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# FORMULATION AND EVALUATION OF 5-FLUOROURACIL CONTROLLED RELEASE CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM (CTDDS) FOR COLORECTAL CANCER

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## ABSTRACT

**Objective:** As most of the drugs disintegrate and dissolve in stomach before reaching the target site and to substitute intravenous (IV) route based chrono modulated chemotherapy, oral colon target drug delivery system was formed. The aim of this study was to design, develop, and evaluate a colon targeted tablet containing 5-Fluorouracil (5-FU) to give a controlled release effect of drug for colonic cancer with a goal to increase the bioavailability and improve the patient compliance. **Methods:** Varied concentration of different polymers such as Xanthan gum and Eudragit were used to get an optimized formulation of 5-FU tablet. The prepared formulation was evaluated for pre compression and post compression parameters such as hardness, weight, friability and drug content uniformity. The optimized formulation was further evaluated by Fourier Transformed Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), *in-vitro* dissolution studies, dissolution kinetic modeling and stability analysis. **Results:** All pre-formulation tests were within range of USP standards. Friability of all tablets was satisfied. The interference of the polymers was ruled out by FTIR. *In-vitro* release studies of 5-FU tablets in phosphate buffer of pH 7.0 were performed using a modified diffusion cell that resulted sustained release (90.99% to 92.69% after 12h) and kinetic models depicted the combined diffusion and dissolution mechanism of release. The optimized tablets were found having only physical interactions based on DSC. The product was found stable when evaluated using accelerated stability studies. **Conclusion:** It was concluded from the studies that the colon target tablet of 5-FU prepared by different concentration of polymers were optimized and can be efficiently used to control the rate of drug release to the colon in the belief of improved therapeutic efficacy and tolerability. Therefore, it is a better alternative for intravenous route based chrono modulated chemotherapy.

**Keywords:** 5 Fluorouracil, Eudragit S100, Colon cancer, CTDDS, pH dependent delivery system

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## INTRODUCTION

Colorectal cancer involves the abnormal growth of cells in colon or rectum. If diagnosed in early stage there is 91% chance of recovery but if diagnosed in late stage in which cancer has spread throughout the tissues, organs and lymph nodes there is still 72% chance of recovery **[1]**. Treatment usually involves surgery, radio therapy as well as chemo therapy depending upon condition **[2]**. 5 - Fluorouracil is among the drugs used in chemotherapy. Fluorouracil is an anticancer that is the backbone of all chemotherapeutic drugs for the patients dealing with advanced colorectal cancer **[3]**. It is antimetabolite that is fluorinated of the pyrimidine uracil. IV administration of this drug is clinically in use because of its mercurial bioavailability but IV use produce severe side effects due to cytotoxic effect on non-tumour cells **[4]**. So, a colon targeted 5-FU that overcome the side effects using various polysaccharides was formulated **[5]**. It used to be a common practise that every anti-cancer medication would cause effect on all sites that comes in its path before reaching the required site **[6]**. But now with advancement of knowledge and polymeric based products this field had successfully advanced in terms of providing site specific action. The pH specific drug release is the key feature of colon targeting drug delivery systems **[7]**.

Conventional non targeted drug delivery system may have low efficacy and undesirable side effects because drug is systemically absorbed before reaching the targeted site. Therefore, colon targeted drug delivery system was introduced to increase the bioavailability of drug and to selectively release the drug as a result of colonic environment without premature drug release in upper GI tract **[8]**.

Colon targeted drug delivery system is highly desirable for local treatment of bowel diseases such as Crohn's disease, colonic cancer, ulcerative colitis and local treatment of colonic pathologies **[9]**. The colonic contents have a longer retention time (up to 5 days), and the colonic mucosa is known to facilitate the absorption of several drugs, making this organ an ideal site for drug delivery **[10]**. However, targeting the drug to colon is a very complicated task because of its location to distal portion of alimentary canal, also because of the presence of enzymes and wide range of pH values **[11]**.

Drug localization at the colon helps in releasing the drug at colon as a result, major amount of the drug enters the colon. Main goal is to develop 5-fluorouracil tablet using micro emulsifying drug delivery method so to administer the drug orally to improve the patient compliance and also making available the dosage form directly to large bowel through the GIT to localize the maximum amount of drug in the colon region and also attaining the sustained release effect **[12]**.

## MATERIALS

5-fluorouracil was received as gift from Pharmedic Labs Lahore, Microcrystalline cellulose (MCC), Sodium starch glycolate, Guar gum, Xanthan gum, Tri ethyl citrate, Eudragit S100 and PVP K30 were purchased from Sigma Aldrich Pakistan. Lactose, Acetone, Starch, Isopropanol, Mg Stearate, Talc, Aerosil and Pectin were purchased from Merck Pakistan. All the chemicals used were of analytical grade. Distilled water was used throughout the study.

## METHODS

2% w/v starch slurry was prepared as a binder and added it into the ingredients such as Xanthan Gum and Eudragit S 100 and 5FU to form dough. Granules were formed by passing it through sieve #12. The granules were dried in hot air oven for half an hour and then granules were properly sized by passing through sieve #40. After that dried granules were kept at room temperature for 3-5 hours for moisture content adjustment. The granules were blended with glidants and lubricant i.e., magnesium stearate and talc for 30 minutes. After that granules were punched by punching machine and tablets were formed. The formulation design is described in **Table 1**.

### Preliminary Studies

The preliminary studies were performed for the development of formulation to evaluate the purity and compatibility of the active substance of the drug.

***Angle of Repose***

Fixed the funnel on the stand and placed the paper below the funnel. A heap of powder was formed. The height of the peak was measured by the scale. The radius was calculated from the diameter where up to the powder disperse and calculated the angle of repose.

***Crystallinity***

A pinch of 5-fluorouracil of powder was taken onto the glass slide. The glass slide was placed onto stage of microscope. Crystal was observed by using different objective lenses.

***Melting Point***

Placed a small amount of sample drug on the hot stage of apparatus. Observed the sample through eyepiece lens and recorded the temperature through thermometer.

***Hygroscopicity***

5- Fluorouracil was weighed and placed in the China dish. Heated it with the help of oven at 80℃ for 15 minutes. Noted the difference in weight.

LOD was calculated by using the following formula:

$$i = [(Initial\ weight\ W1 - Final\ weight\ W2) / (Initial\ weight\ W1)]x\ 100$$

### Post-formulation Evaluation

***Tablet Hardness***

For each formulation, 20 tablets were randomly selected. Monsanto hardness tester was used and hardness of each tablet was checked.

***Thickness***

Twenty tablets were randomly selected from each formulation. Thickness of each tablet was measured using the micrometer. Thickness was expressed as Mean ± Standard Deviation.

***Friability***

Twenty tablets were selected randomly. Initial weight of tablets ($w_1$) was recorded. Tablets were placed in the drum of the friabilator, for 4 minutes at 25 rpm. Percent weight loss ($w$) was calculated as.

$$W = (W1 - W2)/W1\ X\ 100$$

**Table 1:** Formulation Design containing four formulations with fixed.

| Ingredients | Concentration (mg) | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 5- Fluorouracil | 100 | 100 | 100 | 100 |
| MCC | 90 | - | 60 | |
| Sodium Starch Glycolate | - | 2.5 | 4 | |
| Guar Gum | - | - | 150 | 60 |
| Xanthan Gum | 10 | 20 | - | |
| Triethyl citrate | - | 0.6 | - | |
| Eudragit S 100 | 100 | 60 | - | 75 |
| PVP K30 | - | 1 | - | |
| Lactose | 68 | 80 | 32 | |
| Acetone | - | 34 | - | |
| Starch | 20 | - | 10 | |
| Isopropanol | - | 51.4 | - | |
| Mg Stearate 3% | 7 | 2.5 | 4 | |
| Talc2% | 5 | 5 | 4 | 5 |
| Aerosil | - | 5 | - | |
| Pectin | | | | 50 |
| Total Weight (mg) | 300 | 300 | 300 | 300 |

***Swelling Studies***

Swelling studies were performed on core tablets. Tablet from each formulation was selected, weighed (w) and after that 10 ml of phosphate buffer (pH 7.0) was used in petri dish to place the tablet **[13]**. Removed the tablets at regular intervals (10, 20, 40, 80, 120, 160) from petri dish and filter paper was used to remove excess of water. Reweighed (w*) the swollen tablets. Equation was used to find out swelling index:

$$Swelling\ Index = {}^{(W^* - W)}/_{W}\, X\ 100$$

***Calibration Curve***

Standard solution of 1mg/mL was prepared using 5FU 99.9% using distilled water. The standard solution was further diluted to prepare working standard solution of 100µg/mL. The working solution was used to prepare five dilutions of fixed concentration i.e., 2, 4, 6, 8, 10µg/mL. These dilutions were scanned (n=3) at 265nm using UV spectrophotometer.

***Drug Content***

20 tablets from each formulation were weighed and crushed in pestle and mortar. 10% of the total powder was weighed and soaked in 10ml of phosphate buffer of pH 7.0, stirred for 30 minutes. Stored the soaked part in room temperature for 24 hours to allow the drug to penetrate back from the polymer into the solvent. The suspension was centrifuged at 4000rpm for 15 minutes and the supernatant was separated with the help of 1cc syringe. Supernatant solution was analyzed on UV spectrophotometer at wavelength of 265nm.

Drug Content was determined as:

$$Drug\ Content = Actual\ Yield/Theoretical\ Yield\ \ X\ 100$$

***In Vitro Drug Release***

Buffer of pH 7.0 was made by using distilled water. 450ml of buffer was added in round bottom flask of dissolution apparatus. One tablet was added into this round bottom flask. Samples of 1ml was taken after intervals of 0.5, 1,2,3,4,6,8,12,18 and 24 hours of placing the tablet in dissolution apparatus. Dilutions were made by adding 9ml of Phosphate buffer of pH 7.0 to each sample. Absorbance was observed of these dilutions using UV spectrophotometer at 265nm.

***Kinetic modeling of Drug Release***

Calibration curve was obtained by using UV absorbance. After that theoretical yield was calculated and dissolution data of four formulations was taken, the percentage release was calculated, and curve was obtained against time in hours and percentage release of formulations. By using DD Solver models were obtained to check which model was best followed by our formulations. The models applied were Zero-order, First-order, Higuchi model & Korsmeyer Peppas model to understand release kinetics of our formulation.

***Differential Scanning Calorimetry (DSC)***

5FU, polymers and ten tablets from formulations were crushed to powder and 5mg of powder was sealed in the aluminum pan for analysis. Q1000,

TA software were used for enthalpy reading of every peak. At a scanning rate of 10°C/min the thermal behavior was analyzed.

***FTIR Analysis***

Powder samples (5FU, plolymers, Formulation) were placed at the stage of spectrometer (Bruker FTIR Alpha spectrometer). The diamond tip of spectrometer was placed on the sample to analyze the sample. A beam of infrared was passes through the sample and curve was obtained 4000-400cm$^{-1}$ spectra wavelength.

***Stability Studies***

Stability studies for the optimized 5-FU colon-targeted tablets were conducted as per ICH guidelines by storing for 3 months at the temperature 40 ± 2 °C and 75% ± 5% RH. Physical characteristics and drug content was noted at the start and after that at the end of 1$^{st}$, 2$^{nd}$, 3$^{rd}$ months. Zero-day samples were set as control.

**RESULTS**

Various parameters that were studied to physically characterize tablets (**Table 2**).

**Table 2:** Physiochemical properties of 5-FU.

| **Physical Characterization Parameters** | **Results** |
|---|---|
| Crystallinity | Monoclinic |
| Melting Point | 280°C |
| Hygroscopicity | Non-Hygroscopic |
| Flow Properties | Passable Flow |

**Post-formulation**

All the tablets formed showed the hardness within the variable range. Thickness of all tablets showed within range of 2.3 – 2.7 mm. Friability of all tablets was found out to be less than 1%. Weight variation of all tablets was within range.

**Calibration Curve**

Calibration curve was found linear with value of $R^2$ value of 0.9995. The prepared curve is given in **Fig. 1**.

**Kinetic Modeling of Drug Release**

The kinetics of drug release were evaluated by applying DDSolver based mathematical models such as zero order, first order, Higuchi and Korsemeyer Peppas. The drug release kinetics of above 4 formulations were presented in the **Table 3**.

**DSC Analysis**

DSC analysis was performed on all the formulations which showed the absence of any incompatibility in the physical mixture of the drug with excipients. The different endothermic peaks are represented in **Fig. 2**.

**FTIR Analysis**

FTIR analysis was also performed on the powder mixtures of all tablets, and it confirmed the results of DSC in showing an absence of any incompatibility. The different IR transmission peaks are represented in **Fig. 3**.

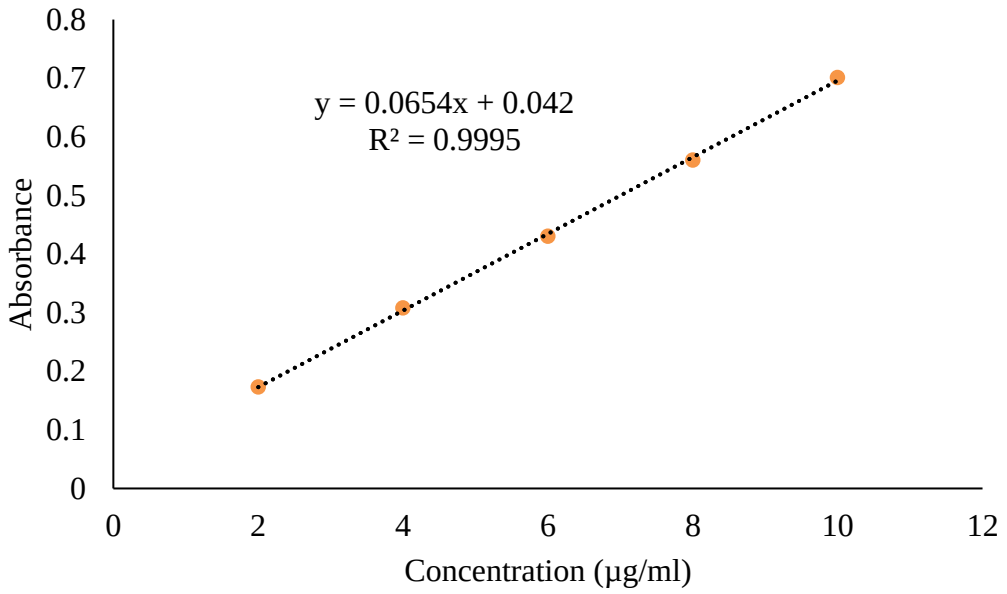


**Figure 1:** Calibration curve of 5-Fluorouracil using fixed dilution method.

**Table 3:** Describing various parameters ($R^2$, AIC, MSC, n) of release kinetics based on four release models i.e., First, Zero order, Higuchi and Korsmeyer Peppas.

| Formulations | Zero Order | | | First Order | | | Higuchi | | | Korsmeyer Peppas | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | AIC | MSC | $R^2$ | AIC | MSC | $R^2$ | AIC | MSC | $R^2$ | AIC | MSC | n |
| F1 | 0.964 | 73.61 | 2.162 | 0.976 | 68.73 | 3.569 | 0.894 | 86.64 | 2.077 | 0.991 | 58.47 | 4.424 | 0.900 |
| F2 | 0.873 | 91.02 | 2.162 | 0.976 | 71.12 | 3.562 | 0.930 | 83.93 | 2.494 | 0.971 | 74.19 | 3.306 | 0.671 |
| F3 | 0.946 | 78.74 | 2.758 | 0.980 | 66.99 | 3.738 | 0.913 | 84.59 | 2.271 | 0.990 | 58.89 | 4.413 | 0.756 |
| F4 | 0.922 | 83.58 | 2.387 | 0.976 | 69.31 | 3.577 | 0.926 | 82.96 | 2.439 | 0.987 | 62.90 | 4.111 | 0.717 |

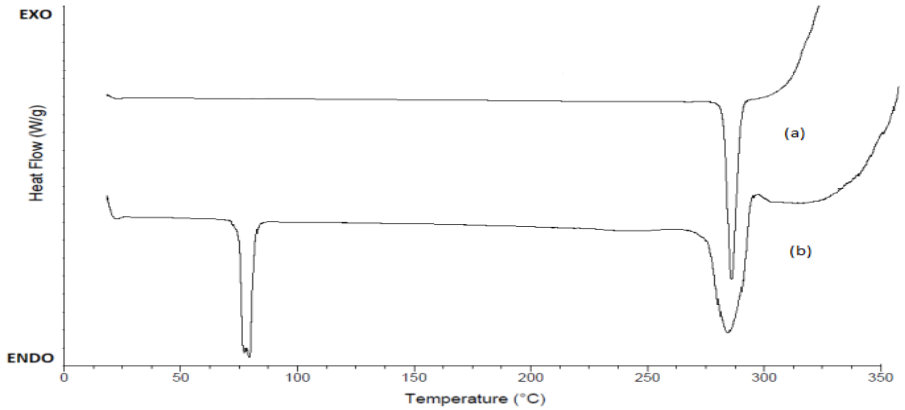


**Figure 2:** DSC thermographs of (a)5-FU, (b) Physical mixture F1.

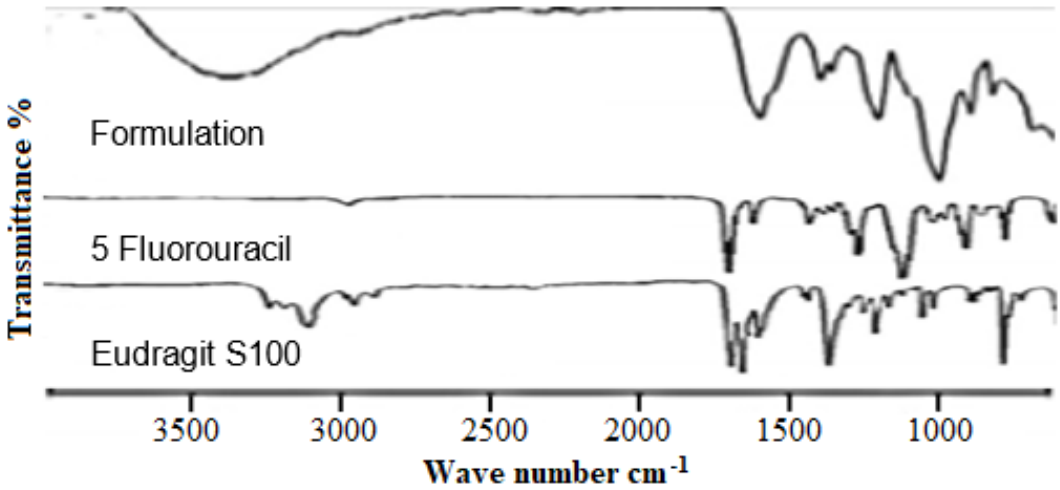


**Figure 3:** Representation of FTIR transmittance of drug, polymer and formulation F1.

**Stability Studies**

Accelerated stability studies were carried out on tablets of 5- Fluorouracil and drug content was calculated after 1, 2, 3 months. %CDR was found out during the drug release study conducted in simulated physiological environment of various regions of GIT after storage (**Table 4**).

**Table 4:** Mean drug contents of 5-FU after storage at 40°C and 75% RH for 6 months.

| Duration of storage for stability | Mean drug content ±S.D. (%) |
|---|---|
| 1 month | 99.85± 0.53 |
| 3 months | 98.25 ± 0.33 |
| 6 months | 96.66 ± 0.56 |

**Table 5:** %age cumulative 5-FU release after dissolution in simulated GIT and Colonic fluid when stored for 6 months.

| Drug release region of GIT | Duration of storage | % CDR |
|---|---|---|
| Stomach | 1 month | 87.84 |
| Small Intestine | 2 months | 78.44 |
| Colon | 6 months | 76.89 |

## DISCUSSION

**Post-formulation**

The weight variation and the drug content of the prepared tablets were found to be uniform and within the pharmacopeial limits. The hardness of the tablets was within the range of 4.1 - 6.5 kg/cm$^2$ and the friability was below 1.0%, respectively.

**In-vitro Drug Release**

Dissolution studies were performed to determine the percentage drug released over time by the tablets. The percentage drug release depends on the type and concentrations of polymers used. Hydrophilic polymers release drug at a faster rate leading to higher percentage release than hydrophobic polymers. Therefore, a blend is required for optimum release. In-Vitro drug release is presented in **Fig. 5**.

**Kinetic Modeling of Drug Release**

After evaluating zero order model on formulation F1 it was found out that value of $R^2$ was 0.9642. Which evaluated that it was in the standard range. The value of AIC was 73.64 which was not in the standard range because its reference range should be less than 50. Drawing out the conclusion by above results indicated that zero order was not followed by F2 formulation **[14]**.

Zero order model shows rate of reaction is independent of concentration of reactants. Moving onto next model, First-order model after evaluating $R^2$ 0.976 which was in the range of being a standard value. The value of AIC was 68.74. It was deviated from standard range. The value of MSC was 3.56 (should be greater than 3). So, this formulation followed First order Model. If we talk about Higuchi model all 3 values of $R^2$, AIC, MSC were 0.89, 86.63, 2.07 respectively which showed that all values were not following the standard range of Higuchi model. Then next model Korsemeyer Peppas was applied which showed that the values of $R^2$, AIC, MSC were 0.9906, 58.47, 4.42 respectively were in the standard range. If the value of n is greater than 0.45 but less than 1 then it is non Fickian mechanism. If 0.45 < n indicates that it is obeying a Fickian diffusion mechanism and n=1 represents a pure relaxed controlled delivery. If it is greater than 1 than it is super case 2. The value of n was 0.900 for F1 showed it was non Fickian Case 2 diffusion mechanism **[15]**.

For F2 the Zero-order model was not followed as the values of $R^2$, AIC, MSC were 0.87, 91.02, 1.97 respectively. Here AIC value was greater than 50 which was out of standard range along with MSC that is less than 6 and $R^2$ that is less than 0.95 as well **[16]**. Due to deviation of values from standard range F2 formulation was not following Higuchi Model. It was following First Order Model because $R^2$ and MSC values are in range of standard value. So, first order model is valid. It also followed Korsmeyer Peppas Model because values $R^2$ 0.97 and MSC 3.30 were in range. And according to value of n 0.671 it had non Fickian diffusion mechanism **[17, 18]**. For F3 formulation the First-order values were in range for $R^2$ and MSC which were 0.97 and 3.7 but AIC value was 66.9 which was greater than 50 so it followed this model. For Zero-order and Higuchi values again varied from standard range so it didn't follow both models. F3 obeyed the Korsmeyer Peppas model as values of $R^2$, AIC, MSC were 0.991, 58.93, 4.41 respectively. The value of n was between 0.5 and 1 means it was following non Fickian diffusion mechanism.

The last formulation F4 due to its greater MIC value than 50 and MSC value being less than 3 didn't follow zero-order and Higuchi. On the other hand, it followed Krosmeyer Peppas model because $R^2$ and MSC were in range and n showed it has non Fickian diffusion. So, we will take formulation was F1 as our ideal formulation because of its linearity of percentage release in graph **[19]**.

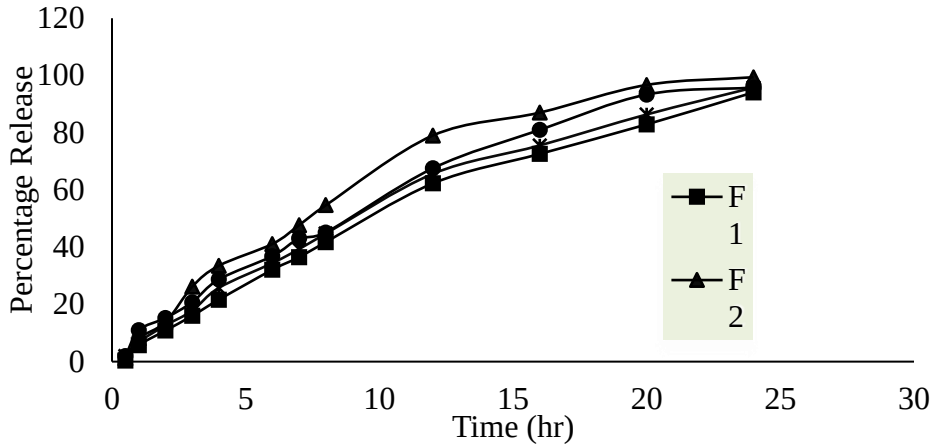


**Figure 4:** Percentage of drug release presented against time in phosphate buffer pH 7.4.

**Drug Uniformity**

According to USP guidelines, the percentage drug content should lie between 85% - 115%. The drug content in the tablets were uniformly distributed. The content of tablets was found in the range of 90.9 – 92.6. From the results it was concluded that there was proper distribution of drug in all formulations.

**DSC Analysis**

The DSC thermal curve at a scan rate of 20°C/min of 5-FU and physical mixture of tablet excipients at a melting point of 70.8 + 0.2°C and 282.4 + 0.2°C showed a single sharp endothermic peak. Both drug peaks showed a slight peak broadening. Absence and shifting of peaks were not observed **[20]**

**FTIR Analysis**

Two carbonyl functional groups at 1730 and a C-N at 1245 $cm^{-1}$ were observed in FTIR analysis of pure 5-fluorouracil. Due to C-H and N-H bond the broad stretch occurs between 3150-28 $cm^{-1}$. Characteristic band of methyl and methylene were displayed at the spectrum of ES-100 at 2997-2952 $cm^{-1}$. The other polymers show similar peak to Eudragit at 1730-1734, corresponding to carbonyl stretch of 5-FU **[18]**

**Stability Studies**

Stability studies were carried out for 3 months at the temperature of 40 ± 2 °C and RH level of 75% ± 5%, morphology of tablets didn't change and drug content level remains unchanged. During storage time, these results stated that the drug formulation remains stable chemically and physically. **[6]**

**CONCLUSION**

The Colon Target Drug Delivery system of 5-Fluorouracil will help for the targeted and controlled release of drug in the colon. The formulations prepared showed good results for this system of 5-Fluorouracil. F1 being the best formulation provided excellent results and is optimized for the target delivery system with effective results giving controlled release effect.

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