RESEARCH ARTICLE

Development and Analysis of Colon-Specific, pH-Responsive Polymer Delivery of Irinotecan Hydrochloride Tablets for Colon Cancer Treatment

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Received: 24th March, 2024; Revised: 12th July, 2024; Accepted: 09th August, 2024; Available Online: 25th September, 2024

ABSTRACT

For the formulation of enteric-coated tablets containing irinotecan hydrochloride, this thesis focuses on HPMC and ethylcellulose, both of which are pH- and oxidation-resistant polymers. The integrated polymer-drug tablet mixture was coated with 15% of eudragit S100 and L100, which is a methacrylic acid copolymers, that's soluble at pH 7. Both the physical characteristics with the *invitro* release kinetics pattern of the enteric-coated tablets were characterized. In the invitro release study, different pH environments were used, comparable to the gastrointestinal tract (GIT): 0.1 N HCl solution for two hours, pH 6.8 phosphate buffer for three hours, and pH 7.4 phosphate buffer for six hours. Using this device, you can simulate the pH level of the mouth, the digestive tract, and the urinary tract. As a result of consistent release studies, formulation F7 released 88.2% of the drug after 12 hours. Models such as Higuchi, Korsmeyer-Peppas, and zero-order reactions were used to analyze the GIT. This directed the development of a sustained delivery pattern that may be perfect for colonic IRT administration in the eventual treatment of colon cancer. Among the nine formulations, F7 formulated with EC and HPMC extended best sustained release pattern of drug, hence it is suitable for treating colon cancer.

Keywords: Irinotecan hydrochloride, colon cancer, hydrophilic polymer, hydrophobic polymer, methacrylic acid copolymer.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.17

How to cite this article: Author Name. Title. International Journal of Drug Delivery Technology. 2024;14(3):1370-1376.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Colonic drug delivery system (CDDS) has grew attention and significance in current years due to the colon's suitability for both localised treatment of bowel diseases and systemic drug action, which can lead to complications such as poor constancy or asymmetrical intake in the greater gastrointestinal tract.[1,2] To accomplish a good colon specific release, the body must defend the drug absorption in the gut plus small intestine environmental condition and permit an unanticipated start of drug delivery after reaching the colons environment. Over the last ten years, a variety of delivery methods has been developed to focus oral medications to the colon area. The main types of techniques includes, pro-drugs, time-dependent, pH-sensitive, and micro flora activated systems are among that have been put forth.[3,4] One way to enhance colonic targeting is by integrating time-dependent and pH-sensitive functionalities into a single dose form. This will reduce the impact of fluctuations in gastric residence time by inhibiting drug release in the stomach.[5] Therefore, the goal of this work was to concurrently utilize the prolonged-release properties of the pH-dependent polymer and enteric coating to create an enteric coated and timed delivery matrix tablets for an oral medication to target colon region. Hydrophilic polymer was formed by combining hydroxypropyl methylcellulose with ethyl cellulose in matrix tablets. With Eudragit S100 and L100, methacrylic acid copolymers have been found to release products according to pH.[6-9]

MATERIALS AND METHODS

Materials

The Irinotecan hydrochloride (IRT) was gifted from sun pharmaceuticals. microcrystalline cellulose (MCC), ethyl cellulose, hydroxypropyl methylcellulose, Eudragit S100 and L100 and lactose were all obtained from Sigma-Aldrich. Other analytical grade materials were purchased from ibuy chemicals.

Drug-Polymer Interaction/Compatibility Study

The potential drug-excipient incompatibility was evaluated using compatibility studies.

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Fourier Transform Infrared Spectroscopical Analysis

In FTIR experiments, the polymers were thoroughly blended with FT-IR rating KBr in the ratio of 100:1 separately, with the drug-polymer physical combination was combined in a 1:1 ratio. The drug excipient interface was examined using FTIR analysis. Using the hydraulic press FTIR Spectrophotometer, 5.5 metric tons of pressure was used to create corresponding KBr discs. A wave number range of wave length between 4000 to 400cm was employed to scan the sample. The Figure 1 displays the IR spectra of Irinotecan hydrochloride containing colon-targeted tablet.[10,11]

Differential Scanning Calorimetry (DSC) Study

Drug, polymer, and drug polymer physical mixture at 1:1 ratio were all the subjects of DSC tests. Using a differential scanning calorimeter, the samples of irinotecan colon-targeted tablet were placed on a pan made up of aluminum and heated up to the level of At a rate of 10°C per minute, 200°C will be reached. Figure 4 represents the DSC characterization of the IRT colon-targeted tablet.[12]

Standard Calibration Curves of Irinotecan Hydrochloride

As part of the scan, we also scanned a buffer solution with a pH of 6.8 and one with a pH of 7. The wavelength of all cases has been reported to be 254 nm in previous reports. Based on Bier-Lambert's law, GIT's pH can be determined based on five different media (0.1N HCl; pH 7.4 and 6.7 phosphate buffers).[13-15]

Preparation of Matrix Tablets

Wet granulation was used for making the granules with 40% ethanol as the granulating fluid to avoid the undesired swelling of certain polymers that may occur with aqueous granulating fluid. Nine distinct batches of the matrix tablets were developed using various combinations of the polymers such as hydroxypropyl methylcellulose and ethyl cellulose. Irinotecan hydrochloride, (10 mg), was added into each nine formulations. The drug was combined with the appropriate amount of each polymer dispersed individually in ethyl alcohol to create a homogeneous wet form. Following the combination of wet mixtures, the mixtures were dried for one hour at 50°C in an air oven. Using a tablet press, magnesium stearate was applied after the dried granules were sieved with sieve no.40. In Table 1, the formulas are the same for both batches.

Molecular Characterization of Matrix Tablets

Examining the physical features of tablets

The tablet physical characterization such as weight variation, thickness, and friability of the IRT colon-targeting tablets were tested. The weight variation test was carried out in accordance with the standards. Using the Monsanto tablet hardness tester, the breaking strength (kg/cm2) of the tablets was ascertained. The tablet's friability was tested using a Roche friabilator (25 revolutions per minute for 4 minutes) and the content homogeneity was assessed as per the method outlined in the Indian Pharmacopoeia.[16,17]

Determination of drug content in tablet formulations

IRT core tablets were tested according to the tested method to determine the drug concentration. Following the dissolution of 100 mg of powder through 10 tablets in 50ml of methanol, we periodically sonicated the blend for 6 hours, ensuring full solubility. Filters were used to filter the solution once it reached volume. The concentration of IRT sample was recorded using UV spectrophotometer at 254 nm and methanol as a blank.[18,19]

Swelling studies

In order to determine swelling, medium 7.4 phosphate buffer was used for each batch of tablets of the IRT matrix tablets with the dissolution testing apparatus (U.S.P. Type-II) was used for the study, without applying rotational speed. The swelling index of the tablet was evaluated by using the formula below, after an hour the tablets were wiped with paper towel for the removal of surface droplets, following that weighed on a digital weighing device.[20,21]

$$\text{swelling index} = \frac{Wet\ weight\ of\ tablet - Dry\ weight\ of\ tablet}{Dry\ weight\ of\ tablet} \times 100$$

Enteric coating

Eudragit S100 and L100 were dissolved in acetone at 15 % w/v to make the enteric-coating solution. The acetone was chosen as a solvent to dissolve the enteric polymer. By immersing the tablets in the coating solution and then evaporated the solvent using rotary evaporator, and the tablets were coated.

Table 1: Capsules containing irinotecan hydrochloride target the colon

S. No	*Ingredients (mg)*	*Formulations*								
		F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
1	Irinotecan hydrochloride	10	10	10	10	10	10	10	10	10
2	HPMC	20	40	60	-	-	-	10	10	30
3	Ethyl cellulose	-	-	-	20	40	60	10	30	10
4	Lactose	64	44	24	64	44	24	64	64	64
5	MCC	2	2	2	2	2	2	2	2	2
6	Magnesium stearate	4	4	4	4	4	4	4	4	4
7	Ethanol 40%	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

The procedure was recurring, till the necessary quantity of coating to the tablet was attained.[22]

Dissolution of drugs in-vitro

Dissolving the tablets is easy with 0.1 N HCl in the presence of buffers that have a pH range of 6.8 and 7.4. The tablets disintegrated after 12 hours of rotation at 37°C. Every 1 hr 2ml of the sample were taken out consequently for 12 h and substituted with In order to keep the sink's condition, the medium must be replenished. The sum of drug delivery was examined using UV spectroscopy at 254 nm.[14,22]

Release kinetic models

IRT delivery rates from coated matrix tablets were calculated using kinetic modeling. Higuchi, Korsmeyer-Peppas, The analysis was conducted by using zero-order, first-order, and first-order models drug delivery effects. First-order models provide the best fit for artificial formulations based on correlation coefficients (R2) between 0.7447 and 0.9496. According to Korsmeyer-Peppas, all formulas invented can be described by this model. As described by Korsmeyer–Peppas, drugs are released from a polymeric network by the diffusion coefficient, or n. The Higuchi method was used for the preparation of all formulas. A polymer network is shown to release medicine through holes and diffusion. To suit the Higuchi, Korsmeyer-Peppas, and zero-order models, 24 artificial formulations were developed. Release kinetics were determined using DD Solver. Researchers have explored different dissolution models, including Higuchi and Korsmeyer-Peppas. By using algebraic formulas, illustrate kinetic systems (Table 2).

RESULTS AND DISCUSSION

A combination of HPMC polymer and ethyl cellulose is used in Eudragit S 100 and L 100 coatings. This design allows for the targeted release of the medication into the colon. The tablets were granulated using wet granulation technology and were tested against different criteria.

Drug-Polymer Interaction/Compatibility Study

The Fourier transform is used to represent the infrared spectrum of a flower

The FTIR spectrum was analyzed conducted with an FTIR spectrophotometer (FTIR-8400SCE, Shimadzu Corporation, Japan). Dry potassium bromide and irinotecan hydrochloride were mixed, and the scan range was 4000–400 cm-1. The resulting spectrum showed that the combination of irinotecan hydrochloride and polymer contains several functional groups (Figure 1 and 2). The findings of the investigation revealed there is no relationship concerning the excipient and the drug being studied.

Differential scanning calorimetry (DSC)

The combination of Irinotecan hydrochloride with polymer and other excipients such as ethyl cellulose, HPMC, MCC, and lactose were visible in DSC thermograms. Figure 3 displays the DSC thermogram of irinotecan hydrochloride and the figure 4 shows the combination of irinotecan hydrochloride with another excipient.

Calibration curves of Irinotecan hydrochloride

For 254nm wavelengths, the buffer consists of 0.1N HCl and phosphate at pH 6.8-7.4are mixed together to produce calibration curves. (Figure 5-7)

Characterization of the matrix tablets

Physical characterization of tablets

Drug dissolution, uniform thickness, hardness, and amount are measured. This were accomplished and the statistics are given in Table 3 and in Figure 8.

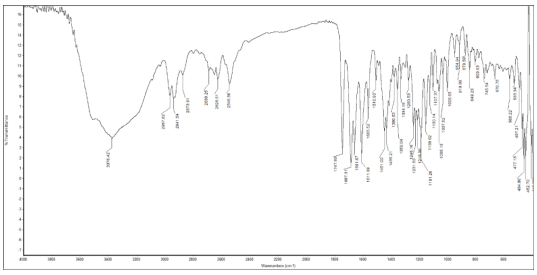

Figure 1: Irinotecan hydrochloride's FTIR spectrum

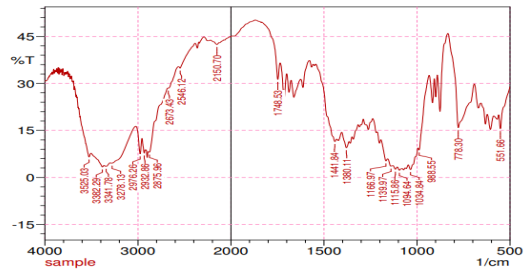

Figure 2: FTIR spectrum of optimized formulation Irinotecan hydrochloride tablets

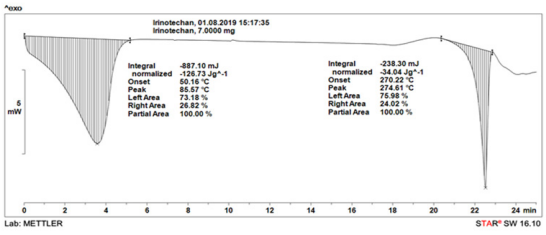

Figure 3: DSC analysis of pure drug

Table 2: Mathematical Modeling equations for kinetics

Kinetic model	*Zero-order model*	*First-order model*	*Higuchi model*	*Korsmeyer–Peppas model*	*Hixson–Crowell model*
Equation	$Q = k_0t+Q_0$	$Q = Q_0 \times ek_1t$	$Q = k_H \times t^{1/2}$	$Q = k_{kp} \times t^n$	$^{Q1/3}=k_HC+Q_0^{1/3}$

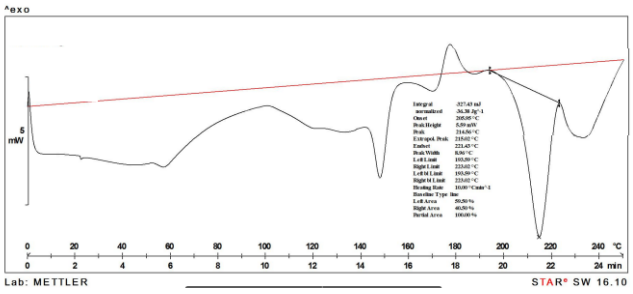

Figure 4: DSC analysis of optimized tablet of irinotecan hydrochloride

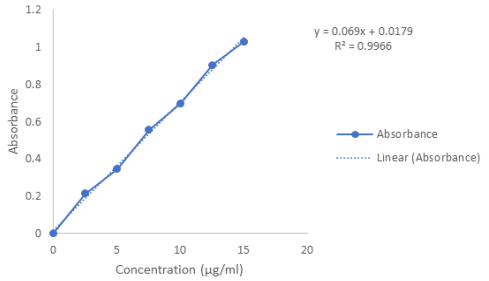

Figure 5: IRT calibration curves for 0.1N HCl

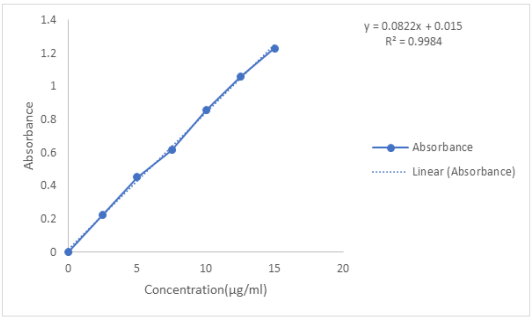

Figure 6: IRT using UV illumination in phosphate buffer pH 6.8.

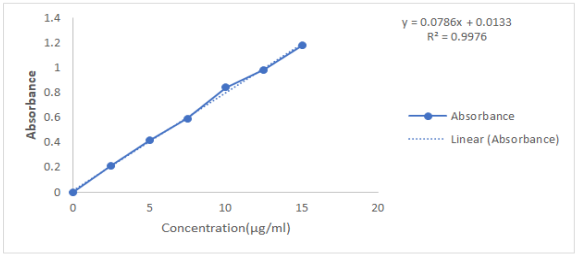

Figure 7: pH 7.4 buffered phosphate buffer

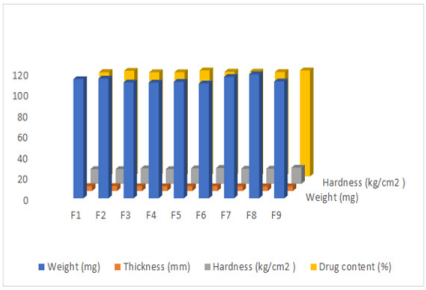

Figure 8: Physical characteristics of compression and core-coated tablets

Swelling studies

From the swelling study (Figure 9), it was known that the polymers included in IRT tablet have a swelling property due to its hydrophilic nature. The enhancement in swelling percentage increased corresponding to the time above 6 hours. Formulation F7 having a composition of two polymers showed more swelling index.

In-vitro drug release

Study examined the release patterns of drugs from tablets over a period of three weeks at different temperatures of 37°C and 37.5°C using the USP paddle-type dissolution apparatus II. For the dissolution experiment, water and 0.1N HCl were used to simulate stomach conditions, followed by water and phosphate buffer at a pH of 6.8 to simulate small intestine conditions, since food takes approximately two hours to leave the stomach. The small intestine passage time was recorded for a further 3 hours. The pH of the solution was then increased to 7.4 in order to simulate colon conditions for an additional 5 hours. After the sample has been dissolved, it is normally removed and replaced with a dissolution solution. With spectrophotometry, drug release at 254 nm was measured. On the basis of drug release percentages, Figure 10 illustrates the percentage of drugs released over time.[23-27]

Release kinetic models

Releases of Microsoft Excel were made possible thanks to DD Solver.[28,29] Several drug release models were additionally created, including Higuchi, Korsmeyer-Peppas, and Hixson-Crowell. The Figures 11-15 and Table 4 illustrate various formulations.

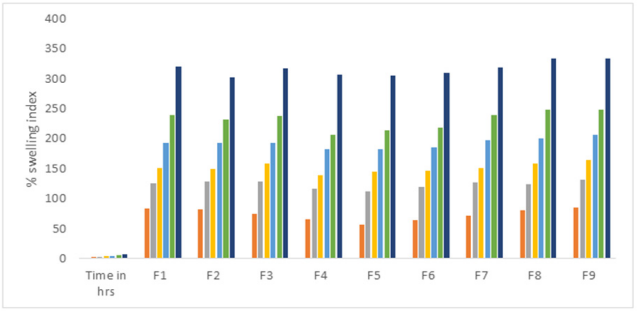

Figure 9: Swelling index of the formulations

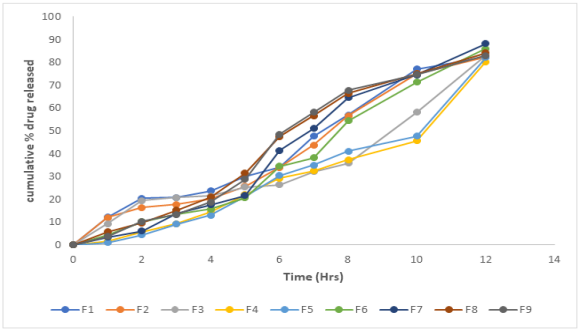

Figure 10: *In-vitro* drug release pattern

Table 3: A tablet with a compression coating

Formulation	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)
F1	113.50 ± 0.12	4.6 ± 0.00	14 ± 0.00	99.37 ± 0.56
F2	114.02 ± 0.13	4.65 ± 0.04	14 ± 0.00	100.68 ± 0.53
F3	110.32 ± 0.00	4.50 ± 0.004	14.66 ± 0.47	99.27 ± 1.01
F4	110.18 ± 0.2	4.54 ± 0.12	14 ± 0.00	99.31 ± 0.50
F5	110.99 ± 0.33	4.49 ± 0.00	14.66 ± 0.47	100.96 ± 0.83
F6	109.37 ± 0.77	4.55 ± 0.00	15 ± 0.00	99.76 ± 0.28
F7	115.61 ± 1.22	4.52 ± 0.02	14.33 ± 0.47	99.87 ± 0.73
F8	118.01 ± 0.36	4.43 ± 0.00	14.33 ± 0.47	99.47 ± 1.00
F9	111.24 ± 1.47	4.42 ± 0.00	15.33 ± 0.47	101.03 ± 1.14

Table 4: kinetic models and R^2 values for the formulations

R^2 values					
Formulations	*0 order*	*1st order*	*Higuchi*	*Korsmeyer-Peppas*	*Hixson Crowell*
F1	0.966	0.813	0.837	0.752	0.885
F2	0.958	0.795	0.8098	0.772	0.87
F3	0.898	0.745	0.766	0.739	0.805
F4	0.934	0.852	0.768	0.983	0.834
F5	0.942	0.777	0.772	0.991	0.845
F6	0.962	0.852	0.799	0.919	0.904
F7	0.967	0.898	0.821	0.956	0.937
F8	0.973	0.936	0.537	0.904	0.97
F9	0.958	0.949	0.560	0.935	0.96

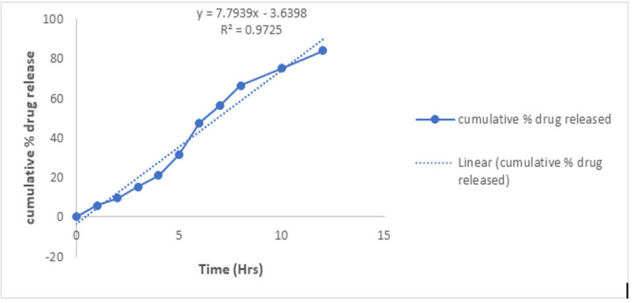

Figure 11: Zero order kinetic models for the formulations

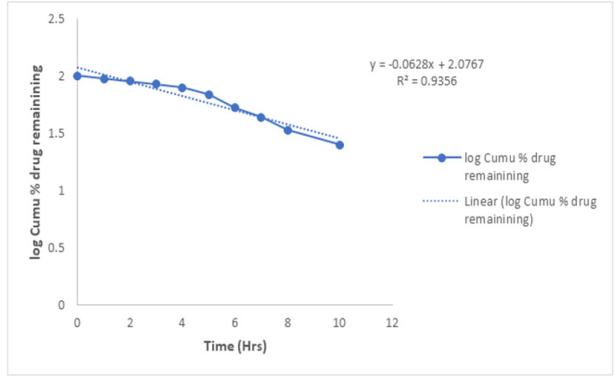

Figure 12: First order kinetic models for the formulations

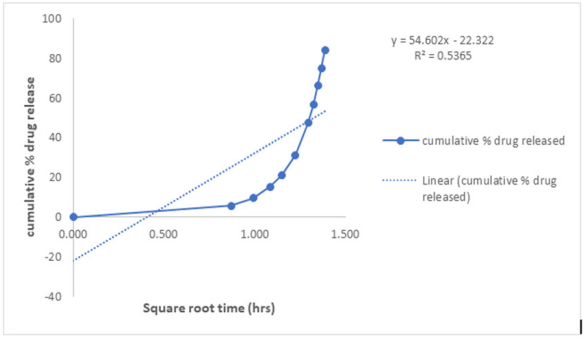

Figure 13: Higuchi kinetic models for the formulations

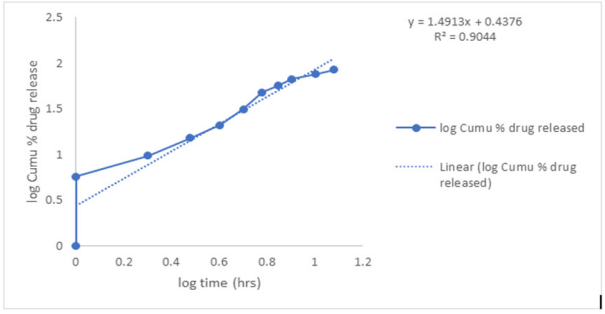

Figure 14: Kors-peppas kinetic models for the formulations

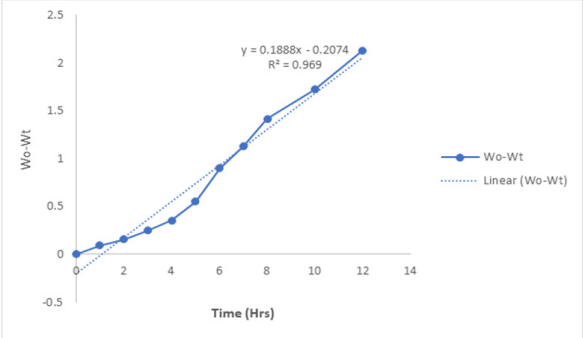

Figure 15: Hixson Crowell kinetic models for the formulations

CONCLUSION

Based on their findings, scientists believe formulations of irinotecan hydrochloride are effective enteric coated tablets formulated with the polymers namely ethyl cellulose and HPMC; after the compression of tablets, coated with methacrylic acid polymers like eudragit L100 and S100, which exhibited acceptable friability, weight variation, hardness and *in-vitro* drug release characteristics. Eudragit L100 and S 100 was the most successfully coating polymer. Irinotecan hydrochloride tablets F7 emerged as a preferred formulation and the coating ratio of 1:1(Eudragit L100 and S 100) was chosen for enteric coating to the extent of 15%, was least at the pH of 6.8 (colonic pH) and highest amount of the medication was released at a pH of 7.4 through a sustained delayed drug delivery, which will reducing the drug related adverse effect in the stomach as well as it will reduce frequency of dosing. From the above *in vitro* dissolution studies with F7 exhibits better controlled drug release. Hence, the drug release pattern from F7 will be beneficial for treating colon cancer. Therefore, further studies will be performed for the final setting up of the proposed dosage form.

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