Research Article

# Development, Formulation and Evaluation of 5 Fluorouracil Tablet as a Viable Colon Targeted Drug Delivery System using Compression Coat of Polymer(s)

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**ABSTRACT**

Considering limitation of pH dependent system and time dependent system, microbial degradation at the required site is effective for treatment. Solventless compression coating is one of the strategies for delivering drugs to the colon based on microbial degradation. The aim of the research was to develop a polymer based compression coated tablet of 5-Fluorouracil and to identify the most suitable polymer either alone or in combinations for colonic delivery. Core tablets of 5-Fluorouracil were compression coated with various proportions of Guar gum, Xanthum gum and Chitosan. Further, 32 full factorial designs were devised using coat weight and proportion of polymers in coat as variables. Drug release studies were performed in simulated gastric fluid (SIG) for 2 hours followed by simulated intestinal fluid (SIF) up to 24 hours, demonstrating that the rate of drug release is dependent upon the nature and concentration of polymer and the pH of environment. The coat containing guar gum or xanthum gum alone showed 30-40% drug release in 8 hours in SIF while guar gum with xanthum gum showed 30-35% drug release in 8 hours in SIF. The coat containing all three polymers showed 45 to 50% drug release in SIF. Further, in vitro dissolution studies performed in the dissolution media with 2% rat ceacal content showed significantly increased drug release because of microbial polysaccharidase enzyme.

**Keywords:** 5-Fluorouracil, Chitosan, Colon targeted drug delivery, Guar gum, Xanthum gum

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## 1. INTRODUCTION

Colonic drug delivery is a relatively recent approach for the treatment of diseases like ulcerative colitis, Crohn's disease, colorectal cancer and amoebiasis. Colonic delivery can be accomplished by oral or rectal administration. Rectal dosage forms such as suppositories and enemas are not always effective since a high variability in the distribution of these forms is observed. Suppositories are only effective in the rectum because of the confined spread, and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred, but for this purpose, physiological barriers have to be overcome. Absorption or degradation of the active ingredient in the upper part of the GI tract is the major obstacle and must be circumvented for successful colonic drug delivery [2].

Colon cancer is the second most important cause of death after lung cancer by cancer diseases. Many different drugs or drug combinations have been tested for successful therapy [3]. 5-fluorouracil is most commonly applied anticancer medicine in the treatment of colon cancer. At present, standard regimen available is intravenous bolus injection of 5-fluorouracil modulated by folinic acid (leucovorin). Only few oral approaches are described for oral administration [4]. Recently, enzyme dependent tablet-based systems have been proposed, which might allow an efficient treatment combined with a reduction of adverse effects. However, due to variation in transit time throughout the GIT, the drug release can be incomplete when the colon specific matrix tablet is not readily disintegrated and treatment will remain insufficient. Especially diarrhea has been observed as one of the major adverse effects and toxicity limiting factor of therapy. This

can render oral treatment insufficient [3]. Enteric coated system was widely reported for colonic drug delivery. However this system limited by the fact the pH difference between small intestine and colonic environment is very narrow. Therefore judicious selection of polymers is very necessary to avoid dose dumping in small intestine. The other system, time dependent system are designed based on normal gastrointestinal transit time is not sensed by formulation and this transit time may vary in pathological condition of colon so similar problems of dose dumping may occur for this system. Considering limitation of pH dependent system and time dependent system, microbial degradation at the required site is effective for treatment condition is most suitable approach. Polysaccharides are good carrier for developing microbial degradation system.

## 2. MATERIAL AND METHODS

### *2.1. Materials*

5-fluorouracil (98-99% pure), was obtained from Alkem laboratory, Mumbai and Guar gum, Xanthum gum were gift samples from Glenmark Pharmaceuticals, Nasik. Chitosan (93% deacetylated) was purchased from Modern Scientifics, Nasik. Other excipients Sodium starch glycolate, Lactose, Microcrystalline cellulose, Talc, Magnesium Stearate were obtained as gift sample from Lupin pharmaceuticals, Aurangabad.

### *2.2. Methods*

#### *2.2.1. Preparation of fast disintegrating core tablets of 5-fluorouracil*

The core tablets of 5-fluorouracil were prepared by direct compression technique using the composition given in Table 1. 5-fluorouracil, microcrystalline cellulose, lactose, Cross carmellose sodium, Microcrystalline cellulose, magnesium stearate and talc were passed through sieve no #80 (179 µm), weighed and thoroughly mixed in a polybags to ensure complete mixing. The mixture was compressed into tablet on a single station tablet punching machine (Rimek, India) using 6 mm round, flat-faced and plain punches with applied force of 4000 kg. Each core tablet consisted 50mg of 5-fluorouracil. The core tablets were tested for hardness, thickness, content uniformity, and friability and disintegration test. After confirming compliance with these tests, the best core formulation showing least disintegration time was further chosen for compression coating with different combinations of polysaccharides.

**Table 1: Composition of different formulae of core tablets of 5-fluorouracil**

| Ingredients | Formulation code | | | | |
|---|---|---|---|---|---|
| | C1 | C2 | C3 | C4 | C5 |
| 5-fluorouracil | 50 | 50 | 50 | 50 | 50 |
| Lactose | 67 | 62 | 57 | 52 | 47 |
| Cross carmellose Sodium | 5 | 6 | 7 | 8 | 9 |
| Microcrystalline cellulose | 23 | 27 | 31 | 35 | 39 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Total weight | 150 mg | | | | |

#### 2.2.2. Preliminary formulations of polysaccharide coated tablets of 5-fluorouracil

Before selection of final polymers ratio, different formulation containing Guar gum, Xanthum gum and Chitosan selected based upon the disintegration of core tablets having formulation code C2 (disintegration time 12.07 sec) was selected to coat with different ratio of single and combination of three polysaccharides with coat weight of 300mg. The composition of compression coating material is shown in Table 2. All the ingredients of each coat formulation were weighed accurately and mixed in a polybag. 120 mg (40%) of coating mixture was placed in the die cavity of single station tablet punching machine, the core tablet was placed on it at centre, remaining 180 mg (60%) of coating mixture was carefully transferred to the die cavity and tablets were compressed using 12 mm flat punches with compression force 5000 kg. Compression coated preliminary tablets were further tested for hardness, friability, drug content and drug release.

**Table 2: Composition of compression coating with formulation code**

| Formulation code | Polymer (%) in coat weight | | | | | | |
|---|---|---|---|---|---|---|---|
| | Guar gum (mg) | Xanthum gum (mg) | Chitosan (mg) | MCC (mg) | Talc (mg) | Magnesium stearate (mg) | Coat weight (mg) |
| P1 | 250 | - | - | 45 | 2.5 | 2.5 | 300 |
| P2 | - | 250 | - | 45 | 2.5 | 2.5 | 300 |
| P3 | - | - | 250 | 45 | 2.5 | 2.5 | 300 |
| P4 | 200 | 50 | - | 45 | 2.5 | 2.5 | 300 |
| P5 | 50 | 200 | - | 45 | 2.5 | 2.5 | 300 |
| P6 | 95 | 95 | 60 | 45 | 2.5 | 2.5 | 300 |
| P7 | 100 | 100 | 50 | 45 | 2.5 | 2.5 | 300 |

*2.2.3. Factorial design*

Based on the results obtained with preliminary formulations, $3^2$ randomized full factorial designs were applied in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The ratio of release rate modifying polymers guar gum: xanthum gum: chitosan(X1) and the amount of coat weight (X2) were selected as independent variables. Percentage of drug release was selected as dependent variables. The probable formulations using $3^2$ randomized full factorial designs are as shown in table 3. Formulation were prepared by using nine different combinations of two factors as shown in table 5 mixing of polymers was done by geometric mixing. The compositions of compression coat material were shown in table 5. For a compression coating about 40 % of coat weight material was first placed in die cavity. Then the core tablets were carefully positioned at the center manually, which was filled with remainder 60 % of the coat material. The coating material was then compressed around the core tablets by using 12 mm round, concave punches with compression force 7000 kg using rotary press (Rimek, India).

**Table 3: Coded formulation**

| Variables | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| X1 | -1 | 0 | 1 | -1 | 0 | 1 | -1 | 0 | 1 |
| X2 | -1 | -1 | -1 | 0 | 0 | 0 | 1 | 1 | 1 |

**Table 4: Coded levels**

| Coded Level | -1 | 0 |
|---|---|---|
| X1 (G:X) | 60:40 | 70:30 |
| X2 coat wt (mg) | 350 | 400 |

**Table 5: Formulation by factorial design**

| Polymers in coat (mg) | Formulation code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Guar gum | 150 | 175 | 200 | 180 | 210 | 240 | 210 | 245 | 280 |
| Xanthum gum | 100 | 75 | 50 | 120 | 90 | 60 | 140 | 105 | 70 |
| Chitosan | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Microcrystalline cellulose | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 | 45 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Coat weight | 350 | 350 | 350 | 400 | 400 | 400 | 450 | 450 | 450 |

*2.2.4. Determination of drug content in tablets formulations*

Both the core tablets and compression coated tablets of 5-fluorouracil were tested for their drug content. Ten tablets were finely powdered, quantities of the powder equivalent to 50 mg of 5-fluorouracil were accurately weighed and transferred to 100ml volumetric flask containing ~50 ml of 7.4 Sorenson's phosphate buffer and allowed to stand for 6 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with 7.4 pH Sorenson's phosphate buffer and centrifuged. A 1 ml sample of the supernatant liquid was taken and diluted to 10 ml using water, filtered through 0.2 um membrane filter and analyzed by U.V spectroscopic method.

*2.2.5. Swelling index*

Tablets from each formulation was randomly selected, weighed individually (W1) and placed separately in a wire basket which was placed in a 100 ml beaker containing 0.1 N HCl for first 2 h and later phosphate buffer (pH 7.4) (24 h). After 2, 4, 6, 8 and 24 h the tablets were removed from wire basket and excess water was removed using filter paper. The swollen tablets were reweighed (W2) and swelling index of each tablet was calculated using the below equation.

Swelling Index (%) = (W2-W1)/W1×100

*2.2.6. Preparation of 2% rat caecal content*

Rat caecal content was prepared using the previously described method [1]. Briefly, male Wistar rats (150-200 gm) on normal diet were used and asphyxiated using carbon dioxide. Caecal content were collected by dissection at the abdominal region and immediately transferred into phosphate buffer (pH 7.4) to prepare a final suspension at a concentration of 2% (w/v). Constant supply of CO2 was maintained throughout the experiment to maintain the anaerobic condition of colon.

*2.2.7. In vitro drug release studies*

Dissolution studies were carried out in a USP basket type apparatus with a basket speed of 100 rpm. During the dissolution studies 900 ml of simulated gastric fluid (SGF; 0.1N HCl, pH 1.2) maintained at 37±1° was used as dissolution medium for the initial 2 h, followed by simulated intestinal fluid (SIF, Sorenson's phosphate buffer, pH 7.4) for remaining durations (i.e., 24 h). An aliquot was withdrawn at regular time intervals and was replenished with fresh dissolution medium to maintain sink condition. The aliquots were assayed on UV-spectrophotometer at 266 nm and 209 nm in SGF and SIF, respectively.

Drug release studies were also performed in presence of rat caecal content to evaluate the effect of microbial degradation on drug release from the prepared tablets. The experimental procedure for dissolution studies in presence of rat caecal content was same as described above but with a modification that 2% w/v rat caecal contents was added to Sorenson's phosphate buffer (pH 7.4), simulating colonic fluid (SCF).

*2.2.8. Release kinetics*

In vitro release data were fit to first order, zero order and Higuchi equations to analyze the kinetics of drug release from the tablets. Further, the dissolution data were fit to the following Korsmeyer-Peppas equation, to analyze drug release mechanism. $Mt/M\infty=Ktn$, Where $Mt/M\alpha$ is the fraction of drug released at time t, K is kinetic constant and 'n' is release exponent that characterize the drug transport.

*2.2.9. Stability studies*

Stability of the formulations was assessed by storing formulations F9 at 40±2°/75±5% RH for 45 days. At the end of study period, formulations were evaluated for physical change, drug content and in vitro drug release.

*2.2.10. Statistical analysis*

The cumulative percent of 5-fluorouracil released from the drug from the compression-coated tablets (n=3) in the dissolution medium at 24 h with and without rat caecal contents (control study) was compared, and the statistical significance was tested by using Student's t-test. A value of P, 0.05 was considered statistically significant.

*2.2.11. Differential scanning calorimetry (DSC)*

The possibility of any interaction between 5-fluorouracil and polysaccharide polymers, guar gum, xanthum gum and chitosan was assessed by carrying out thermal analysis on pure drug (5-fluorouracil), and combination (1:1 ratio) with guar gum, xanthum gum and

chitosan. Samples (10mg) were accurately weighed into aluminum pans and then hermetically sealed with aluminum lids. The thermograms of the samples were obtained at a scanning rate of 10° C/ min conducted over a temperature range of 30-350°C.

## 3. RESULTS AND DISCUSSION

### *3.1. Differential scanning calorimetry (DSC)*

#### *3.1.1. Differential scanning calorimetry of Drug*

The DSC thermogram of 5-fluorouracil showed a sharp endothermic peak at 280.5°C indicated that 5-fluorouracil sample was in pure form as shown in (**Figure 1**).

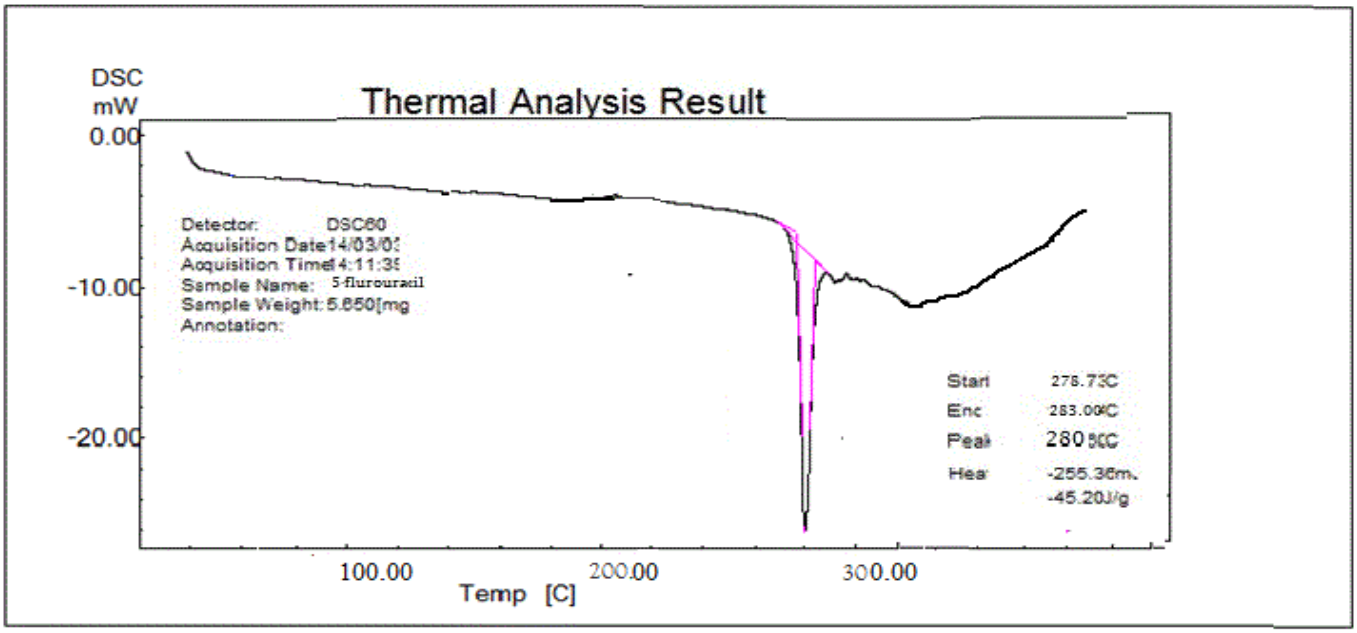


**Figure 1: DSC thermogram of 5-fluorouracil**

#### *3.1.2. Compatibility study by Differential Scanning Calorimetry Studies*

The DSC thermogram of 5-fluorouracil and polymers showed a sharp endothermic peak at 280°C shown Figure 1 and the DSC thermogram of 5-fluorouracil and polymers guar gum, xanthum gum and chitosan showed a sharp endothermic peak at 289°C, 270°C and 100°C as shown Figure 2, 3, 4 respectively. This peak was also retained in the thermogram of the physical mixture of 5-Fluorouracil and polymers. This states that there is no strong interaction between drug and polymer.

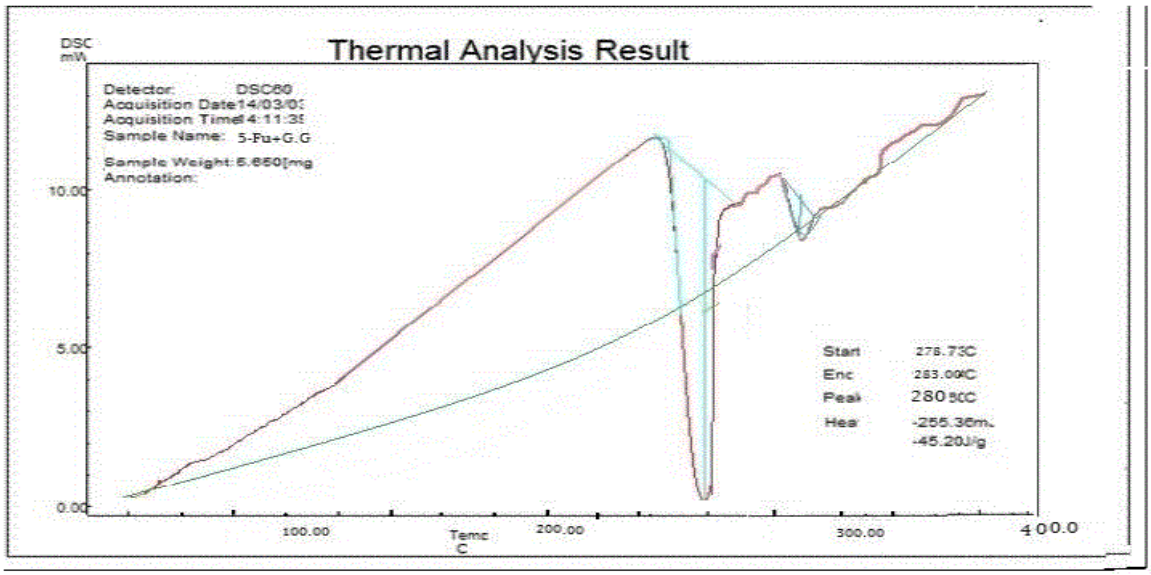


**Figure 2: DSC thermogram of 5-flluorouracil and Guar Gum**

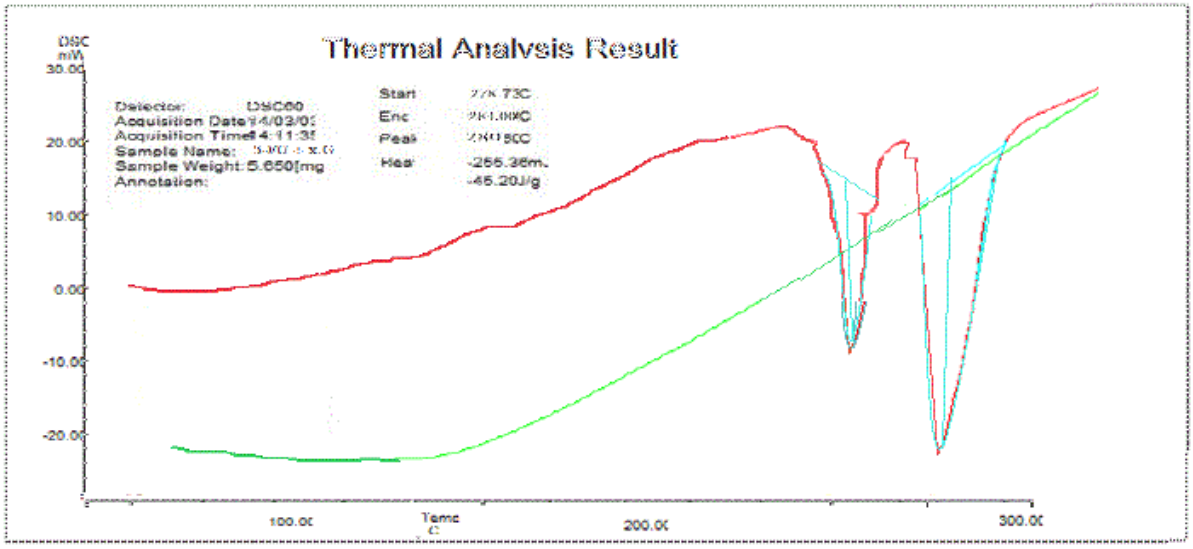


**Figure 3: DSC thermogram of 5-fluorouracil and Xanthum gum**

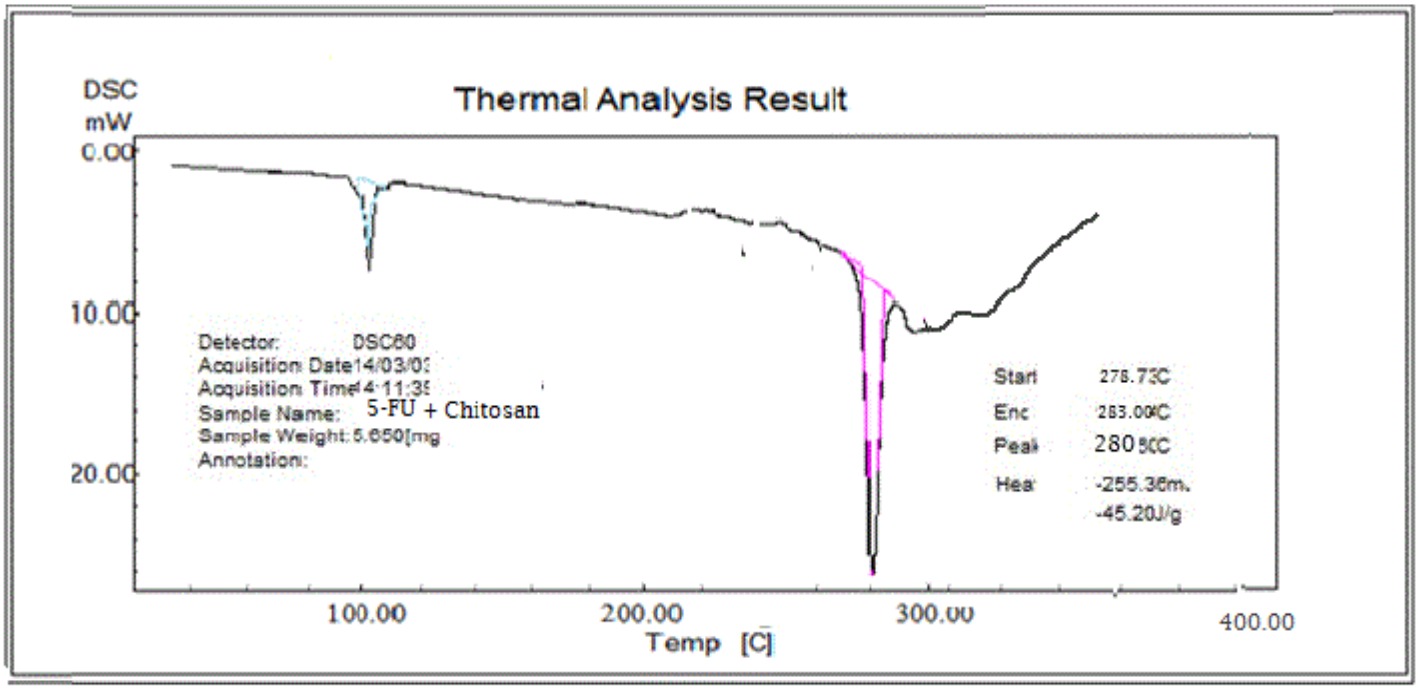


**Figure 4: DSC thermogram of 5-fluorouracil and Chitosan**

*3.2. Formulation of fast disintegrating core tablets of 5-fluorouracil*

Prior to development of polysaccharide coated tablets initial 5 batches of core tablets were prepared to study the effect of binder and filler on the disintegration time and result of this study revealed that the batch C2 shows the least disintegration time hence this batch is selected for further studies.

**Table 6: Evaluation of Core tablets of 5-Fluorouracil**

| Formulation Code | Hardness (Kg/cm²) | Friability (%) | Thickness (mm) | Disintegration time (Sec) |
|---|---|---|---|---|
| C1 | 3.2 + 0.26 | 0.53 + 0.09 | 3.6 | 33.88 |
| C2 | 3.3 + 0.12 | 0.38 + 0.25 | 3.6 | 12.07 |
| C3 | 3.3 + 0.17 | 0.43 + 0.32 | 3.5 | 16.56 |
| C4 | 3.2 + 0.15 | 0.45 + 0.27 | 3.6 | 13.16 |
| C5 | 3.2 + 0.32 | 0.48 + 0.13 | 3.7 | 20.30 |

**Table 7: Physical characterization of preliminary polysaccharide coated tablets**

| Formulation code | Weight + SD (mg) | Hardness + SD Kg/cm² | Friability + SD (%) | Thickness + SD (mm) | Assay + SD (%) |
|---|---|---|---|---|---|
| P1 | 450 + 0.10 | 6.9+ 0.26 | 0.53 + 0.09 | 10.6 | 99.1+ 0.21 |
| P2 | 450 + 0.12 | 7.2 + 0.12 | 0.38 + 0.25 | 10.6 | 98.3+ 0.12 |
| P3 | 450 + 0.16 | 6.8 + 0.17 | 0.43 + 0.32 | 10.5 | 100.8+ 0.27 |
| P4 | 450 + 0.17 | 7.2 + 0.15 | 0.45 + 0.27 | 10.6 | 98.23 + 0.98 |
| P5 | 450 + 0.12 | 7.2 + 0 .32 | 0.48 + 0.13 | 10.7 | 99.97+ 0.56 |
| P6 | 450 + 0.31 | 6.9 + 0.21 | 0.45 + 0.27 | 10.4 | 100.23+ 0.76 |
| P7 | 450 + 0.20 | 6.7 + 0.15 | 0.38 + 0.25 | 10.4 | 99.98 + 0.97 |

### *3.3. Dissolution study (% drug release from preliminary batches of coated tablets)*

**Table 8: Percentage drug release from preliminary batches of coated tablets in 0.1 N HCl for 2 h and in 7.4 pH phosphate buffer for 24 h**

| Time (hrs.) | % Drug Release P1 | P2 | P3 | P4 | P5 | P6 | P7 |
|---|---|---|---|---|---|---|---|
| 30 min | - | - | 98.43 | - | - | - | - |
| 1 | 2.54 | 2.6 | - | 2.1 | 2.18 | 2.82 | 2.05 |
| 2 | 3.86 | 3.69 | - | 3.43 | 3.66 | 3.69 | 3.35 |
| 3 | 6.98 | 7.40 | - | 5.87 | 6 | 9.26 | 7.33 |
| 4 | 9.01 | 9.87 | - | 7.81 | 8.89 | 12.11 | 10.41 |
| 5 | 11.93 | 13.35 | - | 10.34 | 11.60 | 16.56 | 14.88 |
| 6 | 16.13 | 18.68 | - | 13.67 | 15.01 | 25.78 | 22.69 |
| 7 | 24.33 | 26.82 | - | 19.38 | 20.98 | 38.49 | 35.76 |
| 8 | 35.52 | 38.39 | - | 31.65 | 33.08 | 53.63 | 40.74 |
| 24 | 85.12 | 90.62 | - | 75.32 | 83.68 | 97.15 | 95.15 |

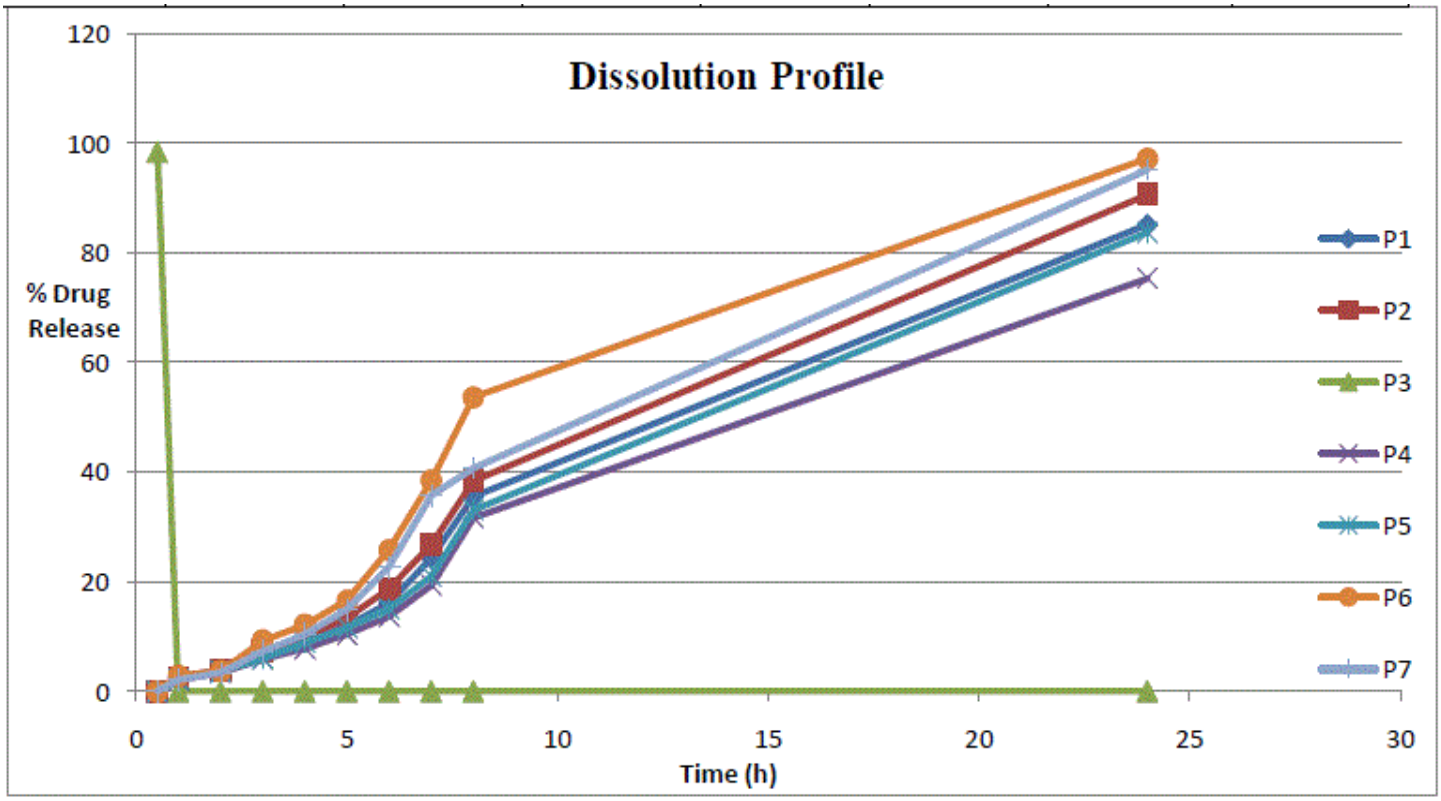


**Figure 5: Percent drug release from preliminary polysaccharide coated formulation**

*3.4. Factorial design*

Among the preliminary formulations P7 formulation shows desirable release. So it is selected for factorial design to optimize effect of variable on the formulation. Thereafter further studies with $3^2$ factorial designs were carried out using coating ratio of guar gum to xanthum gum (X1) and Coat weight (X2) as independent variables. The formulations developed by $3^2$ factorial designs were evaluated for thickness, hardness, friability and assay according to standard pharmacopoeial procedure.

Hardness of tablets was in the range of 6.8 to7.3 kg/cm$^2$. Thickness of tablets was in the range of 10.1 to 11.1 mm. percent weight loss in friability test was found to be less than 0.25 % in all cases. Assay was found within 100+ 3%. All results obtained were complies with the official standard.

*3.5. Physical characterization of final polysaccharide coated tablets*

**Table 9: Physical characterization of final polysaccharide coated tablets**

| Formulation code | Formulation code | Hardness + SD Kg/cm$^2$ | Friability + SD (%) | Thickness + SD (mm) | Assay + SD (%) |
|---|---|---|---|---|---|
| F1 | 500+ 0.10 | 6.9+ 0.26 | 0.53 + 0.09 | 11.6 | 99.35+ 0.23 |
| F2 | 500+ 0.12 | 7.2 + 0.12 | 0.38 + 0.25 | 11.6 | 100.67+ 0.31 |
| F3 | 500+ 0.16 | 6.8 + 0.17 | 0.43 + 0.32 | 11.5 | 101.22+ 0.61 |
| F4 | 550+ 0.17 | 7.2 + 0.15 | 0.45 + 0.27 | 12.6 | 99.76+ 0.37 |
| F5 | 550+ 0.12 | 7.2 + 0.32 | 0.48 + 0.13 | 12.7 | 99.92+ 0.56 |
| F6 | 550+ 0.31 | 6.9 + 0.21 | 0.45 + 0.27 | 12.4 | 99.11+ 0.76 |
| F7 | 600+ 0.20 | 6.7 + 0.15 | 0.38 + 0.25 | 13.4 | 102.45+ 0.41 |
| F8 | 600+ 0.31 | 6.9+ 0.26 | 0.43 + 0.32 | 13.5 | 98.65+ 0.34 |
| F9 | 600+ 0.31 | 6.8 + 0.17 | 0.45 + 0.27 | 13.4 | 99.47 + 0.52 |

**Table 10: Percentage drug release of final polysaccharide coated tablets in 0.1 N HCl for 2 h and in 7.4 pH phosphate buffer for 24 h**

| | % Drug Released | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| 1 | 1.98 | 1.79 | 1.61 | 1.24 | 0.98 | 0.87 | 0.64 | 0.48 | 0.33 |
| 2 | 2.15 | 1.99 | 1.8 | 1.66 | 1.57 | 1.34 | 1.18 | 0.98 | 0.67 |
| 3 | 5.00 | 4.8 | 4.25 | 4.00 | 3.47 | 3.00 | 2.78 | 2.55 | 2.00 |
| 4 | 6.23 | 6.00 | 5.35 | 5.11 | 4.10 | 4.00 | 3.54 | 3.25 | 3.04 |
| 5 | 9.00 | 8.23 | 8.05 | 7.94 | 7.55 | 7.067 | 6.00 | 5.00 | 4.00 |
| 6 | 15.01 | 13.43 | 12.53 | 11.21 | 10.84 | 9.00 | 7.69 | 7.08 | 6.45 |
| 7 | 28.00 | 27.14 | 26.55 | 24.20 | 20.56 | 17.78 | 16.23 | 15.00 | 13.44 |
| 8 | 39.66 | 38.00 | 36.12 | 35.12 | 33.14 | 31.23 | 28.45 | 27.55 | 24.67 |
| 24 | 90.15 | 88.78 | 86.33 | 83.53 | 80.5 | 78.19 | 76.14 | 74.31 | 70.55 |

*3.6. Release Kinetics (Mechanism of drug release)*

To analyze the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order and Higuchi matrix. By comparing the r-values obtained, the best-fit model was selected.

*3.6.1. Zero Order Kinetics*

Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation: Qt=Qo+ Ko. t

Where,

Qt= Amount of drug dissolved in time t,

Qo= Initial amount of drug in the solution and

Ko= Zero order release constant

*3.6.2. First Order Kinetics*

To study the first order release rate kinetics the release rate data were fitted to the following equation: Log Qt = Log Qo + K1.t / 2.303

Where,

Qt = Amount of drug released in time t,

Qo = Initial amount of drug in the solution and

K1 = Fist order release constant.

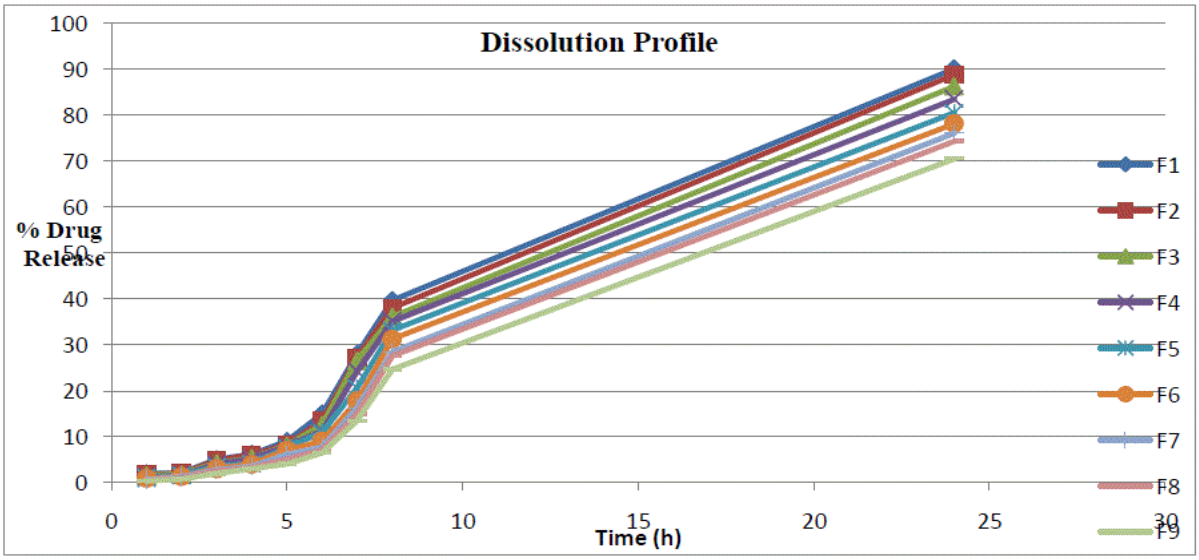


**Figure 6: Percent drug release of final polysaccharide coated tablets**

**Table 11: Percentage drug release from of polysaccharide coated formulation F1,F8, F9 in 0.1 N HCl for 2 h and in 7.4 pH phosphate buffer with 2% rat caecal content for 24 h**

| Formulations | % Drug Release | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 24 |
| F1 | 1.97 ±0.06 | 2.16 ±0.10 | 18.76 ±0.08 | 29.75 ±1.03 | 35.12 ±1.03 | 38.26 ±1.03 | 43.56 ±0.94 | 59.11 ±0.08 | 99.15 ±1.02 |
| F8 | 0.421 ±0.05 | 0.97 ±0.11 | 15.23 ±0.48 | 20.45 ±0.21 | 27.21 ±0.48 | 35.11 ±0.76 | 39.98 ±0.76 | 50.12 ±0.95 | 87.31 ±0.67 |
| F9 | 0.323 ±0.09 | 0.69 ±0.11 | 12.13 ±0.35 | 20.11 ±0.82 | 25.55 ±0.91 | 32.12 ±0.92 | 37.54 ±0.37 | 47.78 ±0.46 | 84.55 ±0.19 |

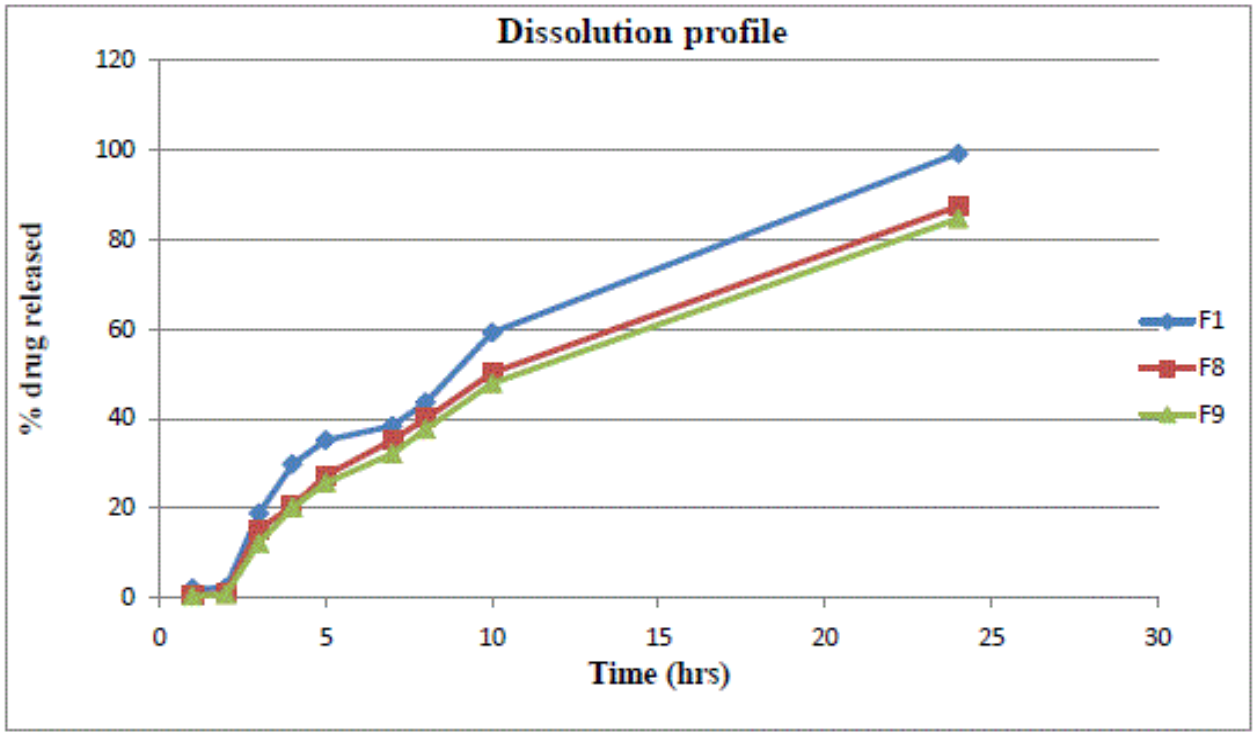


**Figure 7: Percentage drug release from of polysaccharide coated formulation F1, F8, F9 in 0.1 N HCl for 2 h and in 2% rat caecal content for 24 h**

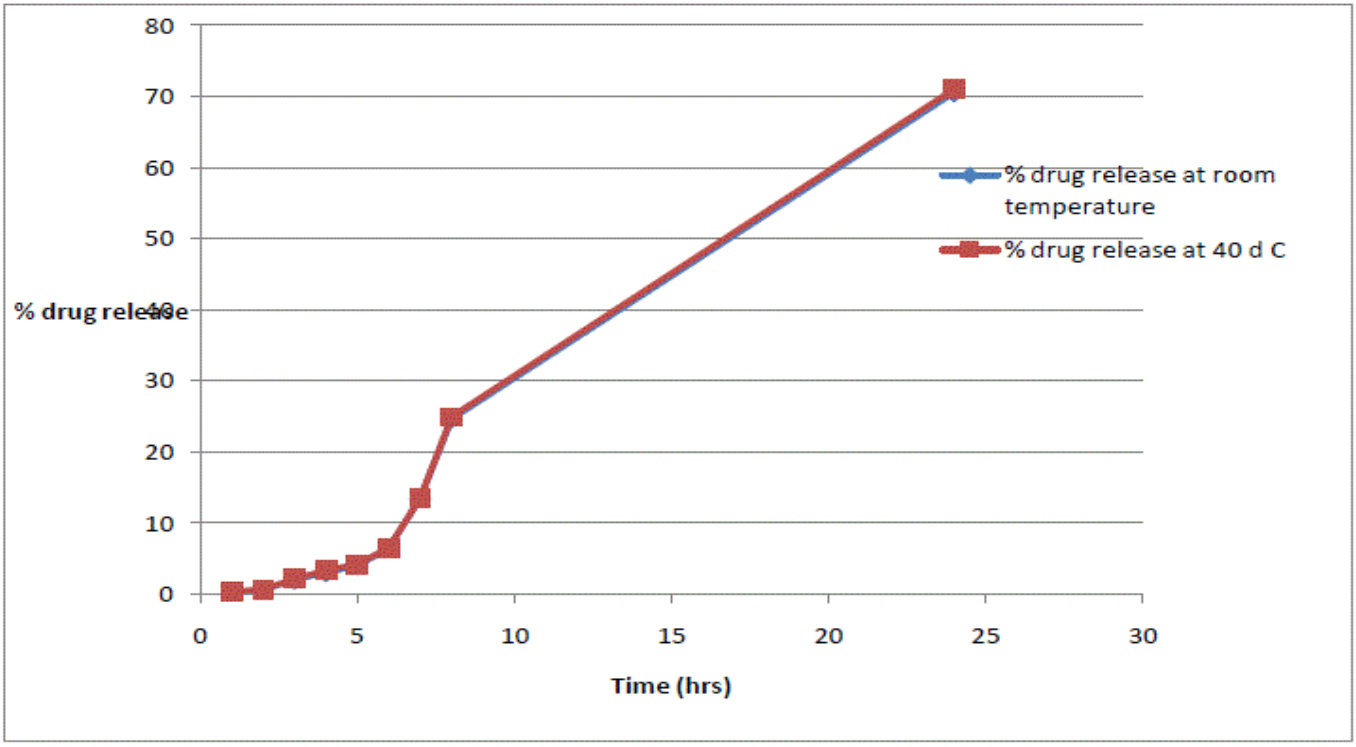


**Figure 8: Dissolution profile of Optimized formulation (F9) in 0.1 N HCl for 2h and in 7.4 phosphate buffer for 24h at room temperature and at 40°C**

*3.6.3. Higuchi Model*

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated into semisolid or solid matrices.

Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is:

$Q_t = KII \cdot t_{1/2}$

Where,

Qt = Amount of drug released in time t and

KII, = Higuchi dissolution constant

**Table 12: Drug Release Kinetics without 2%caecal content**

| Formulations | $R^2$ Values | | |
|---|---|---|---|
| | Zero order | First Order | Higuchi order |
| F1 | 0.9584 | 0.7038 | 0.9247 |
| F2 | 0.9598 | 0.708 | 0.9211 |
| F3 | 0.961 | 0.705 | 0.9208 |
| F4 | 0.9615 | 0.6996 | 0.9188 |
| F5 | 0.9655 | 0.7031 | 0.9161 |
| F6 | 0.9662 | 0.7135 | 0.9081 |
| F7 | 0.969 | 0.7147 | 0.902 |
| F8 | 0.9671 | 0.7054 | 0.897 |
| F9 | 0.9698 | 0.6942 | 0.8938 |

**Table 13: Drug Release Kinetics with 2 % caecal content**

| Formulation | R2 Values | | |
|---|---|---|---|
| | Zero order | First order | Higuchi order |
| F1 | 0.885 | 0.3368 | 0.9686 |
| F8 | 0.892 | 0.3885 | 0.9736 |
| F9 | 0.9007 | 0.3879 | 0.9759 |

From data obtained it clearly indicates prepared formulations with 2 % caecal content follow Higuchi order as mechanism of drug release and all formulations without caecal content follow zero order as mechanism of drug release.

*3.7. Statistical analysis*

The dissolution data, performed with and without rat caecal content was statistically analyzed using students t-test. A value of $P < 0.05$ was considered statistically significant.

*3.8. Stability study*

Hardness was found to be 7 kg/cm2. Thickness was found to be 11+ 0.5mm. Tablet weight was found to be 600 +0.23mg. Assay was found to be 98.41+ 3%. Short term stability testing was carried out for the optimized formulation. The test results for the dissolution profile are as depicted in the graph. Short term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, in-vitro dissolution were within the acceptable limit. Thus the formulation can be said to be stable. All results obtained were complies with the official standard.

**4. CONCLUSION**

In the present work colon targeted compression coated tablets were prepared by direct compression technique using 5-fluorouracil as a model drug for treatment of colorectal cancer. The compression coated tablets of 5-fluorouracil were prepared using natural polymers like guar gum, xanthan gum and chitosan. Further, it was aimed to identify the most suitable polysaccharide either alone or in combinations for colonic delivery of 5-fluorouracil based on microbial degradation. Hence attempts were made to formulate the compression coated tablets using guar gum, xanthan gum, chitosan, either alone or in combination. The formulations were evaluated for physical parameters like diameter, thickness, hardness, friability and drug content. Evaluations of other parameters like swelling index, in vitro drug release, release kinetics and stability were also conducted. Evaluation of 5-fluorouracil compression coated tablets, the hardness was found to be in the range of 5.67±0.15 to 6.23±0.15 kg/cm$^2$ and contain 98.39±0.58 to 101.17±1.18% of the labeled amount of 5-fluorouracil indicating uniformity of drug content. In vitro release study showed that the formulation which containing 50 mg of chitosan as a coating material for one tablet in preliminary coated formulation (P9) was shown good release profile because of chitosan capable of protecting the drug released in physiological environment of stomach and small intestine and susceptible to colonic bacterial enzymatic actions with resultant drug release in colon. But if the chitosan proportion is more than 50 mg, than the maximum amount of drug was released in gastric condition only, not suitable for colonic delivery so 50 mg of chitosan was kept constant for factorial design. Further full 32 factorial design were carried out by using two factors such as proportion of guar gum to xanthum gum (X1) and coat weight (X2) . Formulations F1,F2 and F9 were selected for further dissolution study 2% rat caecal content because F8, F9 formulation shown minimum drug release in SGF in first 2 hours that were 0.98, 0.67 respectively. F1 formulation shown drug release in SGF in first 2 hours was 1.69. Formulations F1,F2 and F9 shown 92.11, 8-.23 and 80.11 % drug release at 24 hours without rat caecal content and 99.72,97.99 and 98.15 % drug release with 2% rat ceacal content respectively at 24 hr and percent drug release proven with and without ceacal content was statistically significant ($p<0.05$). On the basis of release profile of different formulations of polysaccharide coated tablets of 5-fluorouracil F9 formulation proven best candidate for colonic delivery. Stability studies indicated that there appeared no much difference in the physical appearance or drug content, swelling index and in vitro release studies when the selected formulation, F9 stored at 40˚C/75% RH for 90 days in different durations.

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