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Formulation and Evaluation of Colon Targeted Drug Delivery System of Busulfan: Using Combination of pH and Time Dependant Systems

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ABSTRACT

In present work Colon targeting drug delivery system was developed for Busulfan an anticancer drug by using combination of delayed systems one is pH dependant and other is time dependant delayed system. Rapid release core tablet (RRCT) formulations were prepared using Busulfan drug with different disintegrating agents in different concentrations. The pre-compression and post-compression parameters of all formulations were determined and the values were found to be satisfactory. From the In-vitro dissolution studies, F6 formulation with 12% Hydroxy propyl cellulose (HPC) was the best formulation. For optimized RRCT formulation press coat was done by using Xanthum Gum and Ethyl Cellulose (EC) in different ratios. Press coated tablet delays the drug release up to 8 hours based on the nature and concentrations of the polymer. Each press coated tablet was coated using enteric solution made of HPMC phthalate, Myvacet and color dissolved in ethanol. Enteric press coated tablets (EPCT) were delayed drug release up to 2hrs in fed condition due to pH dependant delayed system. Based on dissolution studies of EPCT formulations, C3OPF formulation was optimized and showed delayed release pattern in a much customized manner. As a result of this study it may be concluded that the colon targeted drug delivery tablets using a combination of two polymers in optimized concentrations can be used to increase the delayed action of drug release to deliver the drug in a delayed manner.

Keywords: Colon, RRCT, HPC, Xanthum gum and EPCT

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1. INTRODUCTION

Oral administration is that the most well liked route for systemic effects because of its simple uptake and patient compliance. Additionally, solid oral delivery systems don't need sterile conditions and are so, less expensive to manufacture. Colon is being extensively investigated as a drug delivery site. Oral colon-specific drug delivery system (CDDS)[1] has been developed by means of combination of one or more controlled release mechanisms. The arrival of an oral dosage form at the colon is determined by the rate of gastric emptying and the small intestine time. The presence of food generally increases residence time and in some cases with regular feeding, dosage forms have been reported to reside in the stomach for periods in excess of 12 hours. Small intestine transit is surprisingly constant at 3-4 hours and appears to be independent of the dosage form and fasted or fed state. Therefore a dosage form could take from as little as 4 hours to longer than 12 hours to arrive at the colon following oral administration. In healthy and young adult male, dosage forms such as capsule and tablets pass through the colon in approximately 20-30 hours, although the transit time of a few hours to more than 2 days can occur.

Three types of approaches to colon specific drug delivery: pH dependent delivery[2], timed release dosage forms and delivery based on metabolic activity of colonic bacteria. Timed-controlled formulations have also been prepared using water insoluble ethyl cellulose and swellable polymer. Each of the formulations consisted of a rapid releasing core with drug, swellable and water insoluble polymer. The swelling polymer absorbs liquid and ethylcellulose coat disintegrated as the core swells.

Busulfan is a cell cycle non-particular alkylating anticancer drug. Busulfex and Myleran are two well-known trade names for this drug. Busulfan used in alone or combination with cyclophosphamide as conditioning agent prior to chronic myelogenous leukemia and other lymphomas. This drug recently used to study the role of serotonin in liver regenerations. Busulfan is chemotherapy

drug used to treat blood cancer before stem cell transplant[3].

2. METHODOLOGY

2.1 Materials: Busulfan drug is gifted by Chandra labs, Hyderabad. Micro crystalline cellulose (Avicel pH 102), Hydroxyl propyl cellulose (HPC) and Cross carmellose sodium (CCS Ac-Di-Sol) were purchased from S.D fine chemicals Ltd, Mumbai. Sodium starch glycolate (SSG) was purchased from Mylan chemicals Ltd, Mumbai. Ethyl cellulose (EC), HPMC Phthalate-55 and Xanthum gum were purchased form ESSEL fine chemicals, Mumbai. Other chemicals and reagents were laboratory standards.

2.2 Equipment: Electronic balance (Citizen, India), Tablet compression machine (Cadmach single punch machine), Hardness tester (Monsanto hardness tester), Dissolution apparatus (Lab India), Disintegration apparatus (Campbell Electronics), Friability test apparatus (Riche Rich), UV-Visible spectrophotometer (Shimadzu UV-1601, Japan), Fourier transformer infrared spectrophotometer (Bruker).

2.3 Analytical Methods[4]

2.3.1 Estimation of Busulfan (API): Busulfan drug was studied for physical description like colour, odour and also estimated melting point of pure drug.

2.3.2 Determination of λ max for Busulfan: On the basis of preliminary identification test, it was concluded that the drug complied the preliminary identification.

2.3.3 Preparation of calibration curve in 0.1N HCL

Preparation of Standard Stock solution: 100 mg of Busulfan was dissolved in 100 ml 0.1N HCL to give a concentration of (1000µg/ml).

Sample Preparation and Scanning: 10ml of standard stock solution was diluted to 100 ml with 0.1N HCL respectively to get 100 µg/ml stock solutions. From this stock solution, aliquots of 2, 4, 6, 8, 10 ml were pipetted out and made up to 100 ml in order to get concentration ranging from 2-10 µg/ml. The absorbance of the solution was measured by UV spectrophotometry.

2.3.4 Preparation of calibration curve in 6.8 phosphate buffer[5]

Standard solution: 100 mg of Busulfan was dissolved in acetonitrile and made up to a volume of 100 ml with pH 6.8 buffer solution to give a concentration of 1 mg/ ml (1000 µg/ml).

Sample preparation and scanning: From standard solution take 1 ml of solution in 100 ml of pH 6.8 buffer solution to produce the 10 µg/ml concentration .different aliquots of solutions were taken to produce 2, 4, 6, 8 and 10 µg/ml concentrations. The absorbance of prepared solution of Busulfan was measured in UV/visible spectrophotometer against pH 6.8 buffer solutions as blank.

2.4 Pre-compression flow parameters for RRCT[6]

2.4.1 Angle of Repose: The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

where, h = height of a pile (2 cm), r = radius of pile base.

2.4.2 Bulk density (BD): Bulk density measuring the volume of known mass of powder sample and it is passed into the graduated cylinder and the ratio of given mass of powder and its bulk volume is known as bulk density.

$$\text{Bulk density} = M / V_0$$

Where, M= mass of the powder, V_0=bulk volume of the powder.

2.4.3 Tapped density (TD): Weigh accurately a quantity of powder and transferred into a measuring cylinder and note down the volume as V_0. Now the measuring cylinder is fixed to density determination apparatus, and tapped for 500 times until no further volume changes is observed then note down the volume Vr.

$$\text{Tap density} = M / Vr$$

Where, M = mass of the powder, Vr = final tapping volume of the powder.

2.4.4 Compressibility index and Hausner ratio: Bulk density and tapped density values were used to calculate the compressibility index and hausner ratio following is the equation:

$$\text{Compressibility index (CI)} = 100 \times (TD-BD) / TD$$

$$\text{Hausner ratio} = TD/BD$$

2.5 Drug-Excipient compatibility studies

Drug and Excipient compatibility studies were performed for pure drug and final blend used in enteric press coated tablet formulation using FTIR.

2.6 Formulation of Rapid release core tablets (RRCT)[7]

Direct compression method is used for the preparation of inner core tablets required quantities ingredients like Busulfan, MCC, CCS, SSG, HPC, Starch as shown in the table were taken, make them into a mixture and subjected to dry blending for 20 minutes followed by addition of Magnesium Stearate and Talc. The mixtures were then further blended for 10 min., 200 mg of resultant powder blend was, punched to obtain the core tablet.

Table no.1 Formulation of Busulfan RRCT

Ingredients(%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Busulfan (mg)	2	2	2	2	2	2	2	2	2
Starch	10	10	10	10	10	10	10	10	10
CCS	4	8	12	-	-	-	-	-	-
HPC	-	-	-	4	8	12	-	-	-
SSG	-	-	-	-	-	-	4	8	12
Magnesium stearate	2	2	2	2	2	2	2	2	2
MCC	Qs	Qs	Q s	Qs	Qs	Qs	Q s	Qs	Qs
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200	200	200

2.7 Evaluation of post compression parameters[8]

2.7.1 Size and Shape: Thickness is the only variable to calculate the size and shape of a tablet. Micro - meter is the device which is used to determine the thickness of the tablet. Controlled variation for tablet thickness lies within a ± 5% standard value.

2.7.2 Weight variation test: 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (+5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.7.3 Hardness: Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in Kg/cm^2.

2.7.4 Friability: Weigh about 10 collectively tablets from each batch and place them in the Roche friabilator chamber. Now they were subjected to rolling, a free fall in the chamber from a height of 6cm which is rotated at a rate of 25 rpm. Repeat the procedure till the completion of 100 rotations (4 minutes), and now the tablets were taken out from the friabilator and note their weight. The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1 - W_2) / W_1 \times 100$$

Where, W_1 = Weight of tablets before test, W_2 = Weight of tablets after test

2.7.5 In-vitro release studies for RRCT[9]: Tablet was introduced into the basket of the instrument (USP-II, 37 ± 0.5°C) which is rotated at 50 rpm for time period of 1 hr. Withdraw 5 ml of sample aliquots with predetermined time intervals (5, 10, 15, 20, 30, 45 and 60min) and is replaced by pH6.8 phosphate buffer solutions. Determine the amount of drug in the withdrawn samples.

2.8 Preparation of Enteric press coated tablets (EPCT)

The optimized core tablets were press-coated with 250 mg of mixed blend/granules. Different proportions of barrier layer material (1:1, 0:1, 1:0, 4:2 and 2:4) was weighed and transferred into the die then the core tablet was placed manually at the centre. The remaining mg of the barrier layer materiel was added into the die and punched in to a 12mm die at a pressure of 5tons for 3min using hydraulic press. Press coated tablets were enteric coated using spray drying method and enteric coated solution was prepared as mentioned in table no.3.

Table no.2 Polymer ratio for press coated tablets:

Polymer (mg)	C_1OPF	C_2 OPF	C_3 OPF	C_4 OPF	C_5 OPF
Xanthun gum	250	125	166.6	83.4	0
EC	0	125	83.4	166.6	250

OPF- Optimized RRCT Formulation

Table no.3 Enteric coated solution formula

Ingredients (mg)	
HPMC phthalate 55	15.17
Myvacet	1.52
Ferric oxide (red)	1.58
Ethanol	Qs

2.9 In-vitro Dissolution methods for EPCT[9]

In –vitro Dissolution studies of oral colon targeted drug delivery systems was done with the conventional paddle method and dissolution was performed at 37 ± 0.5°C using 0.1N HCL in USP II paddle method at 50 rpm for first two hours and replaced with pH6.8 phosphate buffer. Samples were withdrawn for every one hour up to 10hrs and replace the same with new fresh dissolution medium to achieve sink condition. The samples were analysed using UV spectrophotometer.

2.10 Release kinetics for optimized EPCT[10]

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

3. RESULTS AND DISCUSSION

3.1 Analytical studies of Busulfan (API)

3.1.1 Description of Busulfan:

Table no.4 Estimation of Busulfan (API)

Description	Color - A white or almost white crystalline powder Odor – Free of odor
Solubility	Acetonitrile – Freely soluble Methanol – Slightly soluble Water – Very slightly soluble
Melting point	106 – 107^{0}C

3.1.2 Scanning of Busulfan (API):

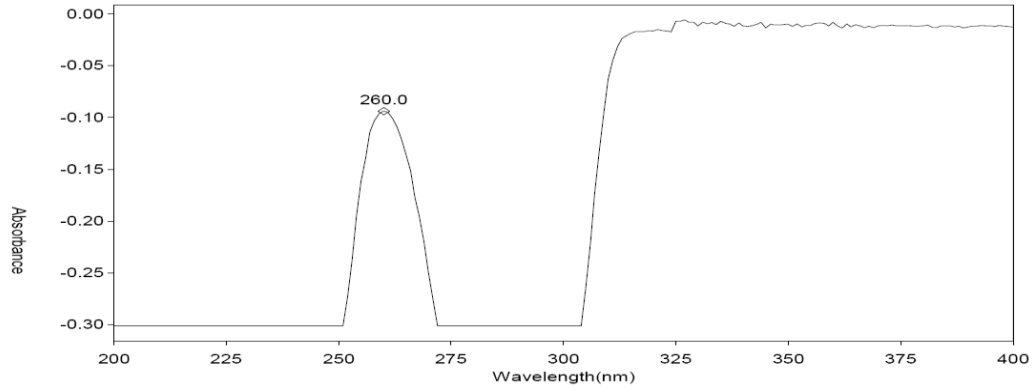

Figure no.1 UV-Visible spectrum observed at 260nm

3.1.3 Calibration curves of Busulfan:

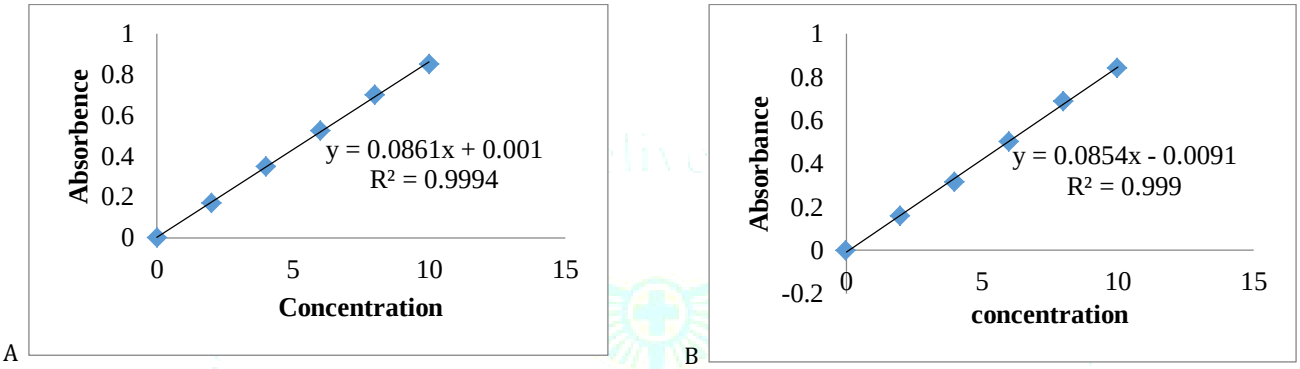

Figure no.2 Standard graph of Busulfan in A) 6.8pH phosphate buffer B) 0.1N HCL

3.1.4 Drug excipient compatibility studies (FTIR):

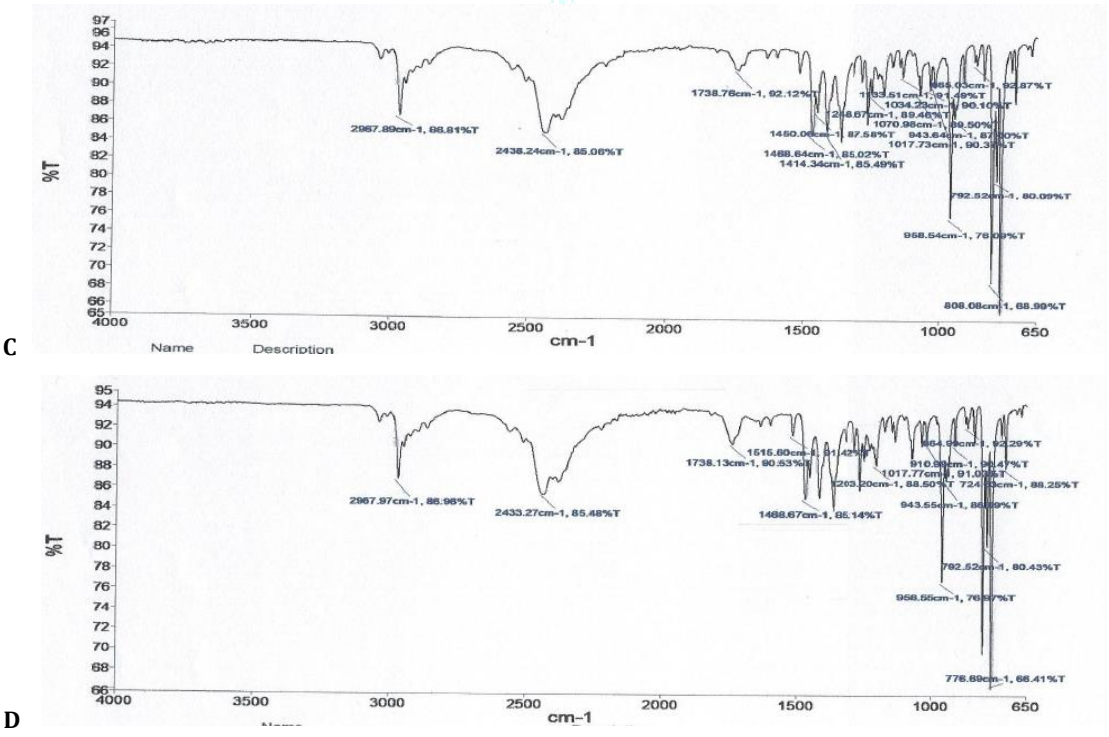

Figure no.3 FTIR of C) Busulfan drug D) EPCT blend

3.2 Flow properties of RRCT:

Table no.5 Flow parameters of RRCT

Formulation	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	Angle of reposeⁿ(⁰)
F1	0.31	0.36	13.88	1.16	27.26±0.12
F2	0.36	0.41	12.19	1.13	25.13±0.08
F3	0.32	0.37	13.51	1.15	26.27±0.02
F4	0.31	0.35	11.92	1.12	27.23±0.25
F5	0.35	0.41	14.63	1.17	26.78±0.11
F6	0.38	0.43	11.42	1.13	25.14±0.15
F7	0.37	0.42	11.90	1.13	25.91±0.16
F8	0.32	0.38	15.78	1.18	26.24±0.21
F9	0.34	0.39	12.82	1.14	25.12±0.14

3.3 Evaluation of RRCT formulations

3.3.1 Characterization of RRCT formulations:

Table no.6 Characterization of Busulfan RRCT

S. No	Physical parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Weight variationⁿ	200± 1.517	199± 1.519	197± 1.521	199± 3.241	199± 1.518	201± 1.518	200± 1.517	199± 3.242	201± 2.020
2	Hardnessⁿ (Kg/cm²)	4.5± 0.1	4.62±0. 03	4.28±0. 04	4.51±0. 04	4.54± 0.05	4.5± 0.05	4.28± 0.05	4.49± 0.05	4.19±0. 2
3	Thicknessⁿ (mm)	2.4± 0.1	2.5± 0.05	2.3± 0.1	2.4± 0.1	2.5± 0.05	2.5± 0.05	2.46± 0.05	2.62± 0.11	2.76±0. 05
4	Friability(%)	0.35	0.34	0.36	0.35	0.34	0.33	0.34	0.35	0.35

Where n=3

3.3.2 Dissolution studies of RRCT formulations

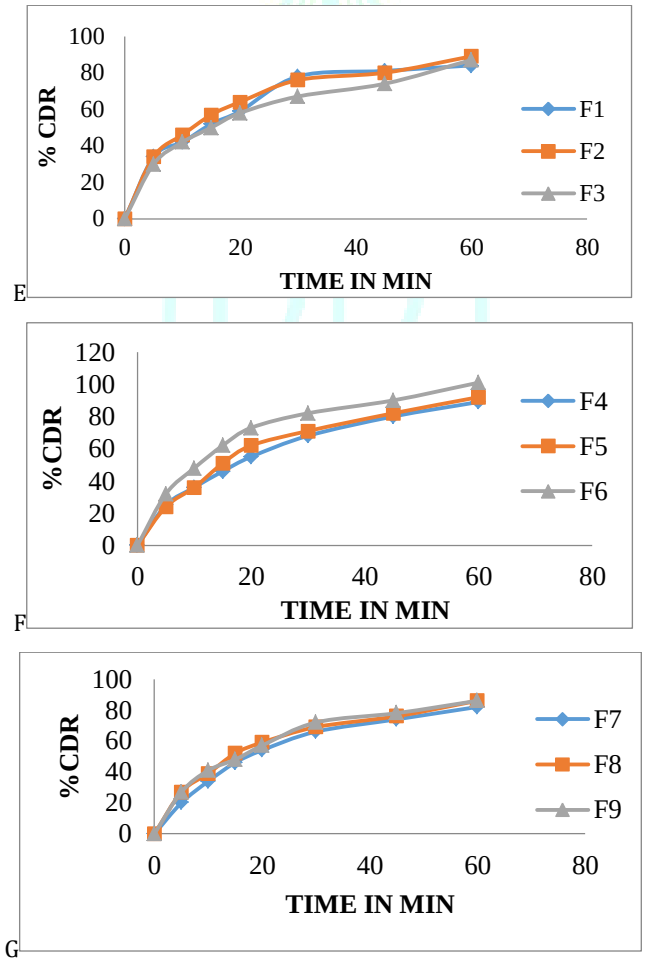

Figure no.4 Dissolution graphs for RRCT formulations F1-F9 (E, F & G)

From RRCT dissolution results F6 formulation was taken for further studies as optimized RRCT formulation containing Busulfan drug.

3.4 Evaluation of EPCT formulations

3.4.1 Characterisation of EPCT formulations:

Table no.7 Evaluation parameters for EPCT

S.no	Physical parameters	C1OPF	C2OPF	C3OPF	C4OPF	C5OPF
1	Weight variation^n (%)	501.114	504±0.047	502±0.058	504±0.121	506±0.031
2	Hardness^n (Kg/cm$^{2)}$	7.2±0.05	7.6±0.010	7.5±0.09	7.4±0.02	7.5±0.06
3	Thickness^n (mm)	4.1±0.011	3.8±0.07	4.0±0.014	3.7±0.011	4.0±0.06
4	Friability^n (%)	0.42±0.001	0.44±0.003	0.45±0.004	0.48±0.004	0.45±0.005

Where n=3

3.4.2 Dissolution studies for EPCT formulations:

Table no.8 Dissolution profile of EPCT of Busulfan

Time in hrs	Enteric Press coat Formulation code				
	C1OPF	C2OPF	C3OPF	C4OPF	C5OPF
Dissolution medium - 0.1NHCl					
1	0	0	0	0	0
2	0	0	0	0	0
Dissolution medium - pH 6.8 Phosphate Buffer					
3	4	7.4	4.9	3.6	4.6
4	5	14.8	9.7	7.4	9.2
5	11	29.7	25.7	9.8	13
6	15	41.2	41.6	14.8	16
7	20	58.7	58.2	29	24
8	29	77.9	72.7	46	35
9	46	89.6	85.9	74	47
10	68	-	94.6	90	74

From EPCT formulations dissolution results C3OPF formulation was selected among all formulations in which 4 parts of Xanthum and 2 parts of EC were present as press coating material based on the percentage of drug release up to 10 hrs.

3.5 In-vitro release kinetic studies

The kinetic data analysis of optimized formulation reached higher coefficient of determination with the First order (R^2 = 0.938). From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

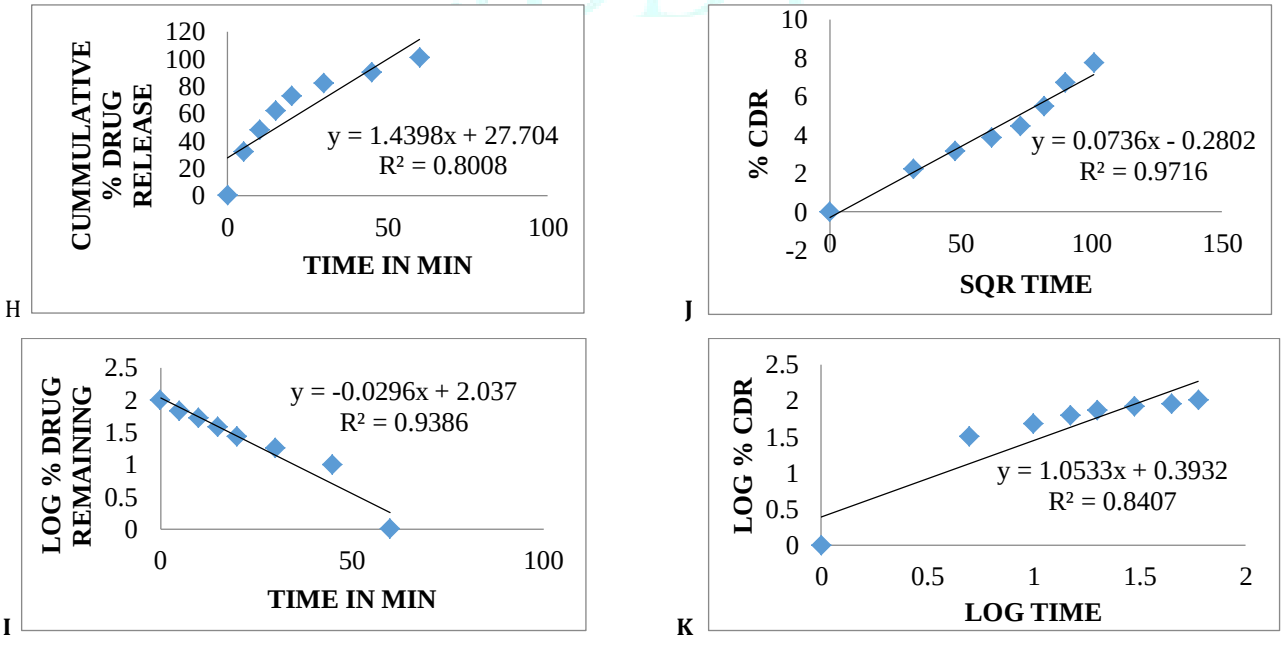

Figure no.5 Release kinetic graphs of H) zero order I) first order J) higuchi model K) korsmeyer model

4. CONCLUSION

Colon specific drug delivery was the most preferable ones in targeting site-specific drug release in the colon with enhanced local or systemic effects. Direct compression method is used for core tablet preparation and all the formulations were evaluated for pre compression parameters like density, flow properties and post compression parameters like hardness, friability, weight variation and In-vitro drug release. Optimized core tablet F6 formulation was press coated using polymers Xanthum gum and EC in different ratios to delay the release of core tablet. Enteric press coated tablets were prepared by spray drying enteric coating solution over press coated tablets. Finally C3OPF enteric coated formulation containing Xanthum gum and EC in 4:2 ratios as press coat was optimized based on dissolution studies. Drug release kinetic study of optimized formulation indicates drug release in present study is combination of diffusion and sphere erosion.

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