# Development and analysis of multiparticulate beads that target the colon with metformin hydrochloride and 5-fluorouracil

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## Abstract

This study uses an ionotropic gelation process with a $3^2$-factorial design to create and optimize multiparticulate beads of sodium alginate that contain 5-flurouracil and metformin hydrochloride. CaCl2 was used as a crosslinking compound throughout the development of the beads. A 32-factorial design was used to optimize the impact of the drug-to-sodium alginate blend ratio and the CaCl2 concentration on the drug entrapment efficiency, bead size, and percent cumulative drug release in six hours. The drug entrapment effectiveness of each of these beads ranged from 33.34±0.05 to 86.39±0.13%, and their in vitro drug release was between 10.83±0.15 and 62.79±0.71% in a period of 6 hours. To stop medication release in the optimized batches of beads, Eudragit S100 (5, 10 and 15% w/v) was coated on them.

**Key words:** sodium alginate, Metformin HCl, 5-fluorouracil, Eudragit s-100, inotropic gelation, colon targeting

## Introduction

There are several important pharmacological issues related to colon medication administration. Inflammatory bowel disease (IBD) can be effectively managed by local medication delivery to the large intestine. Colon focused drug delivery has the potential to administer bioactive molecules for the treatment of a number of colonic illnesses. Local administration of these medications to the bowel is very beneficial in the treatment of colorectal cancer, ulcerative colitis, Crohn's disease, and other colonic illnesses. This method may decrease the amount of medicament absorbed from the stomach and small intestine until it reaches the big intestine.[1]
Numerous drug delivery methods have been developed that carry medications to the large bowel in a quantitative manner, which then initiates the release of the active drug.

Treatments for diseases of the large intestine that require high drug concentrations, such as Crohn's disease, irritable bowel syndrome, colitis, colorectal cancer, and local infectious diseases, can be made more effective by using colon-specific drug delivery systems that use a variety of release mechanisms. Reducing adverse effects and enhancing pharmacological response may be possible with site-specific medication delivery to the target receptor locations. Nonetheless, a number of physiological barriers need to be removed for colonic medication administration to be successful, the primary one being the active drug's absorption or breakdown in the upper gastrointestinal (GI) tract. [2]

The precise release in the colon also influences the amount of time that passes between administration and the start of an effect, which is beneficial for conditions like arthritis and asthma. By utilizing the luminal pH in the ileum and the microbial enzymes in the colon, several colon-specific drug delivery systems are being developed.[1] The development of prodrugs, coatings of pH-sensitive polymers, colon-specific biodegradable polymers, timed-release systems, osmotic systems, and pressure-controlled drug delivery systems are some of the tactics currently available to target the release of drugs to the colon. A method that shows a lot of promise to achieve targeted medication release to the colon is the use of polymers, particularly those that are biodegradable by colonic bacteria. Bacterial enzymes known as polysaccharidases are sufficiently abundant to be used to target the colon with medicines. This method has led to the investigation of other polysaccharides for colon-specific medication release.[2][3]

## Materials And Methods

### Materials

We received a complimentary sample of metformin HCl from IOL Chemicals and Pharmaceutical ltd. in India. 5-FU was bought in Mumbai, India's Kemphasolpopatwadi. We received a gift sample Eudragit S100 from Khasra No-422/349, mouja OGLL,kala amb,distt-sirmour himanchal Pradesh. The remaining reagents and substances utilized in the investigation were all of analytical grade.

### Methods

**Core calcium alginate bead preparation**[1]

As indicated in Table 1, two distinct solutions were made independently, each containing a different formulation of calcium alginate beads. First, a certain amount of sodium alginate was continuously stirred into the phosphate buffer to dissolve it. Concurrently, an aqueous solution of calcium chloride was created, and the medication (5-fluorouracil, metformin HCl) was dissolved in the sodium alginate solution that had already been made. As illustrated in Figure 1, the drug-containing polymeric solution was gradually added to the calcium chloride solution using a 10-milliliter syringe with an inner-diameter needle of 0.45 mm while being stirred.

Therefore, a chemical interaction between calcium chloride and sodium alginate forms the gelatinous precipitate. After 20 minutes of vigorous stirring in the medium at 1000 rpm, the produced beads were filtered out, cleaned with distilled water, and vacuum-dried.

Solvent evaporation was used to coat Eudragit S-100 on optimized alginate beads.[8 The beads were scattered.

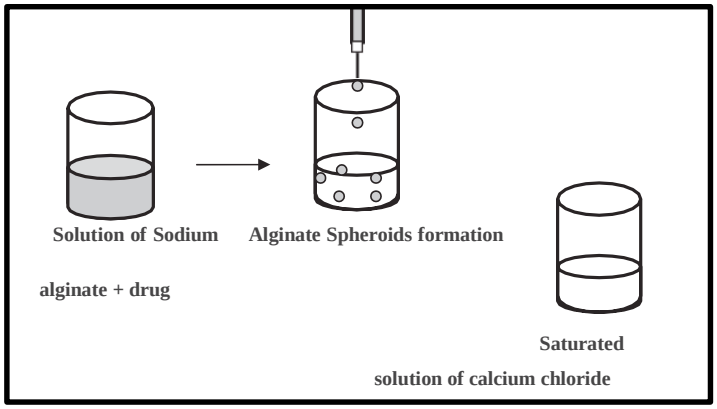


**Figure 1:** Schematic illustration of formation of alginate beads

**Core calcium alginate spheroids coated**[1][3]

Solvent evaporation was used to coat Eudragit S-100 on optimized alginate beads.In a dichloromethane and methanol (4:1) ratio, beads were placed in varying strengths of Eudragit S-100 to produce weight gains of 10% (E1), 13% (E2), and 15% (E3). Additionally, the solvent was vacuum dried in desiccators after being evaporated in an evaporator that rotates with a 300 mmHg vacuum and a 50 rpm rotation rate. The optimized batch was assessed using the release study as a foundation.

**Table 1: Various formulations of alginate beads**

| Formulation code | Polymer to Drug ratio (wt/wt) | $CaCl_2$ % | % entrapment efficiency | Microbeads size in mm | % release after 6 h |
|---|---|---|---|---|---|
| **DL1** | **6:1** | **10** | 33.34±0.05% | 1.00±0.07 | 62.29±0.83% |
| **DL2** | **6:1** | **10** | 55.68±0.02% | 0.86±0.03 | 61.57±0.32% |
| **DL3** | **6:1** | **10** | 51.62±0.07% | 0.90±0.01 | 63.13±0.43% |
| **DL4** | **8:1** | **10** | 58.50±0.32% | 0.96±0.05 | 57.13±0.39% |
| **DL5** | **8:1** | **10** | 86.39±0.13% | 0.83±0.05 | 65.15±0.57% |
| **DL6** | **8:1** | **10** | 49.52±0.10% | 1.00±0.07 | 62.68±0.39% |
| **DL7** | **10:1** | **10** | 70.49±0.11% | 1.03±0.03 | 57.13±0.83% |
| **DL8** | **10:1** | **10** | 62.51±0.09% | 1.06±0.04 | 62.29±1.25% |
| **DL9** | **10:1** | **10** | 71.78±0.48% | 1.16±0.02 | 62.79±0.71% |

***In Vitro* drug release study from core alginate beads**[5][6]

Microbead disintegration experiments were carried out in vitro using the paddle-type dissolution device. The dissolving medium was phosphate buffer with a pH of 7.4 and was agitated at 100 rpm and 37±0.5ºC. 100 mg of microbead-equivalent samples have been placed to the dissolving medium.

Five milliliter portions of the sample were extracted at different intervals (0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, and 6 hours) and passed through a Whatman filter paper 44. The identical volume of new dissolving liquid was added each time a sample was obtained. A UV spectrophotometer set to 238 nm wavelength was used to determine the drug concentration of the filtered solutions after they had been appropriately diluted.

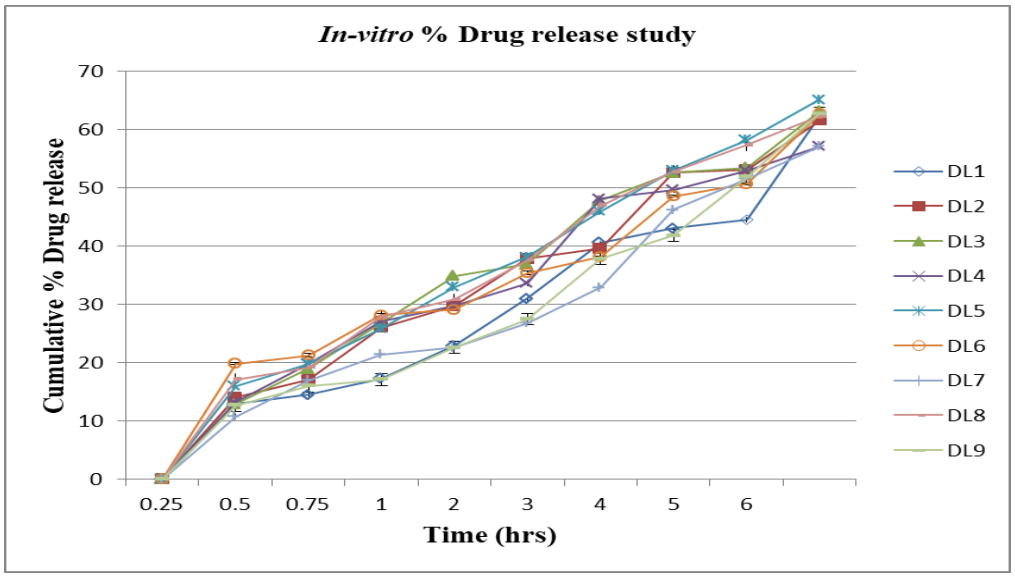


**Figure 2:** *In vitro* drug release study of core alginate beads

### *In Vitro* drug release study from coted alginate beads

For an in vitro drug release investigation, coated alginate beads (E1, E2, and E3) were prepared using a technique akin to that of core beads. The experiment was conducted in a pH progression medium at 37°C ± 0.5°C. Every dissolution investigation was carried out in triplicate.

## Results And Discussion

Based on the quality of the beads and their entrapment, the effect of stirring speed and time to react were optimized. It was assessed by measuring the quality of the beads, the entrapment efficiency at various speeds, and the reaction time. It found that suitable shape, uniformity, and optimum entrapment efficiency were formed at 1000 rpm for 20 minutes.

### Entrapment efficiency

Different medication to polymer and polymer to CaCl2 ratios were tested in different batches. Using the spectroscopic strategy, prepared batches were optimized for drug estimation (5-fluorouracil + Metformin HCl). Entrapment efficiency increased when the ratio of calcium chloride to polymer and the medication to polymer increased. The range of drug entrapment efficiency for the different formulations was 33.34±0.05% to 86.39±0.13%. The entrapment efficiency of the improved batch (DL5) was determined to be 86.39±0.13%.

***In vitro* drug release**

900 milliliters of pH 7.4 dissolution medium were used in the drug release investigation of coated alginate microbeads, which was conducted at 37 ± 0.5 ºC and 100 rpm using a dissolution device.

100 mg of microbead-equivalent samples were added to the dissolving medium. At prearranged intervals, 5 ml of the sample solution was taken out, filtered using Whatman filter paper, adequately diluted, and subjected to spectrophotometric analysis using a UV-Visible spectrophotometer (LABMAN Scientific Instruments) set to detect drugs (MF HCl + 5-FU). As soon as the test sample was removed, an equal volume of new dissolves medium was added. Zero order (Figure 2.14) was determined to be the most fitting explanation for the in vitro drug release from the improved DL5, with the plots exhibiting the highest linearity (R2 = 0.9873), followed by Higuchi's equation.(Figure 2.12) ($R^2$ = 0.9612) and first order (Figure 2.13) ($R^2$ = 0.6433). The corresponding plot (log % cumulative drug release vs log time) for the Korsmeyer-Peppas equation indicated good linearity (Figure 2.15) ($R^2$ = 0.7094).

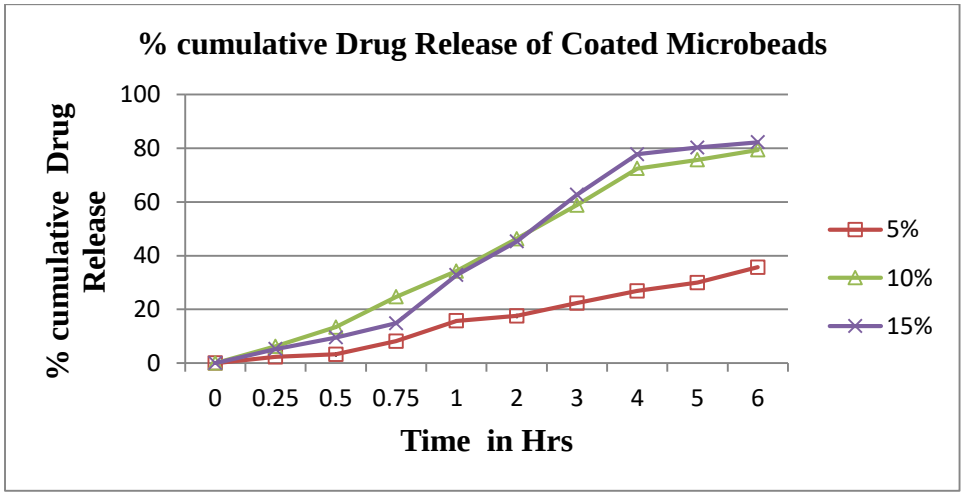


**Figure 3:** *In vitro* drug release study of coated alginate beads

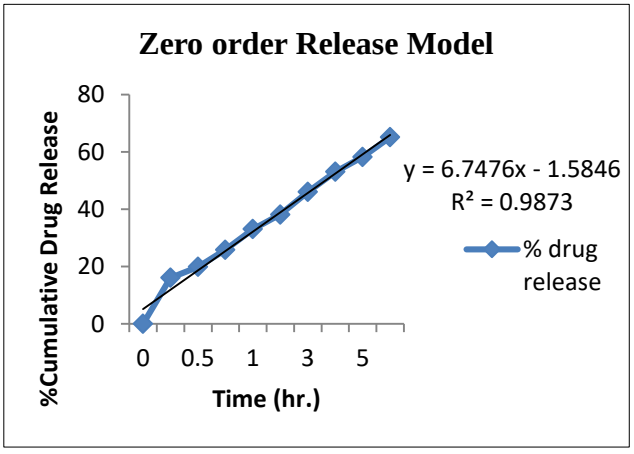


**Figure 4: Zero order kinetics**

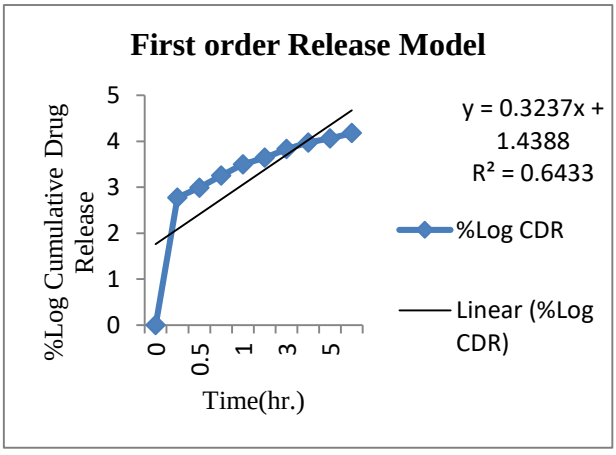


**Fig. 5: First order kinetics**

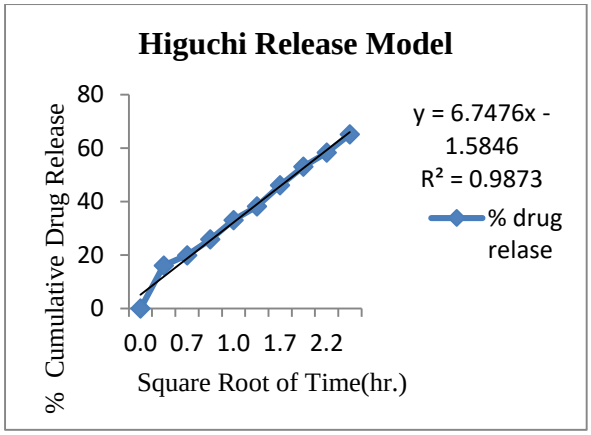


**Fig. 6: Higuchi kinetics**

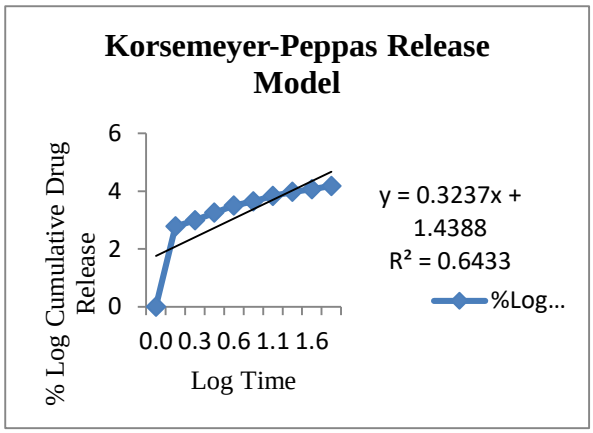


**Fig. 7: KorsmeyerPeppas model**

## Conclusion

In conclusion, the optimized batch of alginate microbeads showed better size, entrapment efficiency and cumulative drug release which makes the formulation more preferable. Thus the sodium alginate microbeads after enteric coating with Eudragit S-100 can be used effectively for the delivery of Metformin hydrochloride and 5- fluorouracil for colon targeting.

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