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# MICROSPHERES OF 5-FLUOROURACIL FOR COLON TARGETING

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**Abstract:**

The purpose of this investigation was to prepare and evaluate the colon-specific microspheres of 5-fluorouracil for the treatment of colon cancer. Dextran microspheres were prepared by emulsion dehydration method using different ratios of drug and polymer (1:2 to 1:4), emulsifier concentrations (1%-3% wt/vol) and stirring speeds (1000-3000 rpm). Eudragit-coating of dextran microspheres was performed by oil-in-oil solvent evaporation method. Dextran microspheres and Eudragit-coated dextran microspheres were evaluated for surface morphology, particle size and size distribution, swellability, percentage drug entrapment, and in vitro drug release in simulated gastrointestinal fluids (SGF). The in vitro drug release studies of the formulations were also performed in simulated colonic fluid in the presence of 2% rat cecal content. The release profile of 5-FU from Eudragit-coated dextran microspheres was pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7.5. It is concluded from the present investigation that Eudragit-coated dextran microspheres are promising controlled release carriers for colon-targeted delivery of 5-FU.

**Keywords:** 5-Fluorouracil, dextran, microspheres, colon targeting.

## Introduction:

Colorectal cancer is the second leading cause of cancer deaths in the United States, and more than 66,000 cases of colon cancer are reported to occur in the Indian subcontinent every year. Conventional cancer chemotherapy is not very effective for treatment of colorectal cancer, as the drug molecule does not reach the target site at therapeutic concentration. Therefore effective treatment of colon cancer by conventional therapy requires

relatively large doses to compensate for drug loss during passage through the upper gastrointestinal (GI) tract. These large doses may be associated with undue side effects. This can be overcome by site-specific delivery of the drug molecule to colon[1]. The approaches used in achieving colonic delivery of drugs include the use of prodrugs[2, 3], pH-sensitive polymer coating[4, 5], and time-dependent formulations[6, 7], In addition, the use of biodegradable polymers such as azo-polymer and polysaccharide (e.g. pectin and dextran) for colon targeting are also reported in the literature[8, 9], Among the different approaches to achieve colon-selective drug delivery, the use of polymers, specifically biodegraded by colonic bacteria, holds great promise. The pH-dependent systems exploit the generally accepted view that pH of the human GI tract increases progressively from the stomach (pH 2-3) to the small intestine (pH 6.5-7.0) to the colon (7.0-8.0)[10]. Most commonly used pH-dependent coating polymers are methacrylic acid copolymer (i.e. Eudragit L100-55, Eudragit L100 and Eudragit S100), which dissolve at pH 5.5, 6.0, and 7.0, respectively.

Since its introduction by Heidelberger et al in 1957[11], 5-fluorouracil (5-FU) has been the only agent with clinical activity against colorectal cancer. It is also used for other types of malignancies, such as those of the breast, head, and neck. Given its structural resemblance to natural pyrimidines, 5-FU interferes with nucleic acid synthesis, inhibits DNA synthesis, and eventually halts cell growth[12, 13]. Because of its incomplete and erratic oral bioavailability, 5-FU is commonly administered intravenously[14]. However, patients prefer oral rather than intravenous therapy[15], with oral treatment potentially more convenient and less costly. The present regimens include an intravenous bolus or continuous infusion of 5-FU modulated with folinic acid (leucovorin)[16, 17]. On intravenous administration, 5-FU produces severe toxic effects of gastrointestinal, hematological, neural, cardiac and dermatological origin[18]. Site-specific delivery of 5-FU may reduce the systemic side effects and provide effective and safe therapy of colorectal cancer that may reduce the dose and duration of therapy when compared with the conventional treatment.

Dextran is a complex, branched glucan (polysaccharide made of many glucose molecules) composed of chains of varying lengths (from 10 to 150 kilodaltons). The straight chain consists of α-1,6 glycosidic linkages between glucose molecules, while branches begin from α-1,3 linkages. Dextran is synthesized from sucrose by certain lactic-acid bacteria, the best-known being *Leuconostoc mesenteroides* and *Streptococcus mutans*[19].

Hydrophilic polysaccharide drug carrier systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance[20-22]. The ability of the hydrophilic polymer carriers to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross-linking makes them particularly suitable for controlled-release applications[21]. These carriers can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes. Recently, many controlled release formulations based on hydrophilic polymer matrices have been developed[22-23].

The objective of the present investigation was to design a multiparticulate delivery system for site-specific delivery of 5-fluorouracil (FU) using natural polysaccharides (dextran) and pH-sensitive polymer (Eudragit S100) for the treatment of colon cancer. This system is anticipated to protect the drug loss in the upper GI tract, which results from the inherent property of Eudragit S100 (ES), and deliver FU in the colon only. The use of enteric polymers (ES) as protective coating on the microspheres makes them able to release the drug at the particular pH of colonic fluid. A combined mechanism of release is proposed, which combines specific biodegradability of polymer and pH-dependent drug release from the coated microspheres.

**Materials and Methods:**

**Materials**

The 5-FU was a gift from Dabur Research Foundation (Ghaziabad, India). Dextran (Sigma-Aldrich) and Eudragit S-100 (Rohm, GmbH, Germany) was obtained from Alembic Ltd (Gujarat, India). Epichlorohydrin, castor oil and Magnesium Chloride were procured from Himedia, India. Isopropyl alcohol, HPLC grade methanol and water were obtained from Spectrochem, India. Hydrochloric Acid obtained from Qualigens Fine chemicals, India. All other reagents were of analytical grade or better.

**Methods**

**Preparation of Eudragit-coated dextran microspheres:**

Dextran microspheres were prepared by using a combined method involving water-in-oil (w/o) emulsification and cross linking method[24]. Dextran (3 g) was dissolved in deionized water (30 ml) and 5 ml of MgCl2 (5% w/v) solution was added. Drug (1 g) was added to the dextran solution through syringe into a continuous oil phase

consisting of 300 ml of castor oil, 100 ml of isopropanol and 2% (w/v) span 80 in a 1 liter beaker at 50±1°C. The dispersion was stirred using a stainless steel stirrer at 2000 rpm for 10 min and thereafter 15 ml of epichlorohydrin was added to the beaker under stirring. The cross linking reaction was allowed to proceed for a total time of 3 hr. Hardened microspheres were filtered, washed repeatedly with isopropanol and water to remove castor oil and unreacted epichlorohydrin. The microspheres were dried under vacuum at 40°C overnight and kept in a desiccator until further use. Similarly dextran microspheres were prepared by taking polymer: drug in a ratio of 1:2, 1:3 and 1:4, stirring rate 1000 rpm, 2000 rpm and 3000 rpm and emulsifier (span 80) concentration 1%, 2% and 3%.

Eudragit coating of dextran microspheres was performed using oil-in-oil (o/o) solvent evaporation method[25]. 250 mg of Eudragit S-100 was dissolved in 10 ml of organic solvent (2:1, ethanol: acetone). 50 mg of dextran microspheres were added to the above solution. This organic phase was then poured into 100 ml of light liquid paraffin containing 2% w/v span 80. The system was maintained under agitation speed of 1000 rpm at 40°C for 3 hr to allow evaporation of the solvent. Finally the coated microspheres were washed with n-hexane and dried overnight in the vacuum desiccator.

**Surface morphology:**

The shape and surface morphology of dextran microspheres and Eudragit coated dextran microspheres were investigated using scanning electron microscopy (SEM). The samples for SEM study were prepared by lightly sprinkling the formulation on a double-adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of ~300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope.

**Particle size and particle size distribution:**

The particle size and particle size distribution was measured in particle size analyzer (Malvern, USA). Microspheres were suspended in distilled water and the particle size and size distribution were determined using the software provided by the manufacturer.

**Swell ability:** A known weight (100 mg) of various FU-loaded dextran microspheres and Eudragit-coated dextran microspheres were placed in enzyme-free simulated intestinal fluid (SIF, KH2PO4/NaOH buffer, pH 7.4) and allowed to swell for the required period of time at 37ºC ± 0.5ºC in the dissolution apparatus (United States Pharmacopoeia [USP] XXIII, model DT-06, Erweka, Germany). The microspheres were periodically removed and blotted with filter paper; then their change in weight (after correcting for drug loss) was measured until attainment of equilibrium. The swelling ratio (SR) was then calculated using the following formula:

$$SR = \frac{W_g - W_o}{W_o}$$

Where SR indicates swelling ratio, $w_o$ is initial weight of microspheres and $w_g$ is final weight of microspheres.

**Percentage drug entrapment:**

The percentage of drug entrapped in the microspheres was determined by digesting the microspheres (50 mg) in sufficient saline phosphate buffer pH 7.4 for 48 hrs. It was centrifuged at 3000 rpm for 30 min and the supernatant were analyzed spectrophotometrically at 266.6 nm. The percentage drug entrapment of coated dextran microspheres was determined in the same manner.

$$\text{Percentage drug entrapment} = \left( \frac{\%\, Drug loading}{\%\, Theoretical loading} \right) \text{X } 100$$

$$\%\text{ Drug loading} = \left( \frac{Weight of drug in microspheres}{Weight of microspheres} \right) \text{X } 100$$

**In-vitro drug release:**

An accurately weighed amount of microspheres, equivalent to 100 mg of 5-FU, was added to 900 ml of dissolution medium and the release of 5-FU from microspheres was investigated using rotating paddle dissolution test apparatus (Electrolab, India) at 100 rpm and 37±0.5°C. The simulation of gastrointestinal transit conditions was achieved by altering the pH of dissolution medium. Initially it was kept at pH 1.2 for 2 hrs with 0.1N HCl. Then $KH_2PO_4$ (1.7 g) and $Na_2HPO_4 .2H_2O$ (2.225 g) were added to the dissolution medium adjusting the pH 4.5 for 3rd and 4th hr and adjusted with NaOH to 6.8 for 5th hr. After 5th hr, the pH of the dissolution medium was adjusted to 7.5 and maintained upto 8 hr. The final volume in all case was kept 900 ml. The

samples were withdrawn from dissolution medium at various time intervals using a pipette fitted with micro-filter at its tips and analyzed spectrophotometrically at 266.6 nm.

Similarly In-vitro study was performed in simulated colonic fluid (pH 7.5 media) with 2% rat cecal matter. Rat cecal content was prepared by the method reported by Van den Mooter et al[26]. Four albino rats, (Sprague-Dawley strain) of uniform body weight (150-200 g) with no prior drug treatment, were used for all the present in vivo studies; they were weighed, maintained on normal diet, and administered 1 mL of 2% dispersion of dextran in water, and this treatment was continued for 7 days for polymer induction to animals. Thirty minutes before starting the study, each rat was humanely killed and the abdomen was opened. The cecal were traced, legated at both ends, dissected, and immediately transferred into phosphate buffered saline (PBS) pH 6.8, which was previously bubbled with $CO_2$. The cecal bag was opened; the contents were weighed, homogenized, and then suspended in PBS (pH 7.5) to give the desired concentration (2%) of cecal content, which was used as simulated colonic fluid. The suspension was filtered through cotton wool and ultrasonicated for 10 minutes in an ice bath at 40% voltage frequency using a probe sonicator at 4°C to disrupt the bacterial cells. After sonication, the mixture was centrifuged (Remi) at 2000 rpm for 20 minutes. Microspheres (100 mg) were placed in 200 mL of dissolution media (PBS, pH 7.5) containing 2% wt/vol rat cecal content. The experiment was performed with continuous $CO_2$ supply into the dissolution medium. At different time intervals, the samples were withdrawn and replaced with fresh PBS. The experiment was continued up to 24 hours. The withdrawn samples were pipetted into a series of 10-mL volumetric flasks, and volumes were made up to the mark with PBS and centrifuged. The supernatant was filtered through 0.45-μm membrane filter (Millipore) and the filtrate analyzed for FU content at 266.6 nm using HPLC method. All the experiments were performed in triplicate.

**Statistical Analysis:**

The mean percentage of FU released in SGF (at different pH) from both dextran microspheres and Eudragit-coated dextran microspheres was prepared by using various drug: polymer ratios and compared. The Student t test was used to find the statistical significance. A value of P less than 0.05 was considered statistically significant.

**Result and Discussions:**

**Preparation of Eudragit-coated Dextran Microspheres:**

**Table-1: Different formulation approaches.**

| **Formulation code** | FA1 | FA2 | FA3 | FB 1 | FB2 | FB 3 | FC1 | FC2 | FC3 |
|---|---|---|---|---|---|---|---|---|---|
| **Variables** | Drug : Polymer ratio | | | Emulsifier (SPAN 80) concentration | | | Stirring rate | | |
| **Values** | 1:2 | 1:3 | 1:4 | 1% w/v | 2% w/v | 3% w/v | 1000 rpm | 2000 rpm | 3000 rpm |

Dextran microspheres of FU were successfully prepared by a combined method involving water-in-oil (w/o) emulsification and crosslinking method. Uniform, surface crosslinked spherical microspheres were obtained as shown in scanning electron photomicrographs (Figure-1). The dextran microspheres were coated with Eudragit S-100 by oil-in-oil solvent evaporation method, using coat: core ratio 5:1. The coated microspheres were found to be of spherical shape as observed in SEM photomicrographs (Figure-2). The method was optimized using different ratios of drug and polymer, stirring speeds and emulsifier concentrations (details of the formulations given in Table-1) to produce microspheres of proper size and narrow size distribution, high drug loading efficiency and controlled drug release at the colonic pH. The details are discussed in following respective sub-headings.

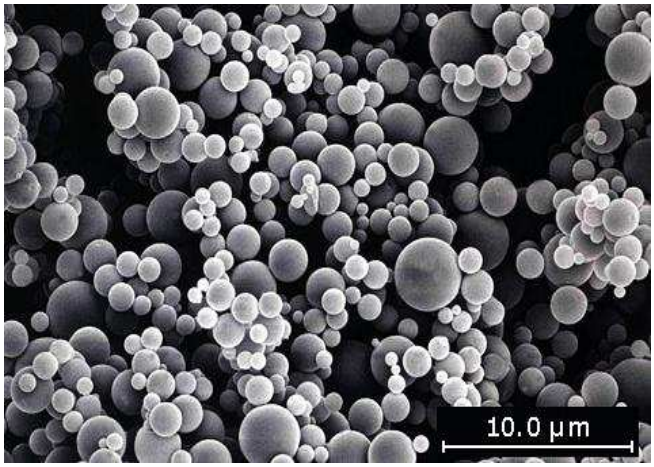


**Figure 1: SEM photomicrograph of uncoated microspheres.**

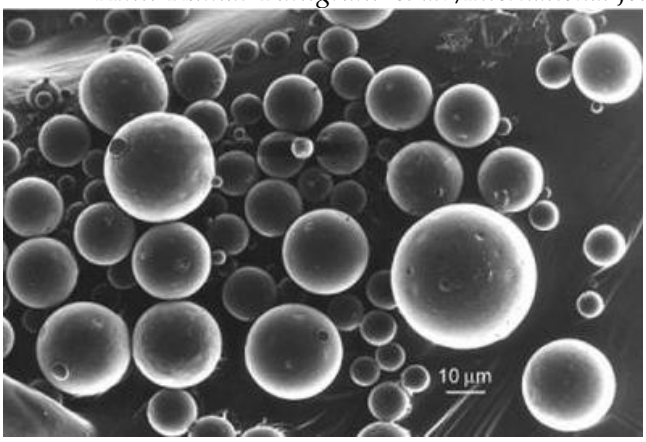


**Figure 2: SEM photomicrograph of Eudragit coated microspheres.**

**Particle size and particle size distribution:**

The particle size distributions of the microspheres of different formulations are given in the Table-2.

**Table-2: Particle size of microspheres prepared by different formulation approaches.**

| Sr. No. | Formulation code | Mean diameter of microspheres (in µm) |
|---|---|---|
| 1 | FA1 | 9.25±0.35 |
| 2 | FA2 | 13.17±0.22 |
| 3 | FA3 | 23.49±0.73 |
| 4 | FB1 | 21.23±0.51 |
| 5 | FB2 | 15.47±0.91 |
| 6 | FB3 | 7.65±0.39 |
| 7 | FC1 | 24.25±0.62 |
| 8 | FC2 | 19.78±0.87 |
| 9 | FC3 | 10.31±0.28 |

The particle size of the microspheres increased from 9.25±0.35 µm to 23.49±0.73 µm as the drug: polymer ratio was increased from 1:2 to 1:4.The increase in size of the microspheres may be attributed to an increase in viscosity of polymer solution with increasing concentration, which resulted in the formation of larger emulsion droplets and finally greater size of microspheres.

As the concentration of the emulsifying agent (Span 80) was increased from 1% to 3% w/v, the particle size of the microspheres was decreased from 21.23±0.51 µm to 7.65±0.39 µm. This may be due to the decrease of interfacial energy between the two droplets and the presence of emulsifying agent in the crosslinking medium, allowing the stabilization of the preformed microspheres to maintain their size until completion of the crosslinking reaction.

As the stirring rate was increased from 1000 rpm to 3000 rpm, the particle size of the microspheres was decreased from 24.25±0.62 µm to 10.31±0.28 µm. This may be due to formation of small size droplets on higher stirring rate.

**Swellability:**

The swellability of different formulations performed in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.5) at 37±0.5°C are given in the Table-3.

**Table-3: Swelling ratio of microspheres prepared by different formulation approaches.**

| Sr. No. | Formulation code | % Swelling ratio | |
|---|---|---|---|
| | | SGF | SIF |
| 1 | FA1 | 1.71±0.13 | 1.87±0.06 |
| 2 | FA2 | 2.74±0.04 | 2.78±0.10 |
| 3 | FA3 | 3.62±0.09 | 3.30±0.01 |
| 4 | FB1 | 3.14±0.15 | 2.98±0.08 |
| 5 | FB2 | 3.37±0.11 | 3.35±0.07 |
| 6 | FB3 | 3.73±0.09 | 3.45±0.09 |
| 7 | FC1 | 2.98±0.08 | 2.36±0.07 |
| 8 | FC2 | 3.52±0.05 | 3.17±0.06 |
| 9 | FC3 | 4.11±0.07 | 3.98±0.11 |

The result indicates that swelling ratio was increased with increase in drug: polymer ratio (from 1:2 to 1:4). A possible reason for this result may be due to the denser crosslink between the dextran molecules, producing more

packed structures in the formulations having more concentration of polymer (drug: polymer ratio less). Such a structure can be characterized by a lower and slower penetration of the solvent through the polymer chain.

**Percentage drug entrapment:**

The percentage drug entrapments of different formulations are given in the Table-4.

**Table-4: Percentage drug entrapment of microspheres prepared by different formulation approaches.**

| Sr. No. | Formulation code | % Drug entrapment |
|---|---|---|
| 1 | FA1 | 76.32±1.45 |
| 2 | FA2 | 81.29±1.17 |
| 3 | FA3 | 86.78±2.71 |
| 4 | FB1 | 71.14±0.81 |
| 5 | FB2 | 74.54±2.23 |
| 6 | FB3 | 76.14±1.17 |
| 7 | FC1 | 85.34±0.78 |
| 8 | FC2 | 79.55±0.26 |
| 9 | FC3 | 75.21±1.08 |

The result shows that, on increasing drug: polymer ratio from 1:2 to 1:4, the entrapment efficiency was increased from 76.32±1.45 % to 86.78±2.71 %.

As the stirring rate was increased from 1000 rpm to 3000 rpm, the entrapment efficiency was decreased from 85.34±0.78 % to 75.21±1.08 %. This may be due to formation of small size microspheres with increased surface area. Higher stirring rate enhanced the diffusion of drug from such microspheres, resulting in the loss of drug from microspheres with a consequent lowering in the entrapment efficiency.

However the results showed that the change in the concentration of the emulsifying agent (span 80) had no significant effect in entrapment efficiency of the microspheres.

**In-vitro drug release:** In-vitro drug release was carried out for uncoated and Eudragit coated microspheres in pH progression medium and for Eudragit coated microspheres in simulated colonic fluid (pH 7.5 media) with 2%

rat cecal matter and without 2% rat cecal matter. The in-vitro release from uncoated microspheres in pH progression media is represented in figure 3.

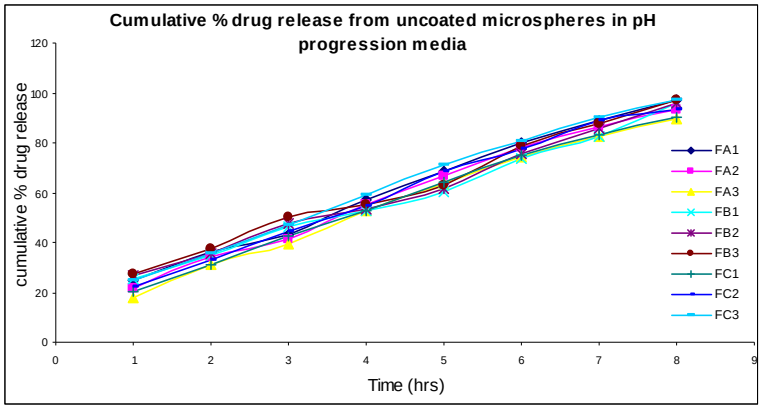


**Figure 3: Drug release from uncoated microspheres in pH progression media.**

The result indicates that, when drug: polymer ratio was increased in the preparation of crosslinked dextran microspheres, the in-vitro drug release from microspheres was decreased which may be due to increased path length for diffusion of drug molecule from microspheres. Drug release after 8 hrs was found to be 99.25±1.75% in case of microspheres prepared using 1:2 drug:polymer ratio, while it was 89.33±1.26% for microspheres prepared with 1:4 drug:polymer ratio.

Microspheres which were prepared using 1% w/v of emulsifying concentration, released 95.56±1.11% of drug after 8 hrs while those prepared using 2% and 3% w/v of emulsifying agent released 96.15±2.01% and 97.23±1.71% of drug after the same period. The result revealed that the concentration of emulsifying agent had no significant effect on drug release of the microspheres.

Microspheres which were prepared at stirring speed of 3000 rpm, released 97.37±2.15% of drug after 8hrs, while those prepared at 2000 rpm released 93.34±1.18% of drug after 8 hrs. The size of the microspheres prepared at 1000 rpm was large and hence effective surface area was less in comparison to those prepared at 2000 rpm and 3000 rpm, which could probably be the reason for the lesser amount of drug release (90.15±2.56% after 8 hr) from microspheres prepared at 1000 rpm.

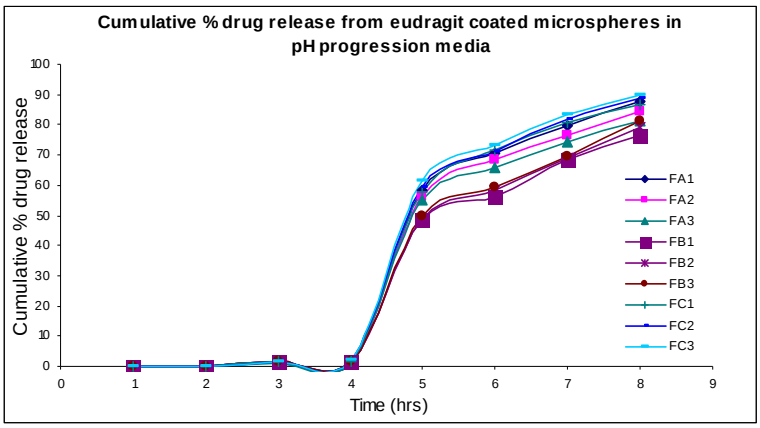


**Figure 4: Drug release from Eudragit coated microspheres in pH progression media.**

The cumulative percentage drug release from Eudragit-coated dextran microspheres showed the desired rate, as there was no measurable drug release observed up to 2 hours in SGF (pH 1.2), while at pH 4.5, the drug release was quite insignificant (<2%) up to 4 hours. Drug release from Eudragit-coated dextran microspheres in pH progression media is represented in figure 4.

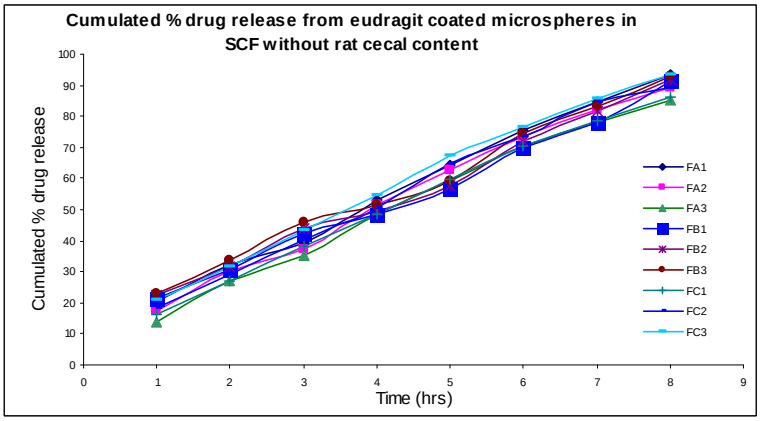


**Figure 5: drug release from Eudragit coated microspheres in simulated colonic Fluid (pH 7.5) without rat cecal content.**

For comparison, the in-vitro drug release study of the Eudragit coated microspheres was performed in simulated colonic fluid (pH 7.5) with and without rat cecal contents. The drug release from Eudragit coated microspheres in simulated colonic fluid (pH 7.5) with and without rat cecal contents is represented in figure 5 and figure 6 respectively.

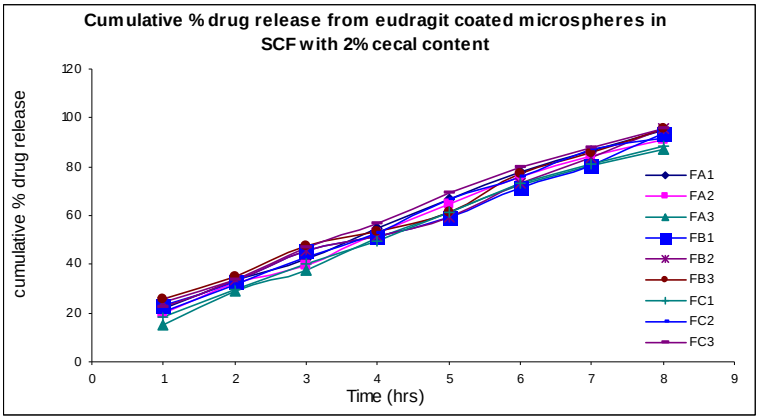


**Figure 6: drug release from Eudragit coated microspheres in simulated colonic Fluid (pH 7.5) with rat cecal content.**

The in vitro release of drug from Eudragit-coated dextran microspheres in presence of 2% rat cecal content in simulated colonic fluid showed faster drug release at different time periods when compared with release study without rat cecal content. This finding could be attributed to the various anaerobic bacteria present in cecal content and responsible for digestion/degradation of dextran in order to release drug from microspheres.

**Conclusion:**

The designed site-specific delivery of 5-FU from the system may reduce the side effects of the drug caused by its absorption from the upper part of the GI tract when given in conventional dosage forms such as tablets and capsules. The experimental results demonstrated that Eudragit-coated dextran microspheres have the potential to be used as a drug carrier for an effective colon-targeted delivery system.

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