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Design And Characterization Of Diclofenac Potassium Tablet For Colon Targeting

Anilkumar J. Shinde*[1], Vinod S.Ingole[1], Gajanan M. Misale[1], Harinath N. More[1]

***[1]Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Near chitranagari, Kolhapur, Maharashtra, India**

***Corres.author: ajshinde07@rediffmail.com**
Tel: +91 231 2637286; Fax: +91 231 2638833;
Mobile no: +91 9823866196;

Abstract: The present study was to formulate tablet of Diclofenac potassium using the hydrophilic polymer hydroxy propyl methyl cellulose (HPMC), Hydroxypropyl Cellulose (HPC), Ethyl Cellulose(N22), Cross Povidone and Sodium Starch Glycolate as a superdisintegrants and Instacoat EN super II as a enteric coat to the colone specific tablet. A 3^3 randomized full factorial design, 3 level and 3 factors were used. The concentration of Hydroxy propyl cellulose (X_1), concentration of HPMC K4M (X_2) and concentration of Ethyl cellulose (X3) were selected as independent variables. The percentage drug release at 12 hours (Q_{12}), percentage friability and hardness of tablet were selected as dependent variables for optimization study. The core, press coat tablets were compressed by rotatory tablet machine evaluated with different parameters like diameter, thickness, average weight, hardness, friability, kinetic release data. Hardness of tablets was found to be in the range of 7–8 kg/cm^2. The enteric coated tablets containing diclofenac potassium released 38.12 % at the end of 12 hrs by in vitro release study. It is concluded that the formulation is prepared of enteric coating of tablet can be used successfully in the systems designed for colon specific drug delivery.

Keywords: Diclofenac Potassium, Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose, Instacoat EN super II**,** colon specific, sustained release tablet

Introduction

Oral delivery of drugs is the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation. From immediate release to site specific delivery, oral dosage forms have really progressed. Oral colon targeted drug delivery system have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration.[1] By this colon targeted drug delivery, it is possible to prevent the side effects of drugs on healthy tissues and enhancement of drug uptake by targeted cells.[2] Colon as a site offers distinct advantages on account of a near neutral pH, a much longer transit time, reduced digestive enzymatic activity and a much greater responsiveness to absorption enhancers.[3] Targeted drug delivery to the colon is mainly useful for the treatment of colonic diseases for drugs like proteins and peptides for delivery of steroids, which absorbable in colon.[4] Also colon is a good site for those drugs, where a delay in drug absorption is required from therapeutic point of view e.g. in case of nocturnal asthma, arthritis, cardiac arrhythmias, which are effected by circadian biorhythms.[5] The advent of slow release technologies increase the chances for a drug to be released in the colon and thus this organ has an important role to play in drug absorption from oral sustained release formulations.

Various approaches have been used for delivery of drugs to the colon *via* oral route which include coating with pH dependent polymers, prodrug, polysaccharides[6,7] such as chitosan, pectin, inulin, alginate, guar gum,[8,9,10] for design of time release dosage forms and the utilization of carriers that are degraded exclusively by the colonic bacteria.[11] To achieve a successful colon drug delivery a drug needs to be protected from degradation, release and/or absorption in upper portion of GI tract and then ensure abrupt or controlled release in proximal colon.

In the present study, diclofenac potassium was used as a model drug, because it has been used for treatment of inflammatory bowel disease. Diclofenac Potassium is 100% absorbed, after oral administration as compared to IV administration and highly protein bound.[12] It has half-life of about 2 hours, therefore very less dose, which is insufficient to elicit therapeutic response upon reaching the colon, when conventional doses are administered. Hence large amount of dose to be administered for this indication. Therefore formulation of tablets containing of Diclofenac Potassium using different polymers, release the drug in the colon.

Materials And Methods

Diclofenac Potassium was received as a gift sample from Peltech Pvt. Ltd., Mumbai. Hydroxy propyl methylcellulose K- 100M was obtained from Colorcon Asia Pvt Ltd (Goa, India) and Hydroxy propyl Cellulose was received as a gift sample from Sisco research laboratory, Mumbai. Ethyl Cellulose N22 was received as a gift sample from Degussa Pvt. Ltd., Germany. Cross Povidone was received as a gift sample from Lupin Pharmaceuticals Ltd., Aurangabad. Instacoat EN super II was received as a gift sample from Ideal cures Pvt.Ltd., Mumbai. Sodium Starch Glycolate was purchased from Finar chemicals, Mumbai. Magnesium stearate, Lactose Monohydrate were purchased from S. D. Fine Chem., Ltd.., Mumbai. All other chemicals were of analytical grades as required.

Experimental:

Characterization of Diclofenac potassium:

The sample of diclofenac potassium was analyzed for its nature, color and taste. The Melting point of drug was determined by open capillary tube method. Standard curve of drug has been quantitatively analyzed by various techniques.[13] The standard solution of Diclofenac potassium was scanned through 200-400 nm region on Jasco V-530 UV spectrophotometer.

Infrared spectra analysis

FTIR spectras were help to confirm the identity of drug to detect the interaction of the drug with excipients and polymers. FTIR spectrum of pure drug and physical mixture of drug with polymer were obtained on FTIR (shimadzu FTIR-8400S) instrument using KBr dispersion method. The spectrum was scanned over the wave number range 4000-400 cm^{-1}.

Preparation of core tablets

The inner core tablet was prepared by direct compression using rotary tablet machine in order to perform different release pattern dependining upon different release mechanism involved the powder mixture of Diclofenac potassium, starlac, Ac-Di-sol were dry blended for 20 min. followed by addition of magnesium stearate & aerosol. The powder mixture was further blended for 10 min. and compressed into tablet using a Rotary tablet machine equipped with 8 mm concave faced punch. Sufficient pressure was applied keep hardness is 5 Kg/cm^2. The composition of inner core tablet given in table 1. The core tablet evaluated for weight variation, thickness, friability & hardness. [14,15]

Table 1: Composition of Inner core tablet

Sr. No.	Ingredients	Formulation code			
		C1 (mg)	C2 (mg)	C3(mg)	C4(mg)
1	Diclofenac potassium	100	100	100	100
2	Sodium starch glycolate	-	7.5	-	12
3	Cross povidone	7.5	-	12	-
4	Lactose monohydrate	39.5	39.5	39.5	39.5
5	Aerosil	1.5	1.5	1.5	1.5
6	Magnesium stearate	1.5	1.5	1.5	1.5
	Total	150	150	150	150

Preparation of press coated tablet:

All the powder mixture was previously pass through sieve no. 44 and the press coating of tablet was performed using a Rotary tablet machine. A half amount of powder was filled into the die to make a powder bed, the center of which was placed core tablet manually. Then the remaining half of coating material filled in the die & content were compressed under a sufficient compression force, using a concave punch 8mm in diameter.[16] To keep the hardness of table 10 kg/cm^2. The total amount of press coat material placed upper & lower shell was 300 mg constant for all formulation. The composition of press coat material given in table 2.

Table 2: Composition of Press Coat Tablet

Formulation code	Coating material	Ratio (%)	Weight (mg)
F1	Ethyl cellulose N22 : Xanthum gum	25:75	75:225
F2	Ethyl cellulose N22: Xanthum gum	50:50	150:150
F3	Ethyl cellulose N22: Xanthum gum	75:25	225:75
F4	HPMC K100 : Ethyl cellulose	25:75	75:225
F5	HPMC K100 : Ethyl cellulose	50:50	150:150
F6	Ethyl cellulose N22: Xanthum gum	75:25	225:75

Preparation of enteric coating solution

The enteric coated solution was prepared by dissolving Insta coat EN Super II in to distilled water. Coating of press coated tablets was performed using a coating machine. Spray air pressure is 3 kg/cm^2, temperature 35–50 ºC, rotating speed of pan 20 rpm.[17] The amount of coating was up to 18mg (8% w/w) per tablet.

Full Factorial design

A 3^3 randomized full factorial design was used in this study. In this design 3 factors were evaluated, each at 3 levels and experimental trials were performed at all 27 possible combinations of batches. The factorial design for formulation given in table 3. The concentration of Hydroxy propyl cellulose (X_1), concentration of HPMC K4M (X_2) and concentration of Ethyl cellulose (X3) were selected as independent variables given in table 4. The percentage drug release at 12 hours (Q_{12}), percentage friability and hardness of tablet were selected as dependent variables for optimization study.[18] The optimized concentration of hydroxy propyl cellulose, HPMC K4M and concentration of ethyl cellulose were incorporated in the tablet, which was used as the check point of the regression analysis model.

Table 3: 3^3 Factorial design for formulation batches

Formulation code	Independent variables			Formulation code	Independent variables		
	X1	X2	X3		X1	X2	X3
F1	-1	-1	-1	F14	0	0	0
F2	0	-1	-1	F15	1	0	0
F3	1	-1	-1	F16	-1	1	0
F4	-1	0	-1	F17	0	1	0
F5	0	0	-1	F18	1	1	0
F6	1	0	-1	F19	-1	-1	1
F7	-1	1	-1	F20	0	-1	1
F8	0	1	-1	F21	1	-1	1
F9	1	1	-1	F22	-1	0	1
F10	-1	-1	0	F23	0	0	1
F11	0	-1	0	F24	1	0	1
F12	1	-1	0	F25	-1	1	1
F13	-1	0	0	F26	0	1	1
				F27	1	1	1

Table 4: Independent variables with their actual values

Independent variables	Low (-1)	Medium (0)	High (+1)
HPC (X1) mg	25	50	75
HPMC K4M (X2) mg	25	50	75
EC N22 (X3) mg	25	50	75

The polynomial equation generated by this experimental design (Design Expert 7.1.6 software, State Ease Inc.) is as follows,

$$Y= b0 + b1X1 + b2X2 + b3X3 + b12X1\ X2 + b13X1\ X3 + b23X2\ X3 + b11X1\ X1 + b22X2\ X2 + b33X3\ X3 \ldots\ldots (1)$$

where ,

Y - dependent variable, b0 - intercept, b1 to b33 - regression coefficients,

X1, X2 and X3 - independent formulation variables.

Evaluation of Tablet

The formulated inner core tablets, press coat tablets and enteric coated tablets were evaluated for different parameter like thickness, hardness, diameter, uniformity of weight and in-vitro dissolution studies. Thickness and diameter were measured by using vernier caliper**.** The hardness of tablet of each formulation was measured by Monsanto hardness tester. Uniformity of weight of tablet has been carried out as per I.P.1996.[19] In vitro disintegration time of six tablets from each formulation was determine by using disintegration test apparatus (VEEGO). Friability test was conducted by using Roche friability test apparatus (VEEGO).

In vitro dissolution study

The In vitro drug release study was conducted using USP type II apparatus (Electrolab, India) the temperature kept at 37 ± 0.5^0 C and rotation speed at 50 rpm., using 900 ml of phosphate buffer pH 6.8 as a dissolution medium. At specific time interval i.e. 5 min, 10 min up to 1 hr, 5ml of sample was withdrawn and filtered and replaced with 5 ml of fresh medium to maintain the sink condition and the absorbances were recorded using spectrophotometer at 276 nm.[20]

Fourier transform Infrared spectroscopy study

FTIR spectroscopy was conducted using Jasco 4100 spectrophotometer. Spectrum of physical mixture and formulation was recorded in the wavelength region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well and then mixture kept into sample holder for analysis. FT-IR spectra of the diclofenac potassium, optimized batches and polymers are taken for the study of drug-polymer Interaction.

Differential Scanning Colorimetry study:

Thermograms of diclofenac potassium, formulation and physical mixture were obtained using DSC instrument (TA Instruments SDT- 2960, USA) equipped with an intra cooler. Indium standard was used to calibrate the DSC temperature and enthalpy scale.[21] The powder samples of formulation was kept in the aluminium pan and heated at constant rate 5°C/ min, over a temperature range of 10°C to 300°C. Inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/ min.

Powder x-ray diffraction study

Powder x-ray diffraction studies have been widely used to understand crystallinity of solids, the study was carried out by using X -ray diffractometer (Philips PW-3710, Holland).[22] The samples of pure drug, optimized formulation and physical mixture of the same batch was taken and was irradiated with mono chromatised CuKα radiation and analyzed between from 10° to 60° (2θ).

Stability study

The stability study was conducted as per the ICH guidelines. The samples were withdrawn periodically (30 and 90 days) and evaluated for the different physicochemical parameters i.e. thickness, hardness and in-vitro drug release studies. [23]

Results And Discussion

Physical characterization

The sample of Diclofenac potassium was a faintly yellowish white, odorless and slightly hygroscopic crystalline powder. The melting point was found to be 283 – 285°C. It was found that Diclofenac potassium is soluble in ethanol, methanol and slightly soluble in water.[24]

UV spectroscopy (Determination of λ max)

The ultraviolet scanning of pure Diclofenac was done in the range of 200 to 400 nm. The peak of maximum absorption was observed at 276 nm.

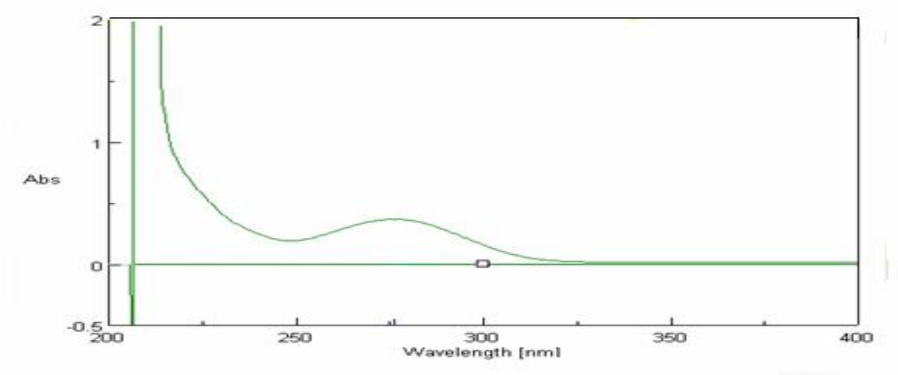

Figure 1: The spectra of Diclofenac potassium in phosphate buffer pH 6.8

Calibration curve of Diclofenac potassium in phosphate buffer pH 6.8

The maximum wavelength of Diclofenac potassium in phosphate buffer pH 6.8 was 276 nm. The calibration curve of Diclofenac potassium of concentration 0- 30 µg/ml in phosphate buffer pH 6.8. The calibration curve show straight line, it obeys Lambert – Beers Law. The regression coefficient is 0.9961, intercept is 0.017 and slope 0.033, shown in table 5. The calibration curve of Diclofenac potassium given in figure 2.

Table 5: Calibration data of Diclofenac potassium in phosphate buffer (pH 6.8)

Regression equation data for Y=A+B*C	Regression parameter
Slope (B)	0.033
Intercept (A)	0.017
Correlation coefficient	0.9961

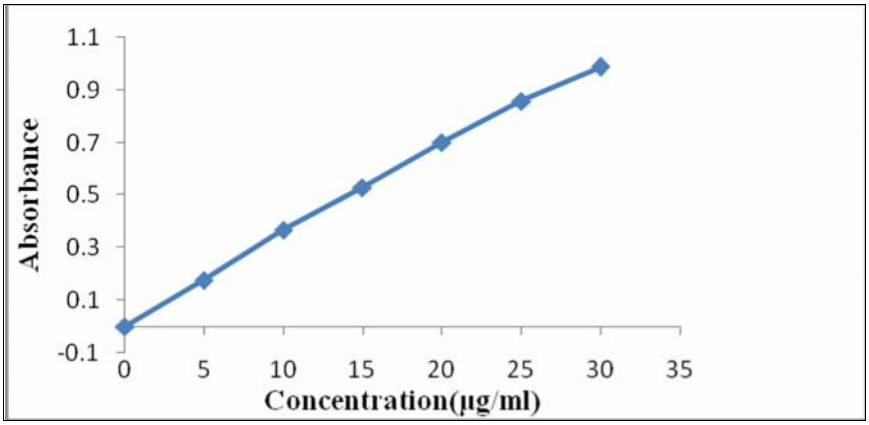

Figure 2: Calibration curve of Diclofenac potassium

Infrared absorption spectrum

IR spectrum indicated that characteristics peaks belonging to measure functional groups such as principle peaks at wave numbers 748.07, 1572, 1199.18, 3431.27cm^{-1}. FTIR spectra of Diclofenac potassium shown in figure 3. The IR spectra of physical mixture of polymers, HPMC K4M, HPC, EC N22 and diclofenac potassium was studied and confirmed that there were no interaction with each other. The spectra showed, all the prominent peaks of drug as well as polymer. Hence it can be concluded that there were no any significant changes in the physical mixture of HPMC K4M, HPC and EC N22 and Diclofenac potassium.

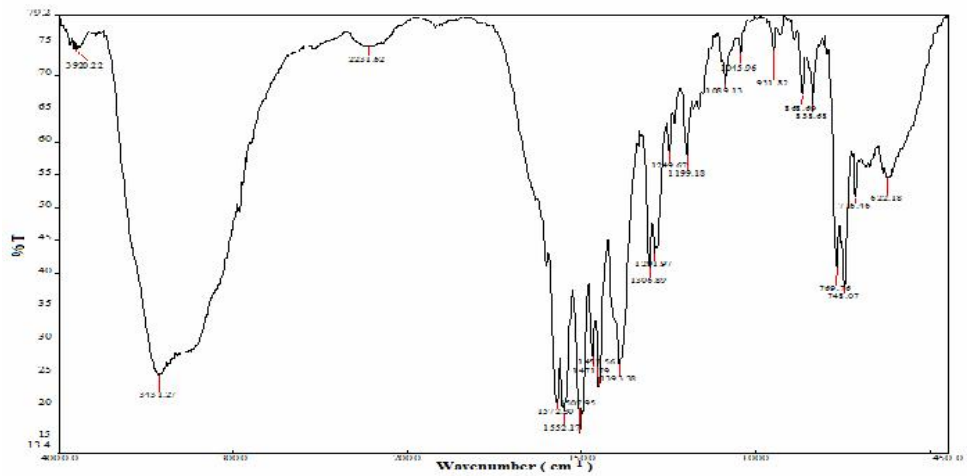

Figure 3: FTIR spectra of Diclofenac potassium

Factorial design

In 3^3 factorial design, a response surface model with 3 independent formulation variables at 3 different levels were used to study the effect on dependable variables. The value of correlation coefficient (R^2) of polynomial regression equation was greater than 0.99, which is equal to 1, thus indicating best fit for all dependent variables. The main effects of X1, X2, and X3 represent the average result of changing one variable at a time from its low to high level. The interaction terms (X1X2, X1X3, X2X3, X1X1,X2X2, and X3X3) show how the drug release at 12 hr, % friability and hardness changes, when two variables are simultaneously changed. The negative coefficients for all 3 independent variables (X1, X2, and X3) indicate a favorable effect on the drug release, while the positive coefficients for the interactions between 2 variables (X1X2, X1X3, X1X1, X2X2, and X3X3) indicate an unfavorable effect on the hardness. Enteric coated tablets were evaluated and to obtained drug release. The % drug release of optimized batch (F1) was 38.12 at 12 hr.

Evaluation of Press coated tablet:

Thickness of all the formulation (F1–F27) varying from 1.91 to 2.97mm. Diameter of all formulation (F1–F27) varying from 11.41to11.51mm. Hardness of tablets was found to be in the range of 5–9 kg/cm$^{2.}$ Tablets form each formulation shows uniformity of weight as per I.P 1996 specifications. The in vitro drug release study conducted for 12 hr. The in vitro dissolution study depends upon the concentration of polymer. The concentration of polymer increases with increase in drug release. The 3^3 full factorial design with observe responses shown in table 6.

Table 6: Coded level as per 3^3 full factorial design with observe responses

Form. code	Dependent variables			Form. code	Dependent variables		
	% rel.	% Fri.	Hardness		% rel.	% Fri.	Hardness
F1	78.86	0.86	7.66	F14	88.88	0.85	7.6
F2	83.61	0.80	6.66	F15	74.49	0.78	8.6
F3	95.29	0.77	7.66	F16	75.68	0.91	7.6
F4	70.00	0.67	8.60	F17	82.86	0.84	8.0
F5	78.80	0.53	7.66	F18	85.84	0.95	8.3
F6	71.83	0.78	7.30	F19	90.89	0.91	8.6
F7	86.70	0.82	8.30	F20	81.69	0.88	7.6
F8	94.25	0.80	7.60	F21	81.73	0.83	8.3
F9	87.04	0.78	8.60	F22	82.68	0.73	7.6
F10	82.98	0.73	8.60	F23	83.54	0.65	7.6
F11	77.21	0.88	7.66	F24	83.98	0.68	8.0
F12	73.64	0.76	8.60	F25	86.71	0.77	7.6
F13	77.31	0.80	7.30	F26	92.57	0.90	7.6
				F27	94.61	0.87	7.6

Response surface analysis

The dependent variables (% drug release, % friability and hardness) obtained at various levels of the 3 independent variables (X1,X2 and X3) was subjected to multiple regression to yield a second order polynomial equation. The coefficient values obtained are shown in table 7. The main effects of X1, X2, and X3 represent the average result of changing one variable at a time from its low to high level. The interaction terms (X1X2, X1X3, X2X3, X1X1, X2X2, and X3X3) show how the Drug release at 12 hr, % friability and hardness changes, when two variables are simultaneously changed. The negative coefficients for all 3 independent variables (X1, X2, and X3) indicate a favourable effect on the drug release, while the positive coefficients for the interactions between 2 variables (X1X2, X1X3, X1X1, X2X2, and X3X3) indicate an unfavorable effect on the hardness. The positive coefficients (X1 and X3) for the independent variables show an unfavourable effect on friability, while the negative coefficients for the interactions between 2 variables (X2X3, X3X3, and X1X1) imply a favourable effect on the independent variables (X1, X2 and X3) point to a favorable effect drug release at 12 hr, but the negative coefficients for the interactions between two variables (X1X1 and X2X2) indicate an unfavourable effect on drug release . The response surface plot shown in figure 4-12.

Table 7: Regression analysis data

Response	Drug release (%)	Friability (%)	Hardness (Kg/cm^2)
A1	0.34	-0.06	0.074
A2	-0.022	-0.0074	0.061
B1	0.26	0.021	0.047
B2	-0.69	-0.0074	-0.032
C1	-2.94	0.026	0.011
C2	2.36	-0.0085	0.13
A1B1	-2.14	0.017	0.081
A2B1	-1.21	-0.041	-0.25
A1B2	5.78	0.016	0.22
A2B2	-4.23	-0.046	-0.039
A1C1	0.88	-0.030	0.0014
A2C1	3.17	0.031	0.32
A1C2	-0.34	0.011	-0.067
A2C2	2.44	0.019	-0.18
B1C1	-1.67	0.022	-0.14
B2C1	3.79	-0.00074	0.28
B1C2	2.09	0.040	0.0037
B2C2	-4.08	-0.048	0.034

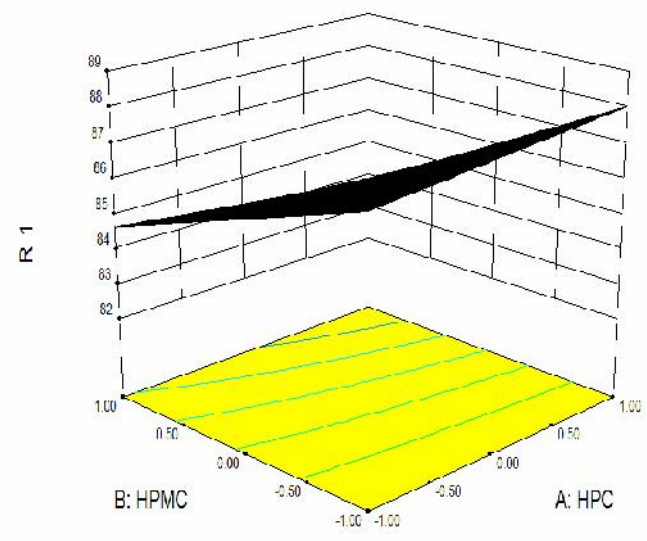

Figure 4: R_1 (Response surface pot) of HPC-HPMC

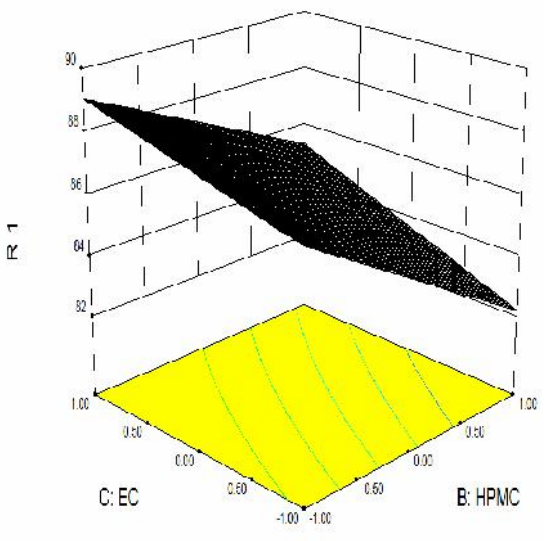

Figure 5: R_1 (Response surface plot) of EC – HPMC

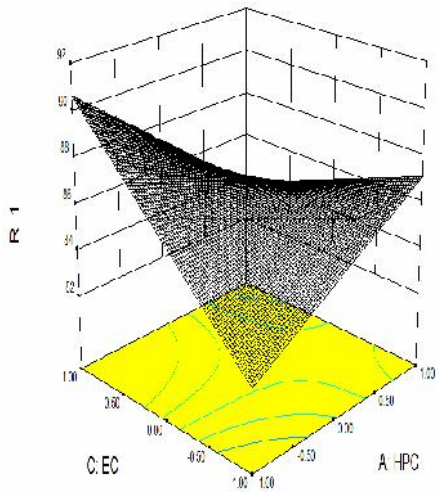

Figure 6: R_1 (Response surface plot) of EC – HPC

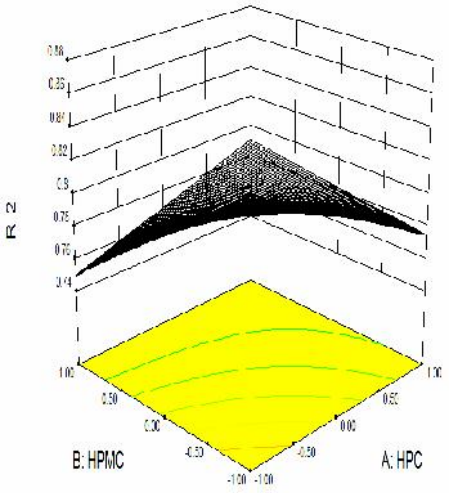

Figure 7: R_2 (Response surface plot) of HPMC – HPC

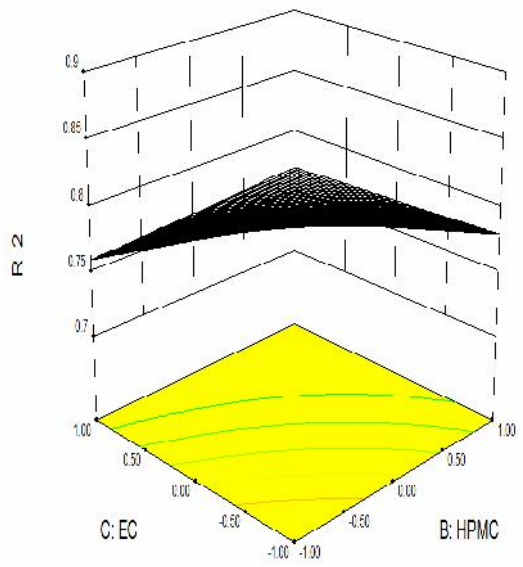

Figure 8: R_2 (Response surface plot) of EC - HPMC

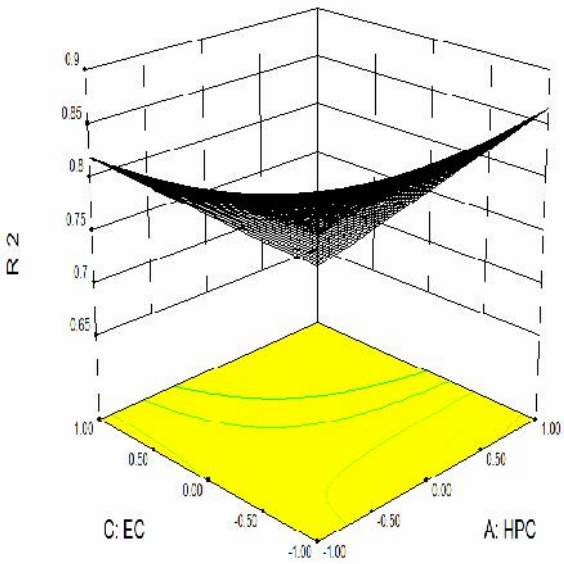

Figure 9: R_2 (Response surface plot) of EC – HPC

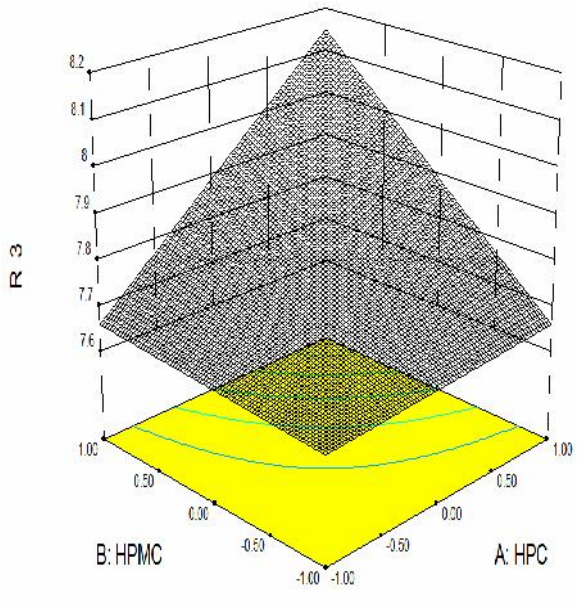

Figure 10 : R_3 (Response surface plot) of HPMC – HPC

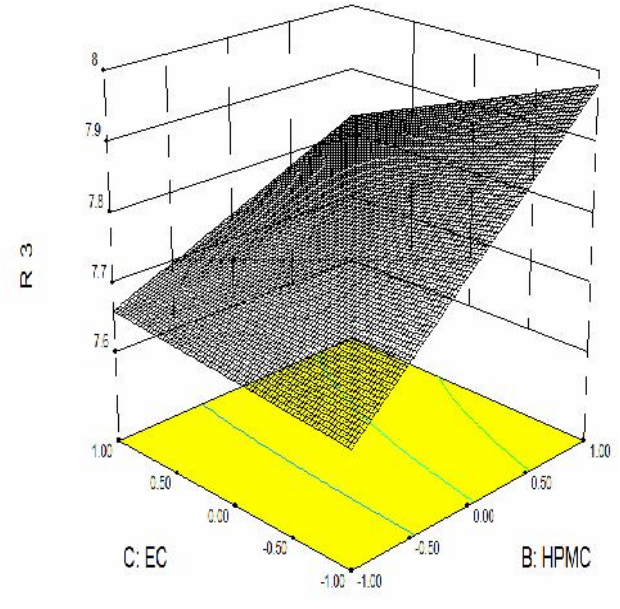

Figure 11: R_3 (Response surface plot))of EC - HPMC

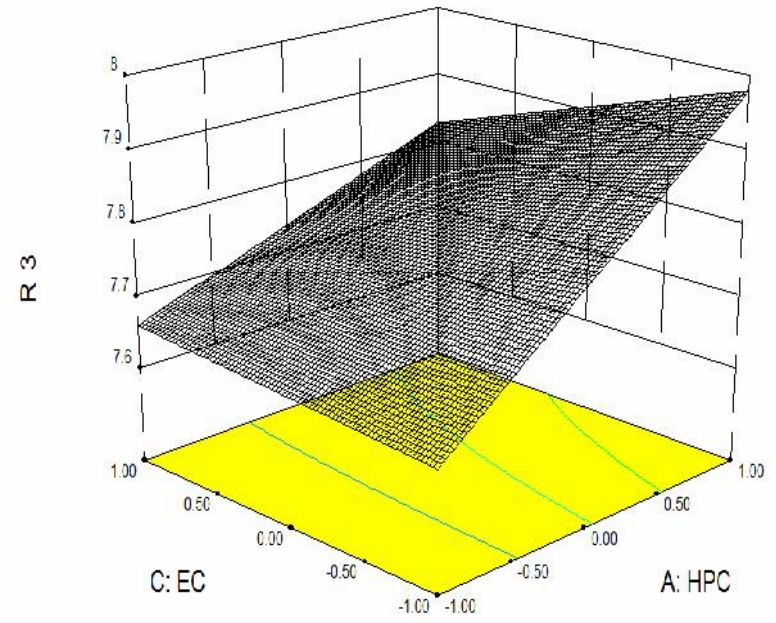

Figure 12: R_3 (Response surface plot))of EC – HPC

Fourier Transform Infrared Study

In FTIR study, it was found that there were no chemical interaction between drug and excipients used. IR spectrum indicated that characteristics peaks belonging to measure functional groups such as principle peaks at wave numbers 748.07, 1572, 1199.18, 3431.27cm^{-1}. FTIR spectra of F1 batch shown in figure 13.

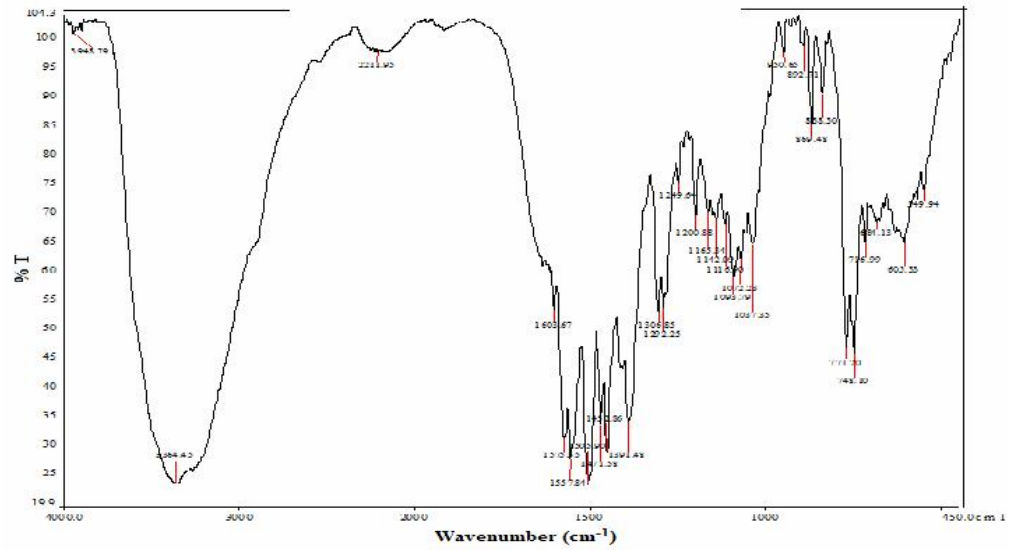

Figure 13: IR spectra of optimized F1 batch

Differential Scanning Calorimetry study

The thermographs of pure drug and optimized batch are shown in figure 14. The thermogram of pure drug showed a sharp endotherm at near about 288.38 ºC and physical mixture of the endotherm was observed at about 153.44 ºC. It indicates that their crystalline structure and no incompatibility of drug with polymers. The other endothermic peak shown at 67.43 ºC, 84.31 ºC,101.79 ºC, 103.63 ºC,149.42 ºC,250 ºC are due to polymers present in the formulation.

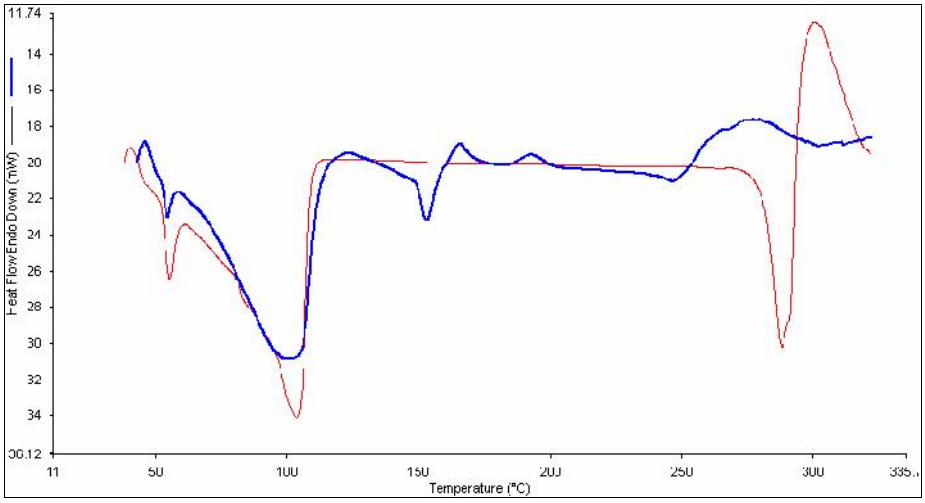

Figure 14: Overlain of DSC thermograms of pure drug (Brown colour) and optimized (Blue colour)

Powder x-ray diffraction study

PXRD pattern of overlain of pure drug and optimized batch (F1) has been shown in figure15. The pure drug showed sharp peak intensity of the peak. But when drug was incorporated into the polymer the intensities of peaks were decrease due to decrease crystallinity of the diclofenac potassium but full amorphosization has not been observed.

Short term stability on the optimized F1 batch of tablet formulation indicated no significant changes in physical parameter like hardness and drug release. From stability study it was concluded that all formulation was stable 40 ± 2ºC ± 5% RH.

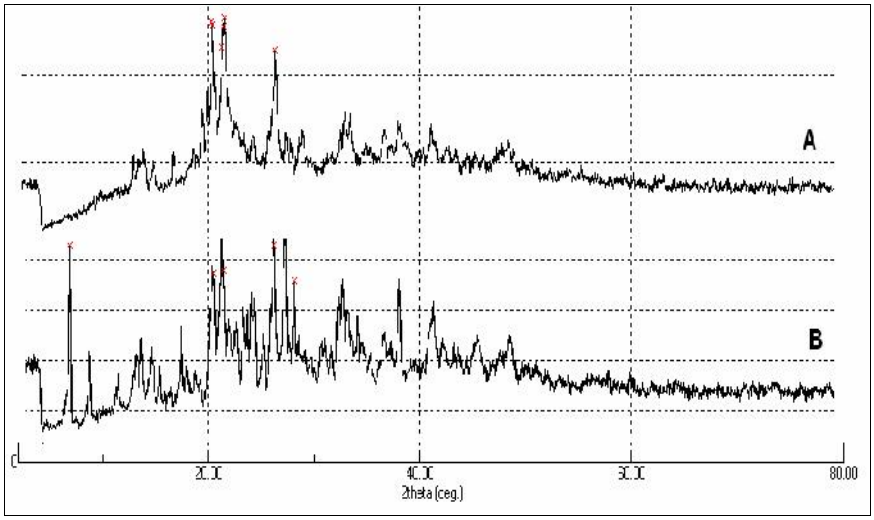

Figure 15: Overlain of PXRD pattern of pure drug (A) and optimized batch (F1)(B)

Conclusion

The present study has been to formulate colonic drug delivery of enteric coated tablet. The colon specific tablet formulations using the time and pH dependent approaches represented interesting forms for delivering of the drug to the proximal part of the colon, avoiding release in the stomach. The enteric coated tablet has been used to provide more uniform distribution of the drug in the colon. If the concentration of polymer increases, drug release also increases because rupturable polymer ethyl cellulose combined with erodible polymer hydroxy propyl Cellulose and HPMC K100. Response surface plot analysis indicates direct relationship between concentrations of different polymer with drug release. This study presented a novel colon specific drug delivery system containing diclofenac potassium. It is concluded that enteric coating of tablet formulation can be used successfully in the systems designed for colon specific drug delivery. The development of colon specific tablet of diclofenac potassium can be beneficial in the colonic disease.

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