Formulation and Evaluation of Coated Microspheres for Colon Targeting

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ABSTRACT

The purpose of this research was to formulate and evaluate coated microspheres of 5-Fluorouracil (FU) for colon targeting. Chitosan is used as polymer, which is a biodegradable polymer and undergo enzymatic degradation in the colon, so it is used as carrier to deliver the drug in the colon. Chitosan microspheres were prepared by emulsion-dehydration method using different ratios of FU and chitosan (1:2 to 1:6), stirring speed (500-2000rpm) and emulsifier concentrations (0.75% to 1.75%w/v). Eudragit S100 coating of chitosan microspheres was performed by oil-in-oil solvent evaporation method using coat: core ratio (5:1). The cumulative percentage drug release after 12 hrs was found to be in the range of 82.39 to 93.67% for F1 to F5 respectively. Among the formulations F2 was found to be the best formulation as it released 5-Fluorouracil 93.67%. The results showed that as the amount of the polymer increased the extent of drug release decreased. It was concluded from the present investigation that Eudragit coated chitosan microspheres are promising controlled release carriers for colon targeted delivery of 5-Fluorouracil.

INTRODUCTION

The major function of the colon is the consolidation of the intestinal contents into the faeces by the absorption of water and electrolytes and to store the faeces until excretion. The absorptive capacity is very high, each day about 2000 ml fluid enters the colon through the ileo-cecal valve from which more than 90% of the fluid is absorbed.

The colon consists of ascending, transverse, descending and sigmoid colon (Alagasundaram et al., 2009). The colon has the pH 6.4-7.6. Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea, and colon cancer. The system designed for the delivery of drug in the colon may be single or multiple unit dosage form which is based on the core being coated with one or more successive layers (Asghar and Chandran, 2006).

Multi particulate approaches tried for colonic delivery includes formulations in the form of pellets, granules, micro particles and nano particles. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targetting showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GIT easily, leading to less inter and intra subject variability. Moreover, multi particulate systems tend to be more uniformly dispersed in the GIT and also ensure more uniform drug absorption (Haris et al., 2006). The methods used for drug targeting into colon are: drug release based on variation on pH, drug release based on gastrointestinal transit, drug release based on the presence of colonic microflora and pressure controlled drug delivery systems (Kaushik et al., 2010, Kumar et al., 2009). Cancer prevention is defined as active measures to decrease the risk of cancer. In the general population NSAIDs reduce the risk of colorectal cancer however due to the cardiovascular and gastrointestinal side effects they cause overall harm when used for prevention. Many management options for cancer include surgery, chemotherapy, radiation therapy, and palliative care.
Colorectal cancer is the cancer that starts in the colon or the rectum. These cancers can also be referred to separately as colon cancer or rectal cancer, depending on where they start. The types of colon cancer include adenocarcinoma, carcinoid tumors, gastrointestinal stromal tumors, lymphomas and sarcomas. Anticancer drugs are the drugs that prevent or inhibit the maturation and proliferation of neoplasms. Antineoplastic agents travel the body and destroy cancer cells. General toxicities associated with these drugs are bone marrow depression, lymphocytopenia, GIT stomatitis, diarrhoea, nausea, vomiting, hyper ureaemia and hair loss etc (Lorenzo et al., 1998, Maestrelli et al., 2008). Microspheres are characteristically free flowing powders consisting of proteins or polymers which are biodegradable in nature and ideally having a particle size less than 200µm and are widely used as drug carriers for controlled release. The various method of preparation includes single emulsion, double emulsion, polymerization, spray drying and spray congealing, solvent extraction, phase separation and co acervation techniques (Mooter and Kinget, 1995, Nayak et al., 2011). In the present study we have targeted colon using coated microspheres, which can considerably reduce the side effects of the drug 5-Fluorouracil.

MATERIALS AND METHODS

Materials

5-Fluorouracil and Span 80 were purchased from Loba chemie, Mumbai. Chitosan was purchased from Indian sea foods, Cochin, Eudragit S100 was procured from Yarrow chemical Products, Mumbai, Iso octane and Acetone were procured from Labort fine Chem Pvt Ltd, Surat. All other chemicals and reagents used were of laboratory or analytical grade.

Methods

Preparation of chitosan microspheres

Chitosan microspheres were prepared by emulsion-dehydration method. Microspheres were prepared by using drug: polymer ratio 1:3, stirring speed 1000 rpm and 1.25%w/v of emulsifying agent. Chitosan and 5-Fluorouracil were dissolved in 20 ml distilled water and stirred to solubilize completely. This drug-polymer solution was dispersed in 50 ml isoctane containing 1.25%w/v span 80 and stirred at 1000 rpm to prepare water in oil emulsion. This solution was rapidly cooled to 15°C and then 50 ml acetone was added in order to dehydrate the chitosan droplets. This system was maintained under mechanical agitation using propeller stirrer at 1000 rpm at 25°C for 30 minutes to allow the complete solvent evaporation. These microspheres were freeze-dried over night and kept in an airtight container for further studies (Paharia et al., 2007, Prasad et al., 1995).

Coating of chitosan microspheres

Chitosan microspheres were coated with ES 100 using oil-in-oil solvent evaporation method. Chitosan microspheres(50 mg) were dispersed in 10 ml of coating solution prepared by dissolution of 500 mg of ES in ethanol: acetone (2:1) to give 5:1 (coat: core ratio). This organic phase was then poured in 70 ml of light liquid paraffin containing 1 %w/v span 80. The system was maintained under agitation speed of 1000 rpm at room temperature for 3 hours to allow the evaporation of solvent. Finally the coated microspheres were filtered washed with n-hexane, and freeze-dried overnight.

Preformation studies

Solubility analysis

The solubility studies were performed in phosphate buffer solution, pH 7.4, by adding excess amount of drug in each case and keeping the excess amount of drug containing phosphate buffer on a rotary shaker for 24 hrs. After 24 hrs, solutions were analyzed spectrophotometrically at 266nm, which was the absorption maxima determined earlier and drug concentrations were calculated.

Drug – Excipient Interaction Study

The infrared (IR) spectra were recorded using an FTIR spectrophotometer by the KBr pellet method in the wavelength region between 7800 and 350 cm⁻¹. The spectra obtained for 5-Fluorouracil and physical mixtures of 5-Fluorouracil with other excipients were compared to check compatibility of drug with excipients.

Evaluation of coated microspheres

Percentage Yield

Microspheres recovered at the end of the preparation were weighed and the yield was calculated as % of total theoretical weight of the material taken for the preparation. The yield of the microspheres was calculated as below.

\[
\% \text{ Yield} = \frac{\text{Actual weight of the product} \times 100}{\text{Total weight of excipient and drug}}
\]

Particle Size Analysis

Particle size analysis of the coated chitosan microspheres was performed by optical microscopy using a compound microscope. A small amount of dry microspheres were suspended in purified water. The suspension was sonicated for 5 sec. A small drop of suspension, thus obtained, was placed on a clean glass slide. The slide containing chitosan microspheres was mounted on the stage of the microscope and diameter of at least 500 particles was measured using calibrated ocular micrometer.

Surface morphology (Ramteke et al., 2010)

The shape and surface morphology of chitosan microspheres and Eudragit coated chitosan microspheres were investigated using Scanning electron microscopy (SEM). The samples for SEM study were prepared by lightly sprinkling the formulation on a double-adhesion tape stuck to an aluminium stub. The stubs were then coated with gold to a thickness of 300 A° under an argon atmosphere using a gold sputter module in a high-vacuume evaporator. The coated samples were then randomly
Scanned and photo micrographs were taken with a scanning electron microscope.

Swellability/ Degree of swelling (Vyas and Khar, 2002)

A known weight (100 mg) of Eudragit-coated chitosan microspheres of 5-Fluorouracil were placed in enzyme-free simulated intestinal fluid (SIF, pH 7.4) and allowed to swell for the required period of time at 37°C±0.5°C in the dissolution apparatus. The microspheres were periodically removed and blotted with filter paper, then their change in weight (after correcting for drug loss) was measured until equilibrium attained. The swelling ratio was then calculated using the formula,

$$\text{SR} = \frac{W_g - W_0}{W_0}$$

Where SR - Swelling ratio
W₀ - Initial weight of microspheres
Wₙ - Final weight of microspheres.

Drug content analysis

Drug loaded microspheres (100 mg) were powdered and suspended in 100 ml methanol. The resultant dispersion was kept for 20 minutes for complete mixing with continuous agitation and filtered through a 0.45 µm membrane filter. The drug content was determined spectrophotometrically at 266nm using regression equation derived from the standard graph.

Drug content $\text{= \frac{\text{absorbance x dilution factor}}{\text{Slope}}} = \text{concentration} \times \text{dilution factor}$

% Drug content = Drug content $\times 100$ label claim

Drug Entrapment Efficiency (Zankhana et al., 2010)

Weighed amount of microspheres (25mg) with phosphate buffer pH 7.4 (10 ml) was added in a vial. The solution was stirred vigorously for 24 hours with mechanical stirrer. Supernatant was collected by centrifugation and drug content in supernatant was determined using UV spectrophotometer at wavelength 266nm. Efficiency of drug entrapment calculated by the following formula.

% Drug Entrapment = \frac{\text{Practical content}}{\text{Theoretical content}} \times 100

In vitro drug release study

In vitro release study of microspheres was performed in pH progression medium at 37°C ±0.5°C. The drug dissolution test of microspheres was performed by the Paddle method. Microspheres (100mg) were weighed accurately and filled into tea bags. The tea bags were tied using thread with paddle and loaded into the basket of the dissolution apparatus. The content was rotated at 100 rpm. The simulation of GI transit condition was achieved by altering the pH of the dissolution medium at different time intervals. The pH of the dissolution medium was kept 1.2 for 2 hours using 0.1 N Hcl. The release study was observed by adjusting the pH to 7.4 and the release rate study was continued for an additional 3 hours. After 5th hour the pH of the dissolution medium was adjusted to 6.8 and maintained up to 12 hours. The final volume in all case was kept at 900 ml. The samples were withdrawn from the dissolution medium at various time intervals. The rate of drug release was analyzed by UV spectrophotometer (Shimadzu 1800).

In vitro drug release kinetics

In order to describe the kinetics of the release process of drug in the different formulations, models were fitted to the dissolution data of optimized formulations using linear regression analysis.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly assuming that area does not change and no equilibrium conditions followed can be represented by the following equation.

$$Q_t = Q_0 + Kt$$

Where,

- $Q_0$ is the initial amount of drug in solution
- $K$ is the zero order release constant

First order kinetics

The application of this model to drug dissolution studies used to describe absorption and / or elimination of drugs. To study the first order release rate kinetics, the release rate data were fitted to the following equation.

$$\log Q_t = \log Q_0 + \frac{K}{2.303} t$$

Where,

- $Q_t$ is the amount of drug released in the time $t$
- $Q_0$ is the initial amount of drug in the solution
- $K$ is the first order release constant

Higuchi model

Higuchi developed several theoretical model to study the release of water soluble and low soluble drugs incorporated in semi solid and /or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The equation is

$$Q_t = \frac{K_{\text{H}} t^{\frac{1}{2}}}{Q_r}$$

Where,

- $Q_t$ is the amount of drug released in time $t$
- $Q_r$ is the initial amount of drug
- $K_{\text{H}}$ is the Higuchi dissolution constant

Korsmeyer and Peppas Model

This model used to analyze the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or more than one type of release phenomena could be involved. The equation is

$$\frac{M_t}{M_{\infty}} = Kt^n$$

Where,

- $M_t/M_{\infty}$ is the fraction of drug release
- $K$ is the release constant
- $t$ is the release time
- $n$ is the diffusion exponent for drug release that is depend on the shape of matrix dosage form.
The results obtained from *in vitro* drug release study were plotted adopting four different mathematical models of data treatment as follows:

1. Cumulative percent drug release Vs Time (Zero order rate kinetics)
2. Log cumulative percent drug retained Vs Time (First order rate kinetics)
3. Cumulative percent drug release Vs square root of Time (Higuchi model)
4. Log cumulative percent drug release Vs Time (Korsmeyer and Peppas Model)

**Stability study**

In the present work, accelerated stability study was carried out for the optimized formulation F2 i.e., at 40±2°C/75±5% RH for 3 months.

**Statistical analysis of data**

Data were expressed as mean±S.D. Statistical evaluation was performed by one-way analysis of variance (ANOVA) at a significance level of p<0.05 by Dunnett’s multiple comparison test using GraphPad Prism software version 4.03.

**RESULTS AND DISCUSSION**

**Solubility study**

The drug 5-Fluorouracil was found to be slightly soluble in ethanol; sparingly soluble in water; insoluble in chloroform and ether. The polymer chitosan was found to be sparingly soluble in water; and practically insoluble in ethanol. Eudragit S 100 soluble in methanol, ethanol; phosphate buffer pH 7.4; dichloromethane; and practically insoluble in petroleum ether and n-Hexane.

**Drug-excipient interaction study**

The FTIR spectra of the samples are shown in figure IA, IB, IC. There were no changes in the major peaks of 5-Fluorouracil in the presence of Chitosan and Eudragit. The characteristic peaks due to pure 5-Fluorouracil at 3131 cm\(^{-1}\), 1658.48 cm\(^{-1}\), 1246.75 cm\(^{-1}\) correspond to NH\(_2\), C=O, C-X respectively. This indicated no chemical interaction, so the drug and excipients are compatible with each other.

**Percentage Yield**

Percentage yield of different formulations, F-1 to F-5, were calculated and the yield was found to range between 80.16 and 90.53% respectively.

**Particle size analysis**

The particle size of the microspheres ranged between 206.23µm to 268.58µm. It was observed that with increase in polymer concentration in the microspheres from F-1 to F-5, the particle size of the microspheres increased.

**Surface morphology**

Surface morphology and internal cross sectional structure of the microspheres were investigated with a scanning electron microscope. The SEM photomicrographs of coated and uncoated formulations are shown in the figure II. The outer surfaces of the coated microspheres were smooth, oval and discrete than uncoated ones.

**Swellability/ Degree of swelling**

The swelling ability of microspheres on physiological media was determined and the results are shown in table II. From the results it was observed that no significant swelling was observed with Eudragit coated microspheres. Thus ensuring better resistance of Eudragit S100 coated microspheres in the upper GIT to swelling and preventing subsequent release at the non target site.

**Drug content analysis**

The percentage drug content in different formulations are shown in table II. The drug content ranged between 80.20% and 94.89%. Formulation F2 had the highest drug content.

**Drug Entrapment efficiency**

The drug entrapment efficiency was determined and the results are listed in table II. As the polymer concentration was increased from 2 to 6g, the drug entrapment efficiency increased with 65.36%, 66.70%, 68.45%, 76.37% and 77.29% for formulations F-1 to F-5. The results indicated that the polymer concentration plays a major role in drug entrapment efficiency.

**In vitro drug release study**

Drug release study of the different formulations was carried out and the results are given in table III. The cumulative percentage drug release after 12 hrs was found to be in the range of 82.39 to 93.67% for F1 to F5 respectively. Among the formulations F2 was found to be the best formulation as it released 93.67% of the drug. The results showed that as the amount of the polymer increases the extent of drug release decreased. The increase in polymer concentration leads to the increased density of polymer matrix into the microspheres which results in an increased diffusional path length. This may decrease the overall drug release from polymer matrix. Furthermore smaller microspheres are formed at lower polymer concentration and have large surface area exposed to dissolution medium.

**Kinetic data analysis of *in vitro* drug release**

The graphical representation of different kinetic models of *in vitro* drug release profile of different formulations F1-F5 is given in figures III A, B, C and D. The r values of zero order of the above five formulations were in the range of 0.9430 to 0.9940. Similarly the r values of first order were in between 0.8480 to 0.8850. The formulations were also treated to Higuchi and Peppas plots, and the values are shown in table 6. These values were compared with each other for model fitting equation. Based on the
highest regression (r) values, the best fit model was zero order and Peppas. Further Korsmeyer and Peppas equation resulted into the values of n>1, which appears to indicate that the release from the prepared microspheres was by Super case-I transport.

**Stability study**

The stability study revealed that there was no significant change in the drug content at the end of 90 days, so the formulation is said to be stable at different atmospheric conditions.

**CONCLUSION**

Colon targeting microspheres of 5-Fluorouracil can be successfully prepared using Chitosan as polymer by emulsion dehydration method and coated with Eudragit S100 by solvent evaporation method. The *in vitro* drug release study showed that the drug release decreased with increasing polymer concentration. The experimental results demonstrated that the prepared microspheres of 5-Fluorouracil for colon targeting may reduce the side effects of the drug caused by its absorption from the upper part of GIT when given in conventional dosage forms. Thus the Eudragit S100 coated Chitosan microspheres have the potential to be used as a drug carrier for an effective colon targeted drug delivery system.

**ACKNOWLEDGEMENT**

I express my sincere thanks to the management, principal, Head of the department for providing the necessary facilities to carry out the work.

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**Table 1:** Formula for preparing 5-Fluorouracil coated microspheres.

<table>
<thead>
<tr>
<th>Si No</th>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-Fluorouracil</td>
<td>1g</td>
<td>1g</td>
<td>1g</td>
<td>1g</td>
<td>1g</td>
</tr>
<tr>
<td>2</td>
<td>Chitosan</td>
<td>2g</td>
<td>3g</td>
<td>4g</td>
<td>5g</td>
<td>6g</td>
</tr>
<tr>
<td>3</td>
<td>Distilled water</td>
<td>20ml</td>
<td>20ml</td>
<td>20 ml</td>
<td>20 ml</td>
<td>20 ml</td>
</tr>
<tr>
<td>4</td>
<td>Isooctane</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>5</td>
<td>Span 80</td>
<td>1.25%</td>
<td>1.25%</td>
<td>1.25%</td>
<td>1.25%</td>
<td>1.25%</td>
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<tr>
<td>6</td>
<td>Acetone</td>
<td>50ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
<td>50 ml</td>
</tr>
<tr>
<td>7</td>
<td>Eudragit S100</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
<td>500 mg</td>
</tr>
<tr>
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<td>Ethanol: Acetone</td>
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<td>2:1</td>
<td>2:1</td>
<td>2:1</td>
<td>2:1</td>
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<tr>
<td>9</td>
<td>Liquid paraffin</td>
<td>70ml</td>
<td>70 ml</td>
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<td>70 ml</td>
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<tr>
<td>10</td>
<td>Span 80</td>
<td>1%</td>
<td>1%</td>
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<td>1%</td>
<td>1%</td>
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<tr>
<td>11</td>
<td>n-hexane</td>
<td>30 ml</td>
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Values are mean ± S.D (n = 6)

**Table 2:** Evaluation of coated 5-Fluorouracil microspheres.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>% Yield</th>
<th>Mean Particle Size (µm)</th>
<th>Degree of Swelling</th>
<th>Percentage Drug Content (%)</th>
<th>Entrapment Efficiency (%)</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>80.16</td>
<td>206.23</td>
<td>0.03</td>
<td>80.20</td>
<td>65.36</td>
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<tr>
<td>F2</td>
<td>85.0</td>
<td>221.45</td>
<td>0.07</td>
<td>94.89</td>
<td>66.70</td>
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<tr>
<td>F3</td>
<td>87.30</td>
<td>245.25</td>
<td>0.12</td>
<td>86.73</td>
<td>68.45</td>
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<td>F4</td>
<td>89.49</td>
<td>251.16</td>
<td>0.14</td>
<td>88.97</td>
<td>76.37</td>
</tr>
<tr>
<td>F5</td>
<td>90.53</td>
<td>268.58</td>
<td>0.16</td>
<td>89.38</td>
<td>77.29</td>
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</table>

**Table 3:** *In vitro* drug release study of formulations F1-F5.

<table>
<thead>
<tr>
<th>TIME (hours)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
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<tr>
<td>0</td>
<td>0.0000</td>
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<td>0.0000</td>
<td>0.0000</td>
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<tr>
<td>1</td>
<td>0.0788</td>
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<td>0.0178</td>
<td>0.0168</td>
<td>0.0124</td>
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<tr>
<td>2</td>
<td>0.8060</td>
<td>1.0000</td>
<td>1.0345</td>
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<td>0.0221</td>
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<td>3</td>
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<td>2.2310</td>
<td>1.1930</td>
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<td>4</td>
<td>6.7890</td>
<td>6.7890</td>
<td>5.7890</td>
<td>4.3690</td>
<td>4.3570</td>
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<tr>
<td>5</td>
<td>12.76</td>
<td>15.689</td>
<td>12.36</td>
<td>11.85</td>
<td>11.70</td>
</tr>
<tr>
<td>6</td>
<td>34.40</td>
<td>40.39</td>
<td>32.46</td>
<td>30.46</td>
<td>31.25</td>
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<td>7</td>
<td>50.25</td>
<td>50.89</td>
<td>43.68</td>
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<td>8</td>
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<td>9</td>
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<td>10</td>
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<td>85.87</td>
<td>78.27</td>
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<td>12</td>
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<td>93.67</td>
<td>89.12</td>
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**Table 4:** Kinetic models of all formulations.

<table>
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<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi Matrix</th>
<th>Peppas Plot</th>
<th>'n' values</th>
<th>Best Fit Model</th>
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<tbody>
<tr>
<td>F1</td>
<td>0.9940</td>
<td>0.8480</td>
<td>0.7790</td>
<td>0.9300</td>
<td>2.52</td>
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<td>F2</td>
<td>0.9500</td>
<td>0.8490</td>
<td>0.7910</td>
<td>0.8610</td>
<td>2.85</td>
<td>Zero Order</td>
</tr>
<tr>
<td>F3</td>
<td>0.9450</td>
<td>0.8520</td>
<td>0.7730</td>
<td>0.8210</td>
<td>3.07</td>
<td>Zero Order</td>
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<tr>
<td>F4</td>
<td>0.9430</td>
<td>0.8770</td>
<td>0.7690</td>
<td>0.8070</td>
<td>3.10</td>
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<tr>
<td>F5</td>
<td>0.9430</td>
<td>0.8850</td>
<td>0.7700</td>
<td>0.8060</td>
<td>3.17</td>
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</tr>
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Fig. 1: FTIR Spectrum of 5-Fluorouracil drug (A), 5-FU and Chitosan (B), Joint spectrum of 5-FU and Eudragit (C).

Fig. 2: (A) SEM photograph of uncoated formulation F2, (B) SEM photograph of coated formulation F2.
REFERENCES


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