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Research Article

Formulation, Optimization and Evaluation of Capecitabine Tablet for Colon Specific Drug Delivery System

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ABSTRACT

Aim: The present research is focused on development and optimization of colon specific, fast disintegrating Capecitabine tablet for the treatment of Colon cancer. Methods: Colon targeted core tablet of Capecitabine was prepared by using CCS (Croscarmellose sodium) as a super disintegrating agent by direct compression method and coating was done over the core tablets by using pectin in different ratios by compression coating method. The colon targeted coating was done on the compression coated tablets by using ES100 and CAP (Cellulose acetate phthalate) in different ratios by dip coating method. *In vitro* swelling studies were carried out at different pH (1.2, 6.8 and 7.4). The Design Expert software (v.10) was used to optimise the best formulation and an *in vitro* cumulative percentage of drug release in different dissolution media (pH 1.2, 6.8 and 7.4) with respect to the time interval (2hr, 7hr and 9hr) as dependable variable. Results: Optimized formulation of Capecitabine tablet shows satisfactory result with respect to all pre and post compression test parameters and it was significantly stable during stability studies conducted for 30& 60 days. Conclusion: From the above research it was found that, the optimised formulation of less half-life period anticancer drug Capecitabine can be properly targeted to colon area with the help of pectin and eudragit S 100.

Keywords: Capecitabine, colon targeted, eudragit S 100, optimisation, pectin.

INTRODUCTION

Oral drug delivery system can divided into three classes: Immediate-release (IR) preparation, second is Controlled-release (CR) preparation and last one is Targeted release preparation or site specific drug delivery system which require important polymer for drug delivery at a particular site within the Gastro Intestinal tract[1]. In such critical challenge the drug delivery approaches to reserve the preparation during its passage through the stomach and which about first six meters of the small intestine. The drug Capecitabine have an anticancer activity and which have short half-life, it is a serious drawback in conditions where localized delivery of the drugs in the colon is needs to be stable environment of upper GIT and which should reach the colon. The colon part has a long retention time and appears highly responsive to agents that increase the absorption of poorly absorbed drugs[2,4]. The Capecitabine tablet are design such as use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form which give repeat action of tablets. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of vermicides and colonic diagnostic agents require smaller doses[4]. There are many approaches are applied for colon targeted drug delivery to the colon, the primary approaches include which is coated drug delivery by using pH sensitive polymer to the colon area, time controlled release (delayed) system release drug delivery to colon area, microbial triggered to colon and newly developed approaches are pressure controlled drug-delivery systems, novel colon targeted delivery system, osmotic controlled drug delivery system[6].

The aim of the present study was to formulate colon targeted tablets of Capecitabine fast disintegrate tablets using Croscarmellose sodium, and direct compression done by pectin as enzyme dependent polymers along with followed by pH dependent polymers like Eudragit S100 and Cellulose acetate phthalate are used as coating material. After preparation of core tablet compression coating was done by using pectin, in different ratios by the direct compression method. The enteric coating was done on the compression coated tablets by using ES100 in different ratios by dip coating method. Optimisation done after formulate the formulation and the optimised formulation targeting to the colon area, using the animal model.

MATERIALS AND METHODS

The drug Capecitabine was obtained as gift sample and used as supplied by Hetero Pharmaceutical Industry, Himachal Pradesh. All other polymers and chemicals obtained were used as supplied by the standard manufacturers.

Experimental Design[7,8]

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In this study, a 2^3 factorial design was used for optimisation of the formulation. In this design, 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The independent variables were percentage of Pectin (X1) and coating level of Eudragit S100 (X 2). The dependent variables were percentage of drug release in 2 hr (Y1), percentage of drug release in 7 hr (Y2) and percent of drug release in 9 h (Y3). The formulation design along with values for variables is presented in the Table 1 & 2.When the release rate obeys a slow or very less profile in the upper GIT and a subsequent optimum release rate profile in the colonic colon targeted delivery becomes successful environment. For a successful colonic drug delivery system, it is essential to release the drug in the colonic environment without any release in the upper GIT. A slow release in the upper GIT can also be acceptable to a considerable extent. Therefore, the dependent variables i.e. the time points (2 h, 7 h & 9 h) are very much significant for the study design. The polynomial equations required for the purpose of ANOVA are obtained from the Factorial designs. The equation is shown as below. Table 1 summarizes the levels of independent variables.

$$Y= \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1X_2 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \quad A.1$$

Preparation of fast disintegrating Capecitabine core tablets:

The core tablets of Capecitabine were prepared by direct compression method shown in Table 3. After number of trials were made in order to reach an optimum and rapid disintegration and dissolution. Each core tablet (average weight 200mg) consists of Capecitabine (150mg), Microcrystalline cellulose (MCC, 6mg), Croscarmellose sodium (CCS 16mg), Lactose (10mg), Magnesium striate (2mg), Colloidal silicon dioxide (3mg) and Mannitol (15mg)were added to obtain fast disintegration of tablets (disintegration time <1min) of Capecitabine. The materials were weighed, blended and passed through a mesh (#60) to ensure proper mixing. Magnesium stearate and talc were mixed to the powder blend and compressed by the compression machine into the tablets by using 8 mm round, flat and plain punches on a 6 station tablet machine (Cadmach Ltd, India)[9].

Preformulation studies

Differential scanning calorimetry

The DSC curves Capecitabine, pectin and physical mixture of polymer and eudragit S100 were obtained using differential scanning calorimeter (Perkin Elmer, Japan) at increasing heating rate at 10˚ C/min and heated over a temperature range of 50˚ C to 300˚ C in an atmosphere of nitrogen (20ml/min). Accurately twelve mg of sample was taken in a hermetically sealed, flat bottom aluminium sealed pan and placed at sample stage and thermogram were recorded.

Fourier transforms Infrared spectroscopy

FT-IR spectra of Capecitabine, pectin and physical mixture of polymer and pectin were recorded at room temperature condition using KBr pellet technique. KBr pellets have been prepare by applying a pressure of 5-7 tons. IR spectrum was recorded using Perkin Elmer Spectrum GX FT-IR, measured at the maximum at 4000 cm-1 using methanol as a blank.

Evaluation of granules

Determination of bulk density and tapped density

Weighed the granules (W), was poured into the graduated cylinder and the volume (V0) was note. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured. The bulk density, tapped density were find out by using the formulae

Bulk density = W/V0

Tapped density = W/Vf

Angle of repose

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan\theta = h / r$

Where, θ = Angle of repose, h = height of the pile, r = radius of plane surface occupy by the powder.

Preparation of compression coated tablets

Fast dissolving tablets of Capecitabine were compression-coated with HPMC as time-dependent, and Pectin, direct compression method. The compression-coated of core tablets were done with 300 mg of compression coating materials as shown in Table 4 by using 10 mm concave punches. About 50% of the coat formulation was placed in the die cavity and core tablet was placed over the coating material then remainder of the coat formulation was placed over the core tablet, then it go for compress and get the compression coated tablet.

Enteric coating of prepared compression coated tablets[9]

Compression coated tablets of Capecitabine were further coated with enteric coating polymers by dip coating method. Required quantity of ES 100 and CAP as shown in Table 5 was dissolved in acetone using a magnetic stirrer. After complete solubilisation of polymer, castor oil (10% w/w of dry polymer) was added as plasticizer. Talc (0.1% w/v) was added as antiadherant and the solution was stirred for 15 min. Pre-weighted compression coated tablets were dipped for 3-5 times into the solution until 10% weight gain.

Evaluation of tablets

Thickness and hardness

Prepared matrix tablets were evaluated for thickness by using vernier calipers. Hardness of the tablets was evaluated using Monsanto hardness tester, which is expressed in kg/cm^2.

Friability

Friability of tablets was determined using Roche friabilator. Twenty tablets were weighed and placed in a chamber. According to guideline friabilator was operated at 100 revolutions (25 rpm for four minutes) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets

drops them at a distance of six inches with every revolution. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$F = Wi - Wf / Wi \times 100$ B.1

Weight variation

Weight variation test of tablets was performed according to guidelines of USP 2004, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation.

Drug content

Drug content of the Capecitabine coat tablets were tested crushing and powdering five tablets from each batch and take separately. The amount of powder equivalent to300 mg of the drug was weighed and dissolved in 100mL of distilled water. After 10 minutes of centrifugation, aliquots of 1mL were taken from this solution and diluted to 100mL with water (10µg/mL). The absorbance of resulting solutions was measured in an UV spectrophotometer at 235nm. Simultaneously, a 10µg/mL of Capecitabine standard solution was prepared in the same medium and the absorbance was recorded. Drug content was calculated.

Water uptake and erosion study

For conducting water uptake studies, the dissolution jars were marked with the time interval of 0.5, 1, 2, up to 9 h. One tablet was placed in each dissolution jar containing 900 ml of phosphate buffer pH 7.4 at 37°C ± 0.5°C and the apparatus was run at 100 rpm using paddle. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an oven at 40°C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was calculate according to following formula

$Q = 100 (Ww - Wi) / Ww$ C.1

Where Q is the percentage of the liquid uptake and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively. The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using following equation.

$E = 100 (Wi - Wf) / Wi$ D.1

Where Wf is the final mass of the same dried and partially eroded sample. The entire process was repeated to get three values for each time point and the average was calculated.

In vitro drug release studies[11,12]

The release studies of all the fast dissolving tablets were performed using a USP type II dissolution test apparatus (basket apparatus, 50 rpm, 37 ± 0.5ºC) in 900 mL of dissolution medium (SGF). 5 ml samples were withdrawn with pipetting syringe at appropriate time intervals and filtered through whatmann filter paper. Samples were estimated for drug using UV spectrophotometer (Simadzu, 1800) at suitable wave length 235 nm. Sink conditions were adjusted with the addition of an equal volume of fresh dissolution medium at the same temperature throughout the test. The pH of the dissolution medium was kept 1.2 for 2h then, pH of the dissolution medium was adjusted to 6.8 for 5 h and last adjust to 7.4 (SIF- simulated intestinal fluid) and maintained up to 24h.

In vitro disintegration study

The *in-vitro* disintegration study of the core tablets were determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the six tubes of the basket. Add the disc to each tube and run the apparatus using 900 ml of PBS pH 7.4 as the immersion liquid. The assembly should be raised and lowered between 30 cycles per min in distilled water maintained at 37ºC. The time in seconds for complete disintegration of the tablets with no palable mass remaining in the apparatus was measured and recorded.

In vitro Swelling study[9]

Swelling index of the tablet was evaluated in different medium (HCl buffer pH 1.2, PBS pH 6.8 and 7.4). The initial weight of the tablet was determined (W1) and then tablet was placed 10 ml HCl buffer pH 1.2 for 2 h then 10 ml of PBS pH 6.8 for 3 h and finally 10 ml of PBS pH 7.4 up to 24 h in a petridish. The tablet was removed at different time intervals (1, 2, 3, 4, 5… 24 h) blotted with filter paper and reweighed (W2). The swelling index is calculated by the formula:

Swelling index (SI),

$SI = 100 (W2 - W1)/ W1$ E.1

Where; W1 = initial weight of the tablet.

W2 = final weight of the tablet.

Preparation of solution

Preparation of 0.1 N HCl Solutions

0.1M HCl prepared by diluting 8.5 ml of concentrated hydrochloric acid to 1000 ml distilled water.

Preparation of 6.8 pH phosphate buffer solution

Weight 27.22g of potassium dihydrogen phosphate and diluted up to 1000 ml to get stock solution of potassium dihydrogen phosphate. Weight 8g Sodium hydroxide and diluted up to 1000ml to get 0.2M sodium hydroxide solution. Take 50 ml of the potassium dihydrogen phosphate solution from stock solution in a 200-mL volumetric flask, add 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution, and then add water to make Volume.

Preparation of 7.2 pH phosphate buffer solution

Weight 27.22g of potassium di hydrogen phosphate and diluted up to 1000 ml to get stock solution of potassium dihydrogen phosphate. Weight 8g Sodium hydroxide and diluted up to 1000ml to get 0.2M sodium hydroxide solution. Take 50 ml of the potassium dihydrogen phosphate solution from stock solution in a 200-mL volumetric flask, add 39.1 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution, and then add water to make Volume.

In-vivo X-ray studies

X-ray imaging technique or roentgenography was used to monitor tablets throughout the GI system. The inclusion of radio-opaque material into the solid dosage form enables it to be visualized by the use of X-rays. By incorporating barium sulphate into the pharmaceutical dosage forms, it is possible to follow the movement, location and integrity of the dosage form after oral administration by placing the subject under a fluoroscope and taking a series of X-rays

at various time points. Three healthy albino rabbit as animal model, male, with an age limit of 2-3 years and 2-3 kg body weight, were participated in *in vivo* studies. Each subject ingested barium sulphate containing pectin and eudragit s-100 compression coated and dip coated (optimised formulation) tablets orally, after an overnight fast. The tablets were visualized using X-ray. Abdominal radiographs were taken after 2, 4 6, and 7 hr in all subjects. The volunteers were served with food and keep it and notice the model. [Approved No – GIPSIAEC/M.Ph./2017/2]

RESULTS AND DISCUSSION

The present study was aimed to develop compression coated Capecitabine formulations for colon targeting using pectin and enteric coating polymers like Eudragit S100. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies. Capecitabine blend was subjected to various preformulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.535±0.03 to 0.561±0.01and 0.604±0.02 to 0.683±0.05 respectively. According to Table6, the results of angle of repose and compressibility index (%) ranged from 31.25±0.13 to 34.08±0.12 and 13.37±0.38 to 14.72±0.62 respectively in Table 6. According to the guideline the angle of repose value and compressibility index indicates fair to passable flow properties if the value angle of (<35) and compressibility index (<23) of the powder mixture. These results show that the powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coated tablets

Tablet quality control tests or post compression parameter such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 250 mg. The results of the post compression tablets were given in Table 7. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

DSC studies

DSC thermogram of Capecitabine, pectin and mixture are depicted in Fig 1 respectively. The thermogram of pure drug indicate a sharp endothermic peak at 121.95˚ C similar relationship to its melting point, while the Capecitabine and pectin exhibited a broad endothermic peak at 121.61˚C owing to its amorphous nature, while the thermogram of physical mixture of Capecitabine and Eudragit S100 was 121.94˚C. And the Physical mixture of Capecitabine and other polymer was 121.41^0 C. The DSC thermogram of Capecitabine and mixture showed identical peaks corresponding to pure drug indicated the absence of well-defined chemical interaction between the drug and the pectin.

FTIR studies

FTIR spectroscopy was performed to identify the supplied pure drug. The FTIR study is carried out to find out the possible interaction between drug and the polymer. FTIR study of Capecitabine showed the peak at 3217.86, 1604.08, 1238.13, 1.37.78, and 769.35 cm-1 due to the functional group like O-H, C=C, C-O, C-F and C-H respectively given in Table 8. The physical mixture of the drug with polymer like pectin, eudragit L 100, HPMC K4M, Lactose are also retaining the same peak, which reveals that, there is no interaction between the selected drug and the polymers.

In-vitro Drug Release Studies

The compression coated tablets containing 150 mg of Capecitabine were tested in 1.2, 6.8 and 7.4 pH phosphate buffer solution for their dissolution rates. The release of Capecitabine from compression coated tablets was carried out using USP paddle-type II and basket type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was prepared by using different dissolution media. Thus, studies of drug release were carried out SGF (in simulated gastric fluid, pH 1.2) for 2 hours as the normal with in 2hour average gastric emptying time. Then, the dissolution medium was substitute with enzyme- free SIF (simulated intestinal fluid, pH 6.8) and continued for drug release for 3 hours, as the average movement time of small intestinal is about 3 hours, and finally enzyme- free SIF (simulated intestinal fluid, pH 7.4) was used until 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Capecitabine tablets, added to 900 ml of dissolution medium. From dissolution medium 5 ml of sample was withdrawn every time and substitute with fresh medium, samples withdrawn at various time intervals were analysed spectrophotometrically at 235 nm respectively. All dissolution runs were performed for nine batches. From the dissolution values it was evident that the formulations F7were retarded the drug release up to 11 hours, they shown drug release of 98.51% respectively. Formulations F1 –F9 contains pectin and eudragit S100. As the concentration of pectin and eudragit S100 increases dissolution nature also decreased. F7 formulation contains 100 mg of pectin and eudragit S100 750mg showed almost negligible amount of drug release in first 3hours, from the 5^{th} hour onwards it shown drug release, polymer undergone erosion as the time proceeds slowly the and allowed the drug to come out from the dosage form. All the formulation showed maximum drug release in 11 hours and retarded drug release up to 12 hours and it showed i.e., in colon region shown in Fig 2. Similarly the formulation F8 containing pectin 80mg and Eudragit S 100 500mgalso showing seemlier releasing pattern of drugs.

Swelling study[9]

The swelling study of coated tablet of Capecitabine was performed in HCl buffer pH 1.2 for first 2 h, PBS pH 6.8 for 3 to 5 h and then 6 to 11 h in PBS pH 7.4 and the results are presented as percentage weight change with respect to time. The swelling behaviour of colon targeted system is an important property for uniform and prolonged release of drug. The swelling behaviour depends upon nature of polymer, concentration of polymer and pH of the medium. Most of the polymer hydrophilicity due to absorb the water and swelling of the tablet and depends on the time. The

Table 1: Factor and responses for experimental design.

Independent variables			Dependent variables
Level	X1 Pectin	X2 Eudragit S100	Y1 =Percentage Drug release at 2 hr
-1	60	250	Y 2= Percentage Drug release at 7 hr
0	80	500	
			Y3= Percentage Drug release at 9 hr
1	100	750	

Table 2: Experimental Design lay out and observed Results.

Std order	Formulation	Independent variables (Factor) mg		Dependent variables (Response) %		
		X1	X2	Y1	Y2	Y3
1	F1	60	250	0.9	20.67	80.58
2	F2	80	750	0.3	15.4	87.4
3	F3	100	500	0.87	10.2	91.5
4	F4	100	250	0.7	12.7	88.09
5	F5	80	250	1.01	16.1	86.7
6	F6	60	500	0.08	15.7	84.6
7	F7	100	750	0.31	7.14	97.2
8	F8	80	500	0.87	9.5	91.09
9	F9	60	750	0.09	12.4	87.8

Table 3: Composition of Core tablets.

Ingredients	Amount (mg)
Capecitabine	150
Microcrystalline cellulose	6
Croscarmellose sodium	16
Lactose	10
Magnesium striate	2
Colloidal silicon dioxide	3
Mannitol	15

hydrophilic polymer layer swells first, after as the hydrated layer increasing dissolves or disperse, the hydration swelling process will continuous towards new expose surfaces thus maintaining the integrity of dosage form. Compression coated tablets of Capecitabine which contains pectin and eudragit S100 formulation (F1 to F9)showed 4.2% to 9.2%, swelling in HCl buffer pH 1.2 after 2 h; when the medium changed to PBS pH 6.8 for 3 h then swelling was found to be 8.9% to 22.6% at the end of 5th h and finally tablet incubated up to 9 h in PBS pH 7.4 , showed 302% to 334% of swelling obtained.F7 and F8 showed swelling in a controlled manner but in case of F7 highest swelling was observed in PBS pH 7.4. All the formulation swells in controlled manner which was determined by swelling studies, shown in Fig 3.

Kinetic results[13]

The drug release mechanism and kinetics of the formulation is determined by the application of kinetics models such as zero order, first order, higuchi's model, korsmeyer-peppas model, and Hixon-Crowel kinetics as shown in Table 9. There are many formulation follows the Korsemayer- peppas release as their r^2 values are between 0.81–0.87. The mechanisms of drug release are non-fickian diffusion (super case-II), since they fitted well with Korsmeyer–Peppas models as their r^2 values in the range between 0.81–0.87 which n value higher than 1. The n value are between in 2.17 to 2.44. This confirmed that drug release kinetics follow the Korsemayer-peppasand drug transport mechanism follow non-fickian super case-II

Statistical optimization of Capecitabine tablets[7,8]

In order to optimize the formulation of colon targeted tablet of Capecitabine, the effect of selected variables amount of pectin and eudragit S100 was studied for drug delivery system. The overall performance independent variables shows the %of drug release in 2 h (Y1), %of drug release in 7 h (Y2) and finally percent of drug release in 9 h (Y3). According to the central composite design, nine formulations were prepared by varying the amount of independent variables. The individual and interactive effects of the dependent variables on the selected responses have been studied and shown in bellow Table 10. The data obtained in the study was statistically fitted to linear, interactive and quadratic models.

Statistical Data Analysis[14]

The statistical analysis of the data obtained from trial batches was performed by multiple linear regression analysis using Design Expert® 10 software (Stat-Ease Inc. USA). The data clearly indicates that the values of three independent variable that was % of drug release 2hr, % of drug release 7hr and % of drug release 9hr depends on

Table 4: Formulation of compression coat Ingredients (mg/tablet).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pectin	60	80	100	100	80	60	100	80	60
`MCC	154	154	154	154	154	154	154	154	154
HPMC K15M	30	30	30	30	30	30	30	30	30

Table 5: Composition of enteric coating material.

Ingredients	Quantity (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eurdagit S 100	250	750	500	250	250	500	750	500	750
CAP	500	500	500	500	500	500	500	500	500
Castor oil	1	1	1	1	1	1	1	1	1
Talc	50	50	50	50	50	50	50	50	50
Acetone	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml

Table 6: Preformulation parameters of core material.

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	34.08 ±0.12	0.561±0.01	0.680±0.01	15.24±0.05	0.852±0.02
F2	33.41±0.13	0.547±0.03	0.611±0.04	13.25±0.04	0.861±0.01
F3	33.67±0.12	0.555±0.01	0.683±0.05	14.05±0.03	0.863±0.03
F4	33.24±0.14	0.541±0.02	0.664±0.03	14.87±0.04	0.864±0.05
F5	32.87±0.12	0.562±0.03	0.620±0.02	14.12±0.03	0.846±0.04
F6	32.45±0.11	0.554±0.02	0.654±0.03	13.54±0.04	0.849±0.06
F7	31.25±0.13	0.535±0.03	0.604±0.02	13.23±0.02	0.845±0.03
F8	32.89±0.11	0.541±0.02	0.637±0.03	13.75±0.03	0.866±0.03
F9	31.81±0.13	0.554±0.01	0.658±0.02	13.81±0.05	0.868±0.02

All the values are represented in mean±SD (n=3).

Table 7: Post compression studies.

Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Deviation in Weight variation (mg)	Drug Content (%)
F1	4.1±0.01	5±0.02	0.51±0.04	250.01±1	84.54±0.1
F2	4.2±0.02	5.1±0.01	0.53±0.05	251.1±2	89.4±0.8
F3	4.1±0.01	5±0.03	0.52±0.04	249.8±2	95.5±0.5
F4	4.2±0.03	5±0.02	0.51±0.03	250.01±1	93.09±0.6
F5	4.4±0.01	5.1±0.02	0.49±0.02	249.7±3	91.7±0.7
F6	4.1±0.02	5±0.03	0.51±0.02	252±0.7	88.6±0.8
F7	4.3±0.01	4.9±0.04	0.48±0.03	248.9±2	98.8±0.6
F8	4.2±0.03	5.01±0.02	0.50±0.03	250.01±4	94.09±0.6
F9	4.1±0.02	4.9±0.03	0.52±0.01	251.07±4	92.8±0.7

All the values are represented in mean±SD (n=3)

Table 8: FTIR interpretation of Capecitabine and Drug polymer mixtures.

Sl No	Functional group	Vibration range (cm-1)	IR absorption bands (cm-1)	
			Capecitabine	Drug polymer mixture
1	O-H stretching	2500-3300	3217.86	3234.95
2	C=C stretching	1610-1620	1604.08	1607.30
3	C-O stretching	1200-1275	1238.13	1240.39
4	C-F stretching	1000-1400	1037.78	1037.93
5	C-H bending	760-800	769.35	768.27

dependent variables i.e. amount of pectin And eudragit s100. Table 11 shows the results of analysis of variance (ANOVA), which was performed to identify significant and insignificant factors. The model F-values for the responses i.e.% of drug release 2hr, % of drug release 7hr and % of drug release 9hr were found to be 12.34, 11.98 and 10.35 respectively. This implies that the models were significant. The values of prob > F (Less than 0.05) for all the responses indicated the significance of the model. The polynomial equations relating the responses to the factors have been generated by multiple linear regression analysis as expressed below (eq. 9-11)

% of drug release 2hr = $+1.31 -1.08A_1- 0.88B_2- 0.52A_1B_2+0.88A_1^2+0.48B_2^2$ F 1

% of drug release 7hr = $+11.07-3.12A_1- 3.24B_2+0.68A_1B_2+1.10A_1^2+1.45B_2^2$ F 2

% of drug release 9hr = $+84.52+4.75A_1+4.32B_2+0.50A_1B+0.72A_1^2+0.72B_2^2$ F 3

Where, $A_1$and B_2 are coded values of the test variables i.e. amount of pectin and eudragit s100 in %w/w. The equations can be used to draw the conclusion after considering the magnitude of the coefficient and the mathematical sign it carries. Contour plot and 3D response

Table 9: Release kinetic studies of tablet.

Model		Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero order	K	6.74	7.03	7.25	7.13	7.08	6.89	7.51	7.21	7.05
	R^2	0.72	0.67	0.64	0.65	0.68	0.67	0.61	0.64	0.66
First order	K	0.09	0.09	0.093	0.091	0.091	0.088	0.096	0.093	0.090
	R^2	0.61	0.56	0.53	0.54	0.57	0.57	0.49	0.53	0.55
Higuchi	K	17.14	17.74	18.22	17.92	17.88	17.36	18.75	18.12	17.75
	R^2	0.48	0.44	0.41	0.43	0.45	0.44	0.39	0.42	0.43
Hixon-Crowel	K	0.027	0.028	0.029	0.028	0.028	0.027	0.030	0.028	0.028
	R^2	0.65	0.59	0.56	0.58	0.60	0.60	0.52	0.56	0.58
Korsemayer-peppas	K	0.54	0.41	0.33	0.34	0.41	0.40	0.27	0.33	0.36
	R^2	0.87	0.84	0.83	0.84	0.85	0.85	0.81	0.83	0.84
	N	2.17	2.32	2.44	2.41	2.32	2.32	2.55	2.44	2.39

Table 10: Coefficient and *p* value of each factor for response R1, R2 and R3.

Factor	R1		R2		R3	
	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
A_1	-1.083	0.012	-3.12	0.013	4.75	0.0132
B_2	-0.88	0.021	-3.23	0.013	4.32	0.017
A_1B_2	-0.525	0.12	0.68	0.43	0.5	0.68
A_1^2	0.88	0.08	1.10	0.36	0.72	0.68
B_2^2	0.48	0.26	1.45	0.26	0.72	0.68

Significant factor (p<0.1)

Table 11: Results of Analysis of variance (ANOVA).

Source of Variation	DF	SS	MS	F	R^2	*P* -value
Response R1 % of drug release 2hr						
Model	5	14.85	2.97	12.34	0.95	<0.0325
Residual	3	0.72	0.24			
Total	8	15.58				
Response R2 % of drug release 6hr						
Model	5	129.87	25.97	11.98	0.9523	<0.0339
Residual	3	6.51	2.17			
Total	8	136.37				
Response R3 % of drug release 8hr						
Model	5	250.23	50.05	10.35	0.9452	<0.0414
Residual	3	14.50	4.83			
Total	8	264.74				

DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, fischer's ratio; R2, regression coefficient.

Table 12: Comparison of experimentally observed responses of the optimized Capecitabine tablet with predicted responses.

Response Parameter	Observed Value	Predicted Value	Error (%)
% of drug release 2hr	0.21	0.19	10.5
% of drug release 7hr	8.12	7.94	2.3
% of drug release 9hr	92.15	94.89	-2.88

Table 13: Results of short term physical stability study.

Parameter	Study Period		
	0	1	3
Hardness	4.3±0.01	4.2±0.02	4.4±0.01
Thickness	4.9±0.04	4.9±0.04	4.90.003
Friability	0.48±0.03	0.48±0.01	0.48±0.02
Drug Content	98.8±0.6	97.54±1	97.5±.5
Dissolution Profile	98.51±1.2	97.15±1	96.4±1

All the values are represented in mean±SD (n=3).

surface graph of Pectin and Eudragit S 100 at different time shown in Fig 4.

Search for optimum formulation[7]

This was the most important part of response surface methodology. Response surface optimization is more advantageous than the traditional single parameter optimization in that it saves time, space and raw material. A numerical optimization technique have been using the desirability approaches employed to develop a new formulation with the desired responses. Upon comprehensive evaluation of the feasibility search and subsequently exhaustive grid searches, the formulation

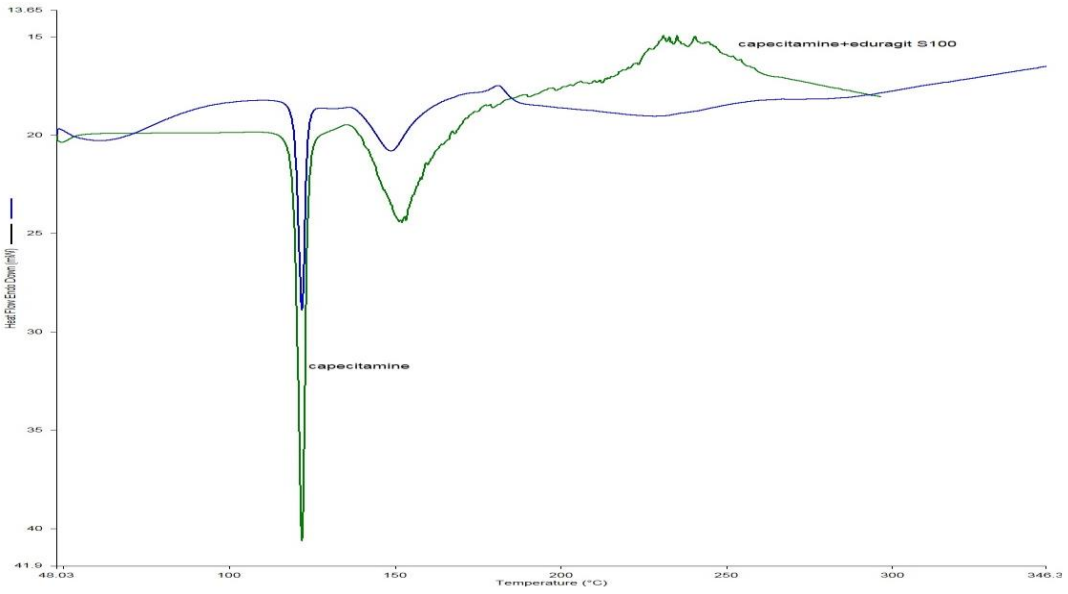

Figure 1: DSC thermogram of pure drug and physical mixture.

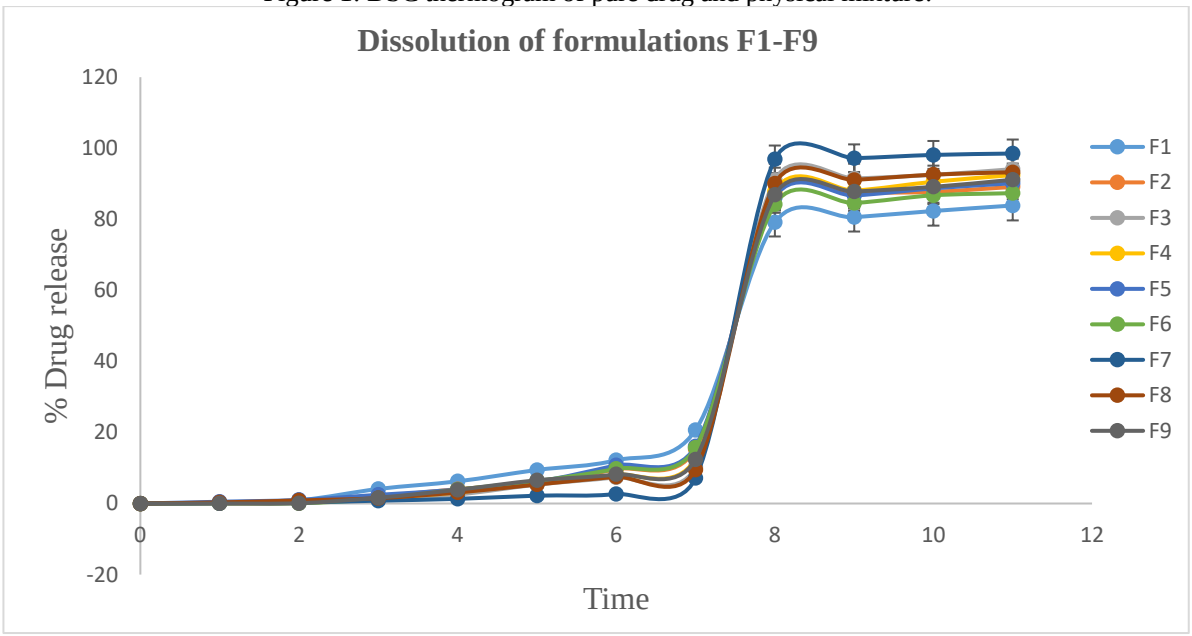

Figure 2: % Cumulative release of Capecitabine from different formulations.
All the values are represented in mean±SD (n=3).

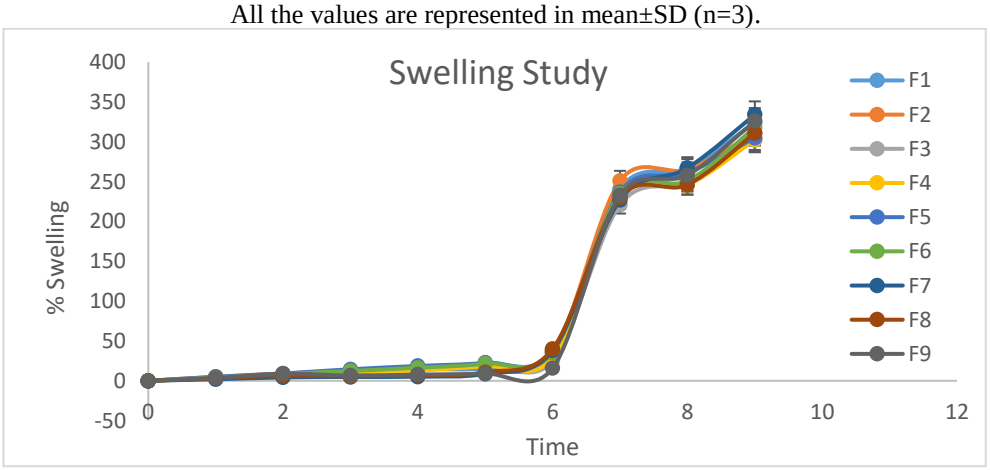

Figure 3: % Swelling study of various tablet formulations.
All the values are represented in mean±SD (n=3).

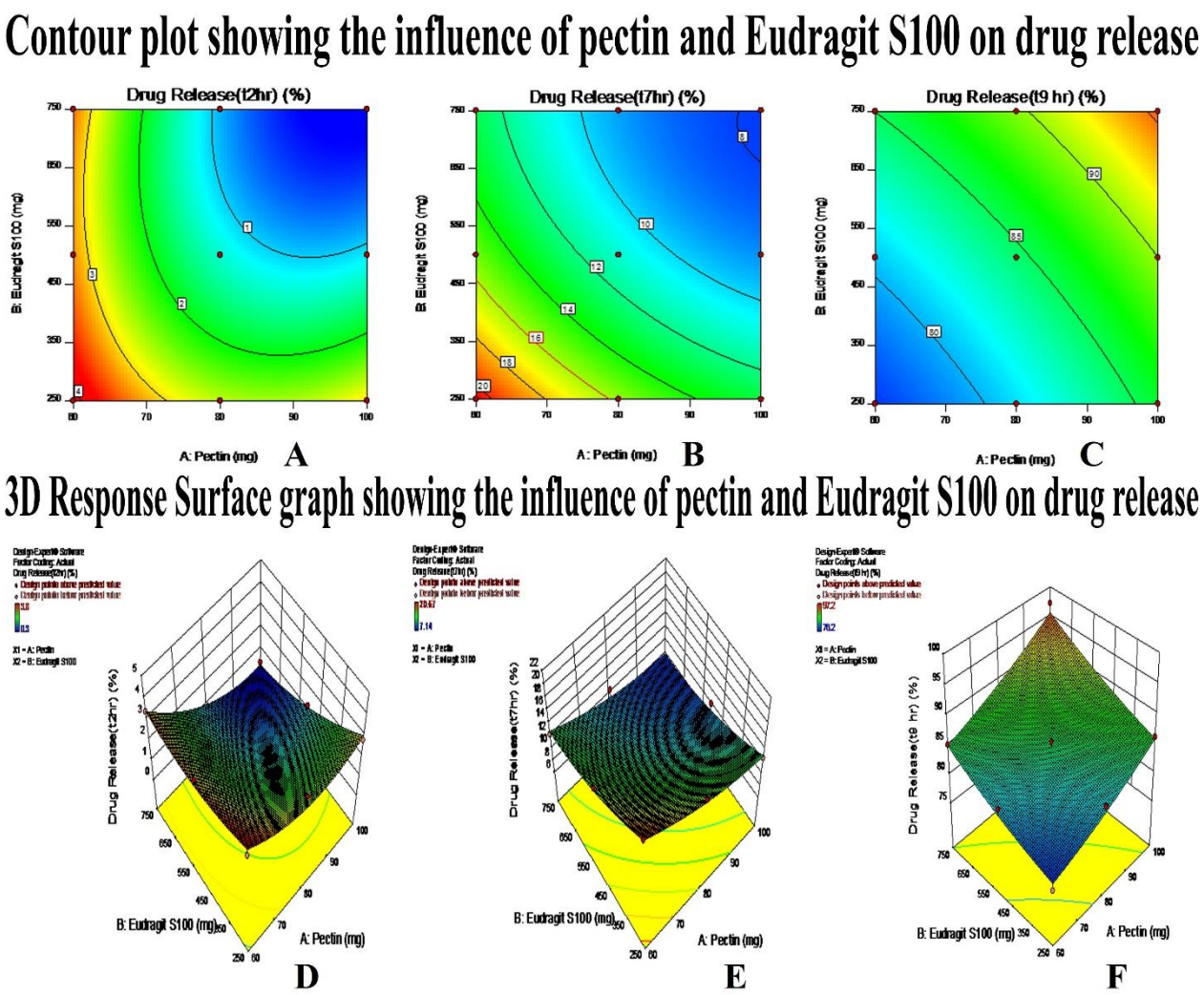

Figure 4: Contour plot and 3D response surface graph of Pectin and Eudragit S 100 at different time.

composition with Pectin amount of 98.68gm and the amount of Eudragit S100 was 742.35gm, fulfilled maximum requirements of an optimum formulation, desirability 1.00. The higher desirability value indicates the more suitability of the formulation in terms of maximized % of drug release in 9hr and better regulation of drug release rate. The optimized formulation was evaluated for various independent variables. The response values were calculated and compared to the corresponding predicted values. Table 12 lists the values of the observed responses and those predicted by mathematical models along with the percentage prediction errors. The prediction error for the response parameters ranged between -2.88 to 10.5%.

In vivo x-ray imaging studies[15]

X-ray studies were carried out the optimised formulation tablets among the formulation, in order to see the coated tablets throughout the GI system. Barium sulphate was used as the marker for the X-ray studies. The position of the tablets in the body was monitored at different time interval i.c. first reading taken at 0hr and 2hr after administration the tablet then monitoring again after 4hr, monitoring after 6hour and finally after 8hr. The abdominal radiograph which shows that, the tablets remains intact in the stomach in all subjects. The transit time of the tablets throughout the GI system was variable. The position of tablets at different time points is shown in the x-ray images of tablet throughout the GI system (Fig 5). From the abdominal radiographs, taken at different time points and the movement of the drug can observe without dissolving or disintegrating. After tablet administration when the drug reached in the colon after 2- 8hr then the drug disintegrate and dissolution occurs it can observe. These results are in agreement with the results of Ashford *et al*. who observed that the gastric emptying times of 0.6–2.9 h, small intestinal transit times of 1.8–8.5 h and colonic arrival time of 3.2–9.8 h while evaluating pectin as a compression coat for colonic delivery, using gamma scintigraphy.

Physical stability study[7]

Statistical analysis of the results, before and after conducting the stability studies for 3 months, was carried out using paired Students t-test. No significant difference ($p > 0.05$) was observed in the tablet appearance, hardness or thickness. The dissolution was calculated for comparison of dissolution profile before and after stability studies. The optimised formulation (F9) values were found more than 50 (96.46 and 88.02 respectively after one and

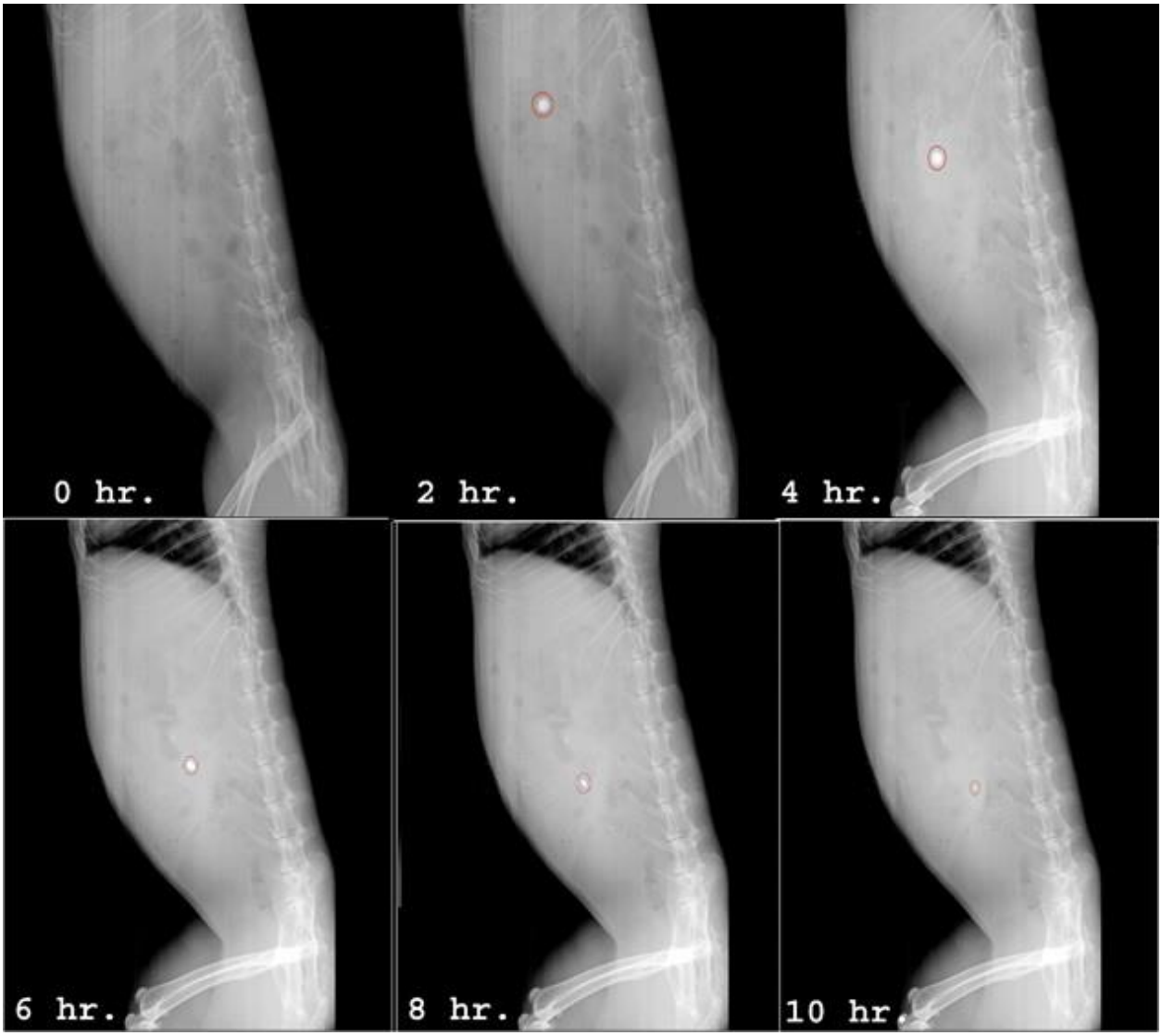

Figure 5: X-ray study of the Capacitabine tablet throughout the GI tract at different time points.

three months) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the post formulation parameter. The periodic data of stability study is presented in Table 13. The results of stability studies indicate that the developed formulation has good stability.

CONCLUSION

The present research work was involved with the development of the colon targeted tablets, which after oral administration were developed to prevent the drug release in stomach and small intestine. It improves the bioavailability of the drug with less time. Different formulations were developed by using pH dependent polymer like Pectin, Eudrgit S 100 by direct compression and coating by dip coating methods. Formulated coated colon targeted tablets and evaluated the required physicochemical parameters like pre-compression and post-compression such as hardness, friability, weight variation, drug content etc. From the above research it was found that, the optimised formulation of less half-life period anticancer drug Capecitabine can be properly targeted to colon area with the help of pectin and eudragit S 100.

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AUTHORS' CONTRIBUTION

All the authors have participated equally in the research work and also extensively helped in preparation of draft of the manuscript.

DECLARATION

The authors declare no conflict of interest.

ANIMAL RIGHTS

The institutional and international Guide for the Care and Use of Laboratory Animals was followed and the study was approved by the Institutional Animal Ethics Committee (IAEC) (Approved No. – GIPSIAEC/M.Ph./2017/2) and all the animals were maintained as per the guidelines of CPCSEA.

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