shaped pieces: the longer piece is called the "body," and the shorter piece is called the "cap."

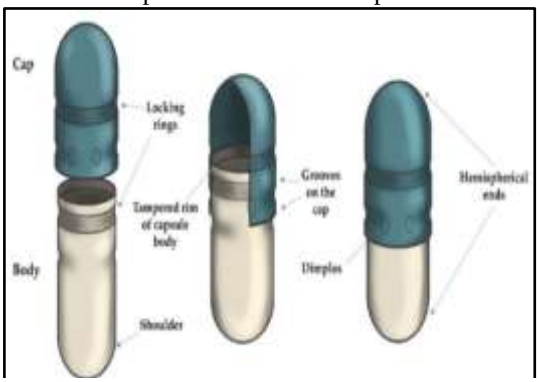


**Figure 1:** Parts of Hard Gelatin Capsule.

The main ingredients of the shell are water, sugar, and gelatin. 12–16% of hard gelatine capsules are wet.Usually, these are packed with solid, dry materials that are:

- Powders
- Granules
- Pellets
- Tablets

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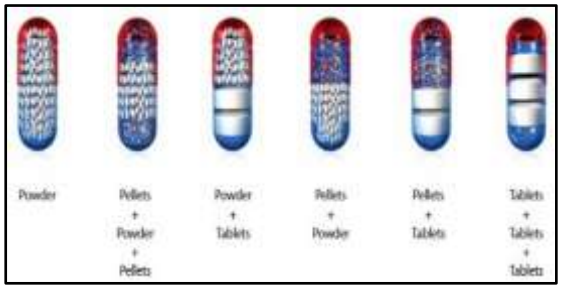


**Figure 2:** Types of different fillings in hard gelatin capsule.

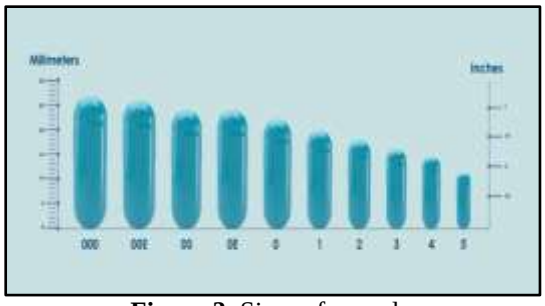


**Figure 3**: Sizes of capsule

- The largest size of the capsule is No: 000
- The smallest size of the capsule is No: 5
- The standard shape of capsules is traditional, symmetrical, bullet shape.

Advantages :

- Simple to ingest.
- Capacity to mask taste.
- Medicine protection.
- Easy to digest and therapeutically inert.
- Simple to carry and handle.
- A variety of sizes are offered.
- Offer effects of continuous and enteric release.
- Content of moisture. [5]

Disadvantages:

- Because of ingestion difficulties, drugs with very large unit doses cannot be dispensed as HGC.
- Drugs that dissolve the capsule shell are not suitable candidates for dispensing in hard gel capsules.
- Hard gel capsules cannot contain hygroscopic or deliquescent materials.
- Iodides, bromides, and chlorides are highly soluble salts that should not be administered in hard gelatin capsules. [15]

b) Soft Gelatin Capsule:

In the nutritional supplement market, solid dosage forms are gaining popularity as a way to administer liquids, suspensions, pastes, and dry powders. They are different from hard gelatine capsules in a number of ways.

A single, hermetically sealed soft gelatine shell that holds a liquid, suspension, or semisolid substance known as fill is called a soft gel capsule. They are ideally created using the rotary die method, which involves shaping, filling, and sealing all in one continuous operation. They can be further classified into two groups: soft gelatine capsules and non-gelatine soft capsules, depending on the polymer that makes up the shell. Gelatine is used to create most soft capsules because of its special physical characteristics, which make it a perfect excipient for the rotary die process. Additional different soft gelatine capsule ingredients are provided. [5]

Advantages:

- Provides the advantages of two or more drugs in a single capsule.
- It keeps its potency, freshness, and effectiveness.
- Attractive and useful, with a simple swallowing process.
- Custom shapes, sizes, and colors are possible.

Disadvantages:

- Heat and moisture sensitivity, along with restrictions on food.
- Danger of dose dumping a High instant Dose. [17]

**Pellets and Pelletization:**

Pellets are spherical or nearly spherical, free flowing granules with a restricted size distribution, often ranging between 500 and 1500 m for medicinal uses. They are typically manufactured by a pelletization process in which a powder combination comprising an API and excipient particles is agglomerated into sphericalgranules. Pellets are often packed into firm gelatin capsules or compacted into tablets after processing. Furthermore, they can be produced as an instant release dosage form or as a sustained drug release over a lengthy period of time, or they can be coated to transport a medication to a specific site of action in the gastrointestinal tract. Pellets give the development scientist a lot of freedom when it comes to designing and developing oral dosage forms.

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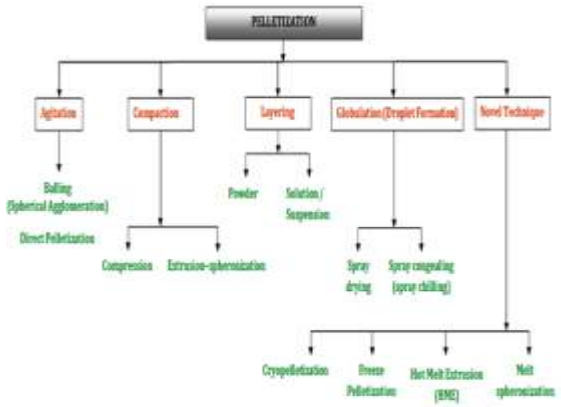


**Figure 4:** Classification of pelletization [18]

Advantages:

- Dose uniformity- Layering methods and extrusion speronization provide high accuracy in medication administration to pellets.
- Spheres have good flow characteristics. This is especially beneficial in automated procedures or when precise dosing is required, such as tableting, molding operations, capsule filling, and packing.

Disadvantages:

- Pellet filling necessitates capsule filling, which raises costs.
- Pellet sizes vary from formulation to formulation, but are typically between 0.05 mm and 2 mm. It is difficult to compress pellets into tablets as they are too rigid. Therefore, they are often delivered encapsulated in hard gelatin capsule shells. [4]

**Flow Properties of Granules: [21]**

**1. Angle of repose:**

The angle of repose is defined as the angle of inclination of the free surface to the horizontal of a bulk solid heap.Assuming a conical heap, the angle of reposeαis the angle between the conical slope of a pile of solids solid materials and the horizontal base.The higher the angle of repose, the higher the cohesiveness of a bulk solid; the lower the angle of repose, the more fluid-like and free-flowing the bulk solid. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

**$\tan \theta = h/r$**

Where,

h = height of the powder heap

r = radius of the powder heap

θ = is the angle of repose

**Table 1:**Significance of Angle of repose

| Angle of repose | Flow property |
|---|---|
| <25 | Excellent |
| 25-30 | Good |
| 30-40 | Passable |
| >40 | Poor |

**2. Hausner ratio:**

The Hausner ratio is an indirect measure of the property of a bulk material to reduce its volume under mechanical influence. It is also a measure of the ability to compress and of the interaction between the particles. A low Hausner ratio means that the material flows more easily. In the case of less flowable substances, there are significantly higher interactions between the particles, and the Hausner ratio is higher. It is calculated by the following formula:

**Hausner's Ratio = Tapped density/Bulk Density**

**Table 2:**Significance of Hausner's ratio

| Hausner's ratio | Property |
|---|---|
| 0-1.2 | Free flowing |
| 1.2-1.6 | Cohesive powder |

3. **Carr's Compressibility Index:**

It is an indirect method of measuring powder flow from bulk densities which is developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. Carr's index is calculated according to given equation:

**Carr's Compressibility Index =tapped density-bulk density/tapped density X 100**

**Fluidized Bed Processor:**

This method is also known as the wurster process. It had several functions, including coating, drying, granulation, and pillarization. This approach is especially useful for creating controlled release formulations. It entails the sequential deposition of numerous layers of the coating substance. It is fitted with concurrent air flow through different perforations in the base plate of the (FBP) spray nozzle, resulting in a customized spray pattern. The particles to be coated are propelled at high speeds inside the wurster tube, and the coating solution is continually sprayed through the nozzle spray. As the process progresses, more particles traveling upward become dried and fall outside the wurster tube, back

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towards the base plate, and then back within the tube, where they are once again trapped.

The Fluidized Bed shows the following properties:

- Particles that are lighter float on top of the bed.
- Because of gravity, the beds have a static pressure head.
- It has a zero angle of repose.

**Figure 5:** Fluidized Bed Processor

Processing parameters:

- Drying parameters:
  - Temperature: The rate of drying increases as the temperature of the incoming air rises. This should be closely monitored because the exposure of thermo labile compounds degrades as the temperature of the inlet air rises.
- Granulation parameter:
  - Position of nozzle: The nozzle location should be adjusted based on the bed height for better drying.
  - Spray rate: To avoid over granulation, the spray rate should be optimized.
  - Spray pressure: Pressure should be regularly checked since changes in pressure cause incorrect drying and granulation.
- Coating parameters:
  - Distance of spray nozzle: The distance between spray nozzles is significant in determining the coating process since a greater distance leads to evaporation of the coating solution and a smaller distance leads to over wetting of the particles or dosage forms.
  - Droplet size: Droplet size is inversely proportional to coating efficiency. The smaller the droplet size, the more uniform the coating of the fluid.
  - Spray rate: The spray rate should neither be excessively quick or excessively sluggish. The optimal spray rate must be maintained in order for proper coating to occur.

Spray pressure: Spray pressure affects coating solution atomization.[1]

Applications of FBP:

- Fluidized bed dryers are used in drying of various materials such as powders, tablets, granules, coals, fertilizers, plastic materials.
- This process is being used in granulation of pharmaceutical powders.
- Fluidized bed coaters are used widely for coating of powders, granules, tablets, pellets, beads held in suspension by column of air. [22,23]

**Colon Targeted Drug Delivery System:**

The goal of a targeted drug delivery system is to deliver a therapeutic amount of medicine to a specific place in the body to achieve the desired drug concentration. It is appropriate and necessary for medications with instability, low solubility, a short half-life, a high volume of distribution, poor absorption, limited specificity, and therapeutic index. Targeting may give the greatest therapeutic activity (by preventing medication breakdown or deactivation). Meanwhile, by lowering the dose, it is possible to reduce the side effects and toxicity of powerful medications. The oral route is the most practical and important means of administering medicines for systemic efficacy.

Furthermore, it was preferable because to less pain, a lower risk of cross-infection, needle stick injuries, patient acceptance, and convenience of administration. Oral medication delivery methods account for over half of all drug delivery systems on the market. Aside from these benefits, the oral route is not appropriate for the administration of medications for lower gastrointestinal (GI) illnesses; this is owing to their release at the upper GI tract (stomach, small intestine), which further reduces drug accessibility at the lower GI tract. To address this issue, colon-specific medicine delivery devices have been extensively researched over the last two decades. A colonic delivery is defined as the accurate delivery of medications into the lower GI tract (by avoiding drug release in the upper GIT). Rectal administration is another method for colon targeting, although it is less pleasant and makes reaching the colon more difficult. Conventional dose formulations used to prevent colon disorders (ulcerative colitis, Crohn's disease, amoebiasis) are

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failing because an insufficient amount of medicine reaches the site of action. The medicine is absorbed from the upper section of the GIT, i.e., the stomach, in the conventional dosage form. The action of traditional dose forms has a significant disadvantage for colonic localized distribution. Thus, for effective and safe therapy, the medicine must be protected from the upper hostile environment.

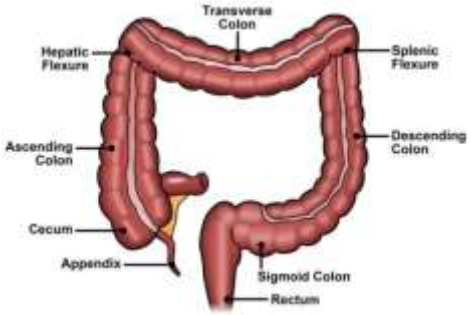


**Figure 6**: Anatomy of colon

Advantages:

- An ideal place for the administration of active drugs to treat colon disorders (ulcerative colitis, Chron's diseases, amoebiasis, etc.).
- For local treatment, smaller drug quantities should be necessary.
- Longer colon retention period, increased bioavailability of poorly absorbed medicinal molecules (up to 5 days).[2]

**Design of colon targeted drug delivery capsule:**

Along with the drug substance, the system contains an organic acid that is filled in a hard gelatin capsule as a pH-adjusting agent. After that, the capsule is coated with a three-layered film made up of an acid-soluble layer, a hydrophilic layer, and an enteric layer. After capsule ingestion, these layers prevent drug release until the environmental pH inside the capsule decreases because of organic acid dissolution, at which time the enclosed drug is quickly released. Thus, the thickness of the acid-soluble layer determines the onset time of drug release. [16]

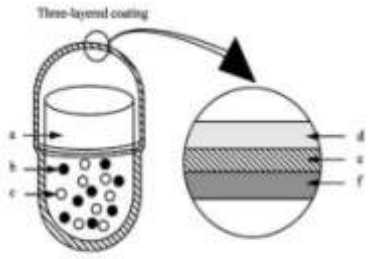


**Figure 7**: Design of the Colon targeted capsule

**Ulcerative Colitis:**

Ulcerative colitis (UC) is a chronic inflammatory illness with unknown cause that affects the large colon, most commonly the rectum, and spreads proximally. Patients frequently report with abdominal pain and diarrhoea, as well as other systemic symptoms such as fever and weight loss. UC incidence and prevalence rates range from 3 to 15:100,000 and 50-80:100,000, respectively, with greater rates reported in the industrialized world (Stevenson and Korzenik 2003). In the United States, the prevalence has been recorded as high as 229 cases per 100,000 people, with around 25,000 new cases each year (Citation Loftus et al 2000). It can affect people of any age, but it is more common in younger people, with a peak onset between the ages of 15 and 25. There is an equal frequency in both genders, with bimodal incidence being prevalent in IBD. African-Americans had the lowest incidence rate in the United States, at 1.4 per 100,000, while Jews have the highest, at 13 per 100000. The treatment of UC has been based on the severity of symptoms, with aminosalicylates serving as first-line therapy. These medications are made up of 5-ASA, the active component of sulfasalazine, without the sulfapyridine carrier molecule, which is frequently the source of side effects. Mesalamine is a 5-ASA-baseddrug that is now approved for the treatment of UC. The evidence for 5-ASAs in the treatment of ulcerative colitis will be examined in this review. The various 5-ASA formulations will be studied and compared, and the most recent data on efficacy, doses, and side effect profiles will be presented. [3]

Over 50,000 people die each year from inflammatory illnesses affecting the gastrointestinal tract, such as bowel diseases that are inflammatory. [7,8]The two most common inflammatory bowel conditions are Crohn's disease and ulcerative colitis. Between these two diseases, the primary distinction is that Crohn's disease can impact any area of the

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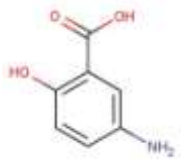
digestive system, but ulcerative colitis belongs to the colon. Currently available options for curing are not always successful and may have harmful side effects. Also, there is currently no long-term cure for inflammatory bowel illnesses, and patients must adhere to a lifetime medication schedule. [9] For patients with inflammation restricted to the left colon, topical mesalamine, hydrocortisone, or budesonide is advised. When treating cases that spread beyond the left colon, it is advised to use oral mesalamine or sulfasalazine in addition to topical treatment. Prednisone used orally or infliximab induction treatment. In severe cases, intravenous steroids, infliximab, or cyclosporine are advised. [10] Mesalamine is also known as mesalazine, mesalamine is a derivative of salicylic acid (5-amino salicylic acid [5-ASA]). Typically, it serves as a first-line anti-inflammatory medication to work directly on the mucosa of the colon and reduce inflammation in order to treat conditions connected to the colon, such as ulcerative colitis and Crohn's disease. [7,11,12]

**In vivo study:**

The medicine must be targeted for localized release to the mucosa of the colon and terminal ileum in order for a colon targeted drug delivery system to be effective. The medication's release in the upper small intestine and stomach is not what you want since it may cause early absorption, medication waste, and maybe systemic side effects. It is Correlating the colon-specific formulation's in vitro performance with in vivo research is essential for determining site-specific selectivity as a result of the formulations' varying GIT conditions targeted for its site-specificity in the ileo-cecal area. In addition to X-ray imaging research, pharmacokinetic research provides the dependability on colon specificity. The Institutional Ethical Committee for Care and Use of Laboratory Animals approved the animal experimentation techniques, and they were carried out according with the code of ethics in study, instruction, and medication testing. The animals were sourced from the animal house of the Institute of Pharmaceutical Education and Research (IPER) Borgaon (Meghe), Wardha, India.The ethics committee approval number is: IPER/IAEC/2015-16/06. [13,14]

**Table 3:** Drug Profile [19,20]

| **Attributes** | **Description** |
|---|---|
| Name of Drug | Mesalamine |
| Structure |  |
| IUPAC name | 5-amino-2-hydroxybenzoic acid |
| Molecular weight | 153.14 gm/mol. |
| Molecular formula | $C_7H_7NO_3$ |
| Melting Point | 260-280 °C |
| Solubility | Almost insoluble in acetone, alcohol, ether<br>Slightly soluble in water |
| BCS class | IV |
| Half life | 5-10 hours |
| Bioavailability | 40% |
| Category | Anti- inflammatory, analgesic non-narcotic, anti- ulcerative colitis |
| Brand names | Canasa (Suppository)<br>Delzicol (Capsule)<br>Mesasal (Tablet)<br>Pentasa (Suspension) |
| Mechanism of action | Mesalamine is an amino salicylate. It acts by inhibiting the synthesis of prostaglandins, which are chemical messengers |

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| | |
|---|---|
| | that induce intestinal inflammation (swelling). This minimises stomach pain, bleeding, and ulcers while avoiding further disease episodes. |
| Side effects | Stomach pain<br>Flatulence<br>Headache<br>Vomiting<br>Diarrhoea<br>Rashes<br>Abdominal Pain<br>Nausea |

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