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Development and Characterization of Colon Targeted Hydrogel Tablet of Methotrexate

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ABSTRACT

Colon cancer is one of the most common internal malignancies. Colorectal cancer is second leading cause of deaths in the United States. Various approaches available for The poor site specificity of pH dependent systems, because of large variation in the pH of gastrointestinal tract, was well established. The timed-release systems release their load after a predetermined period of administration. These are designed to resist the release of the drug in stomach and small intestine and release of the drug takes place in colon. Methotrexate (MTX) is a drug of choice in the treatment of colon cancer and now a days rheumatic disease. MTX is a folate antimetabolite. It is an analog of aminopterin, which is also derived from folic acid. MTX has since been used in the treatment of various malignancies including osteosarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, cutaneous T cell lymphoma (mycosis fungoides), head and neck cancer, lung cancer, colon cancer and breast cancer. The conventional dosage forms which are used for colorectal cancer normally dissolve and absorbs in the stomach and small intestine; thus a very less quantity of dose of drug reaches to colonic region. Aim of present work is to develop and characterize colon targeted tablet of MTX for treatment of colorectal cancer using different polymer and excipient by compression coating technology.

Key Words :Colon cancer, methotrexate, Mycosis, Pro drug

INTRODUCTION

Colon cancer is one of the most common internal malignancies. Chemotherapy is used to treat advanced colorectal cancer. However, conventional chemotherapy is not effective in colorectal cancer as it is in other cancer, as the drug does not reach the target site in effective

concentration[1,2]. Thus, effective treatment demands increased dose size, which may lead to undue consequences. To overcome this situation, pharmaceutical technologists have been working on ways to deliver the drug more efficiently to the colon, where it can target the tumor cells. Ciftci and Groves[3] showed that it is possible for a colon targeted delivery system to selectively deliver drug to tissues, not through tissues. It is possible that delivery of small quantities of antineoplastic agent to the inner surface of the colon could destroy small tumors that arise spontaneously in this region, reducing the need for surgery.The poor site specificity of pH dependent systems, because of large variation in the pH of gastrointestinal tract, was well established. The timed-release systems release their load after a predetermined period of administration. These are designed to resist the release of the drug in stomach and small intestine and release of the drug takes place in colon[4].

Methotrexate (MTX) is a drug of choice in the treatment of colon cancer and now a days rheumatic disease. MTX is a folate antimetabolite. It is an analog of aminopterin, which is also derived from folic acid. MTX has since been used in the treatment of various malignancies including osteosarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, cutaneous T cell lymphoma (mycosis fungoides), head and neck cancer, lung cancer, colon cancer and breast cancer.

The conventional dosage forms which are used for colorectal cancer normally dissolve and absorbs in the stomach and small intestine; thus a very less quantity of dose of drug reaches to colonic region. Aim of present work is to develop and characterize colon targeted tablet of MTX for treatment of colorectal cancer using different polymer and excipient by compression coating technology

MATERIALS AND METHODS

Preliminary screening of formulation variables

In preliminary screening, the formulations were prepared by direct compression of the physical mixture. Tablets were prepared using different grades of HPC in different concentration. The powdered mass containing 30 mg methotrexate (MTX) per tablet, HPC (different grades) and directly compressible Lactose (Tablettose 80) passed through 80 #, blended uniformly and compressed using 10 mm flat punch in Rimek rotary press. The total weight of tablet was kept 300 mg. The composition of all batches is shown in the Table 4.1

Evaluation of prepared tablets

Compressed tablets were evaluated for assay, weight variation and friability according to USP 28. For assay, 20 tablets were crushed and the powder equivalent to 30 mg of MTX was transferred to 1000 ml of 0.1 N HCl in volumetric flask. The solution was analyzed at 303 nm using double beam UV/VIS spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve.

Table 1 Composition of batches for preliminary screening

Batch code	Ingredients (mg)					
	Drug	HPC-SL	HPC-L	HPC-M	HPC-H	Tablettose 80
P1	30	100	-	-	-	170
P2	30	150	-	-	-	120
P3	30	200	-	-	-	70
P4	30	-	100	-	-	170
P5	30	-	150	-	-	120
P6	30	-	200	-	-	70
P7	30	-	-	100	-	170
P8	30	-	-	150	-	120
P9	30	-	-	200	-	70
P10	30	-	-	-	100	170
P11	30	-	-	-	150	120
P12	30	-	-	-	200	70

In-vitro dissolution study

Dissolution study was carried out using type II (Paddle type) Electrolab TDT-06T dissolution test apparatus USP XXIV. The 700 ml of 0.1 N HCl was used as dissolution media for 2 h followed by 22 h study in 6.8 pH by adding 200 ml of 0.2 mol/L trisodium phosphate in dissolution media. Temperature was maintained constant at 37 $\pm$ 0.5^0 C. The stirring speed was kept at 50 rpm. Five milliliters of sample was withdrawn at specific time intervals, suitably diluted and filtered through whatman filter paper (0.7 µ size). The volume of the dissolution fluid was adjusted by replacing 5 ml of suitable dissolution medium after each sampling. The samples were analyzed at 303 nm using double beam UV/VIS spectrophotometer after suitable dilution. Concentration of the drug was calculated using respective standard curve equations. Dissolution test was performed in triplicate. High reproducibility of data was obtained (SD< 3%), hence only average values were considered in the study.

Table.2 Cumulative percentage drug release (CPR) from tablets for preliminary screening

Batch code	Time (h)									
	0	1	2	3	4	6	8	12	16	24
P1	0.00	69.45	101.56	-	-	-	-	-	-	-
P2	0.00	54.74	99.46	-	-	-	-	-	-	-
P3	0.00	48.89	89.34	102.37	-	-	-	-	-	-
P4	0.00	41.65	56.68	73.48	86.48	-	-	-	-	-
P5	0.00	37.49	46.09	61.73	78.36	102.36	-	-	-	-
P6	0.00	34.57	42.36	54.98	68.46	89.23	101.46	-	-	-
P7	0.00	33.46	40.32	46.49	52.16	64.47	73.40	97.39	-	-
P8	0.00	32.49	37.48	42.38	49.48	62.00	72.34	94.38	-	-
P9	0.00	28.39	33.72	36.67	40.35	52.28	61.29	85.39	-	-
P10	0.00	24.36	27.89	31.23	34.59	43.39	50.68	68.49	85.39	100.28
P11	0.00	22.37	25.39	30.49	33.40	41.29	47.66	61.67	78.49	98.46
P12	0.00	20.27	22.39	27.54	31.29	35.39	42.34	57.48	73.46	96.87

Figure 1 Comparative dissolution profiles of the batches P1, P2 and P3

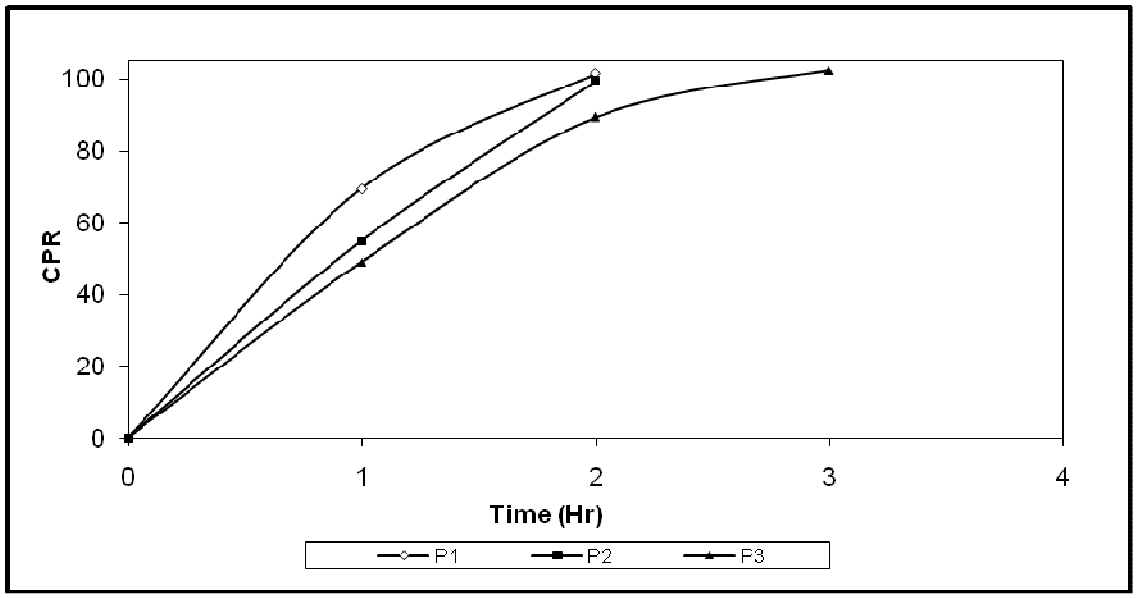


Figure 2 Comparative dissolution profiles of the batches P4, P5 and P6

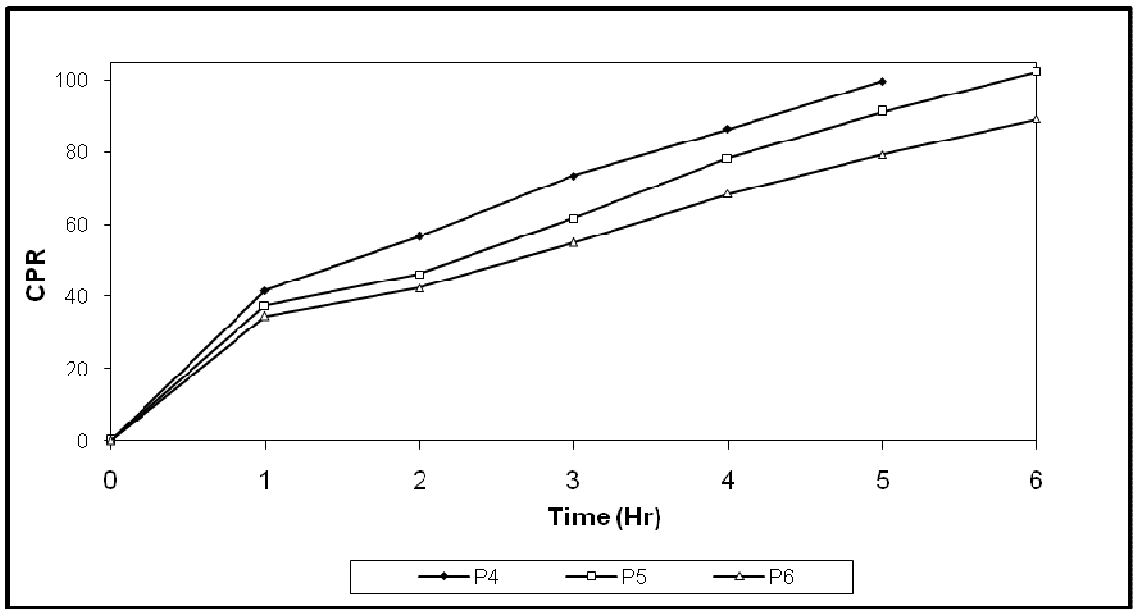


Figure 3 Comparative dissolution profiles of the batches P7, P8 and P9

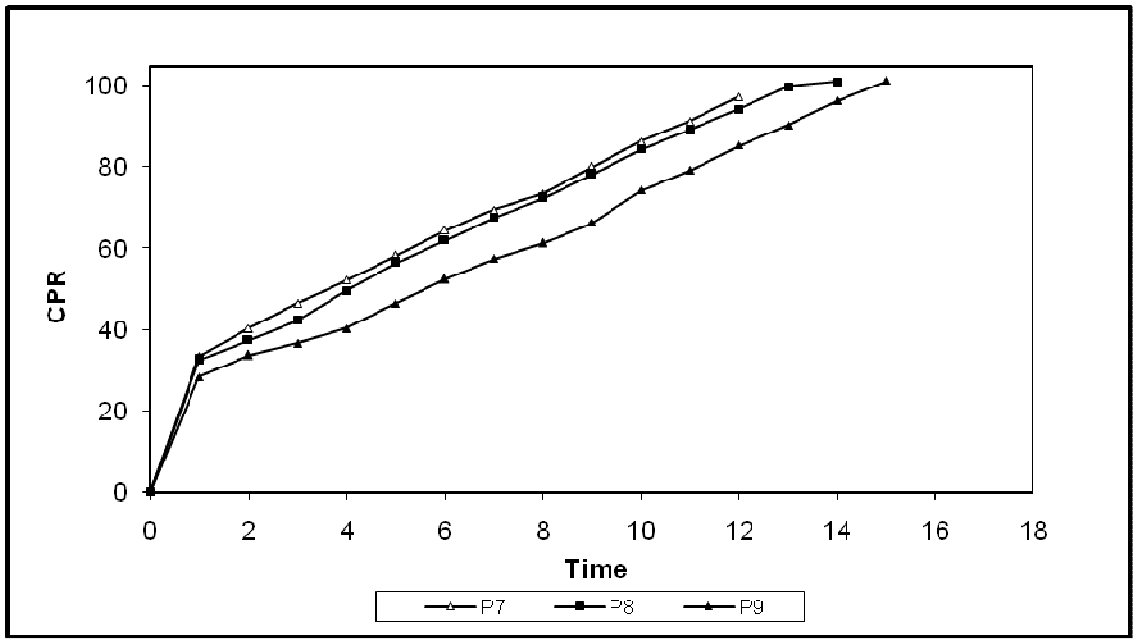
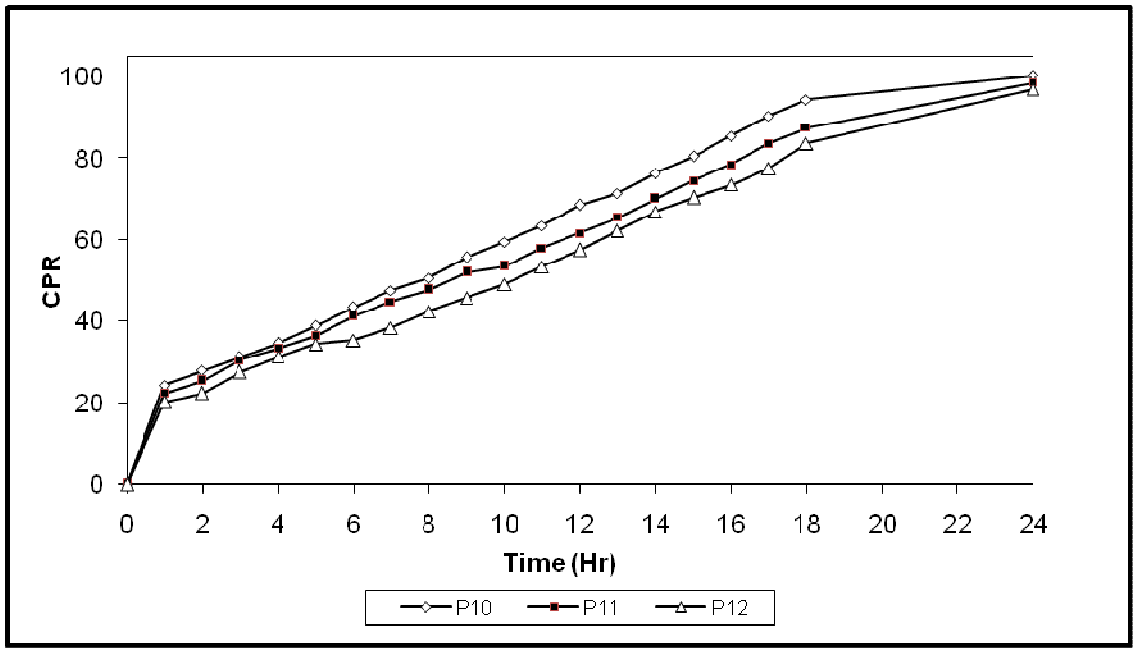


Figure 4 Comparative dissolution profiles of the batches P10, P11 and P12



Optimization of formulation variables using 3^2 factorial design

Optimization of polymer in Core tablet

The ratio of polymer HPC M: HPC H (X_1) and total weight of polymer (X_2) in the core tablet were selected as independent variables. Percentage drug release at 4 h (Q_4), 6 h (Q_6) and 12 h (Q_{12}) were selected as dependent variables. The total weight of polymer (X_2) was kept at the level of 10, 20 and 30 mg respectively in the factorial batches tablets and ratio of HPC M: HPC H (X_1) was evaluated at 1: 0, 1: 1 and 0: 1. Table 4.3 shows the applied full factorial design for core tablet.

Table 3 Full factorial design for core tablets

Batch code	Coded level		Actual value	
	X_1	X_2	X_1 (Ratio)	X_2 (mg) Polymer weight
F1	-1	-1	100:00	10
F2	-1	0	100:00	20
F3	-1	+1	100:00	30
F4	0	-1	50:50	10
F5	0	0	50:50	20
F6	0	+1	50:50	30
F7	+1	-1	00:100	10
F8	+1	0	00:100	20
F9	+1	+1	00:100	30

$\mathbf{X_1}$ is the ratio of polymer HPC-M: HPC-H and $\boldsymbol{X_2}$ is total weight of polymer in the core tablet. All batches contained 30 mg of MTX.

Preparation of core tablets

The core tablets containing MTX (30 mg), Starch 1500 and two different grades, HPC-M , HPC-H were prepared by direct compression using 8 mm flat punch. The total weight of core tablet was kept 150 mg. In order to optimize grade and amount of Polymers in core tablet, the composition of coating material was kept constant for all batches in first factorial design. Composition of coating material is given in Table 4.4. The composition of core tablet for all batches is given in Table 5.

Compression coating of core tablets

The core tablets were coated by compression coating using 10 mm standard flat punch in the Rimek rotary press. Half of the coating material was placed in the die cavity over which the 8 mm core tablet was placed precisely in the centre of the cavity. Other half of the coating material was layered uniformly over the tablet. The tablets were compressed to obtain hardness of 6-7 Kg/cm^3. The weight of all tablets was kept 350 mg.

Table 4 Composition of coating material

Ingredient	Quantity (mg)/ Tablet
HPC-M	80
MCC (Avicel -102)	60
Lactose (Tablettose 80)	60

Total weight of coating material for tablet is 200 mg

Table 5 Composition of core tablets

Batch code	Ingredients (mg)			
	MTX	HPC-M	HPC-H	Starch 1500
F1	30	10	-	110
F2	30	20	-	100
F3	30	30	-	90
F4	30	5	5	110
F5	30	10	10	100
F6	30	15	15	90
F7	30	-	10	110
F8	30	-	20	100
F9	30	-	30	90

Table 6 Results of evaluation of tablets for factorial design batches

Batch Code	Assay (%) (n = 20)	Average weight (mg) (n =20)	Friability (%)
F1	102.62	355 (2.5)	0.42
F2	101.46	348 (1.6)	0.43
F3	101.23	358 (1.4)	0.23
F4	99.84	360(2.8)	0.36
F5	99.75	357 (1.4)	0.28
F6	98.62	362 (3.7)	0.41
F7	101.88	349 (1.8)	0.27
F8	101.66	358 (1.6)	0.36
F9	102.79	354 (2.7)	0.36

Figure 5 Dissolution profiles of tablets for first factorial design

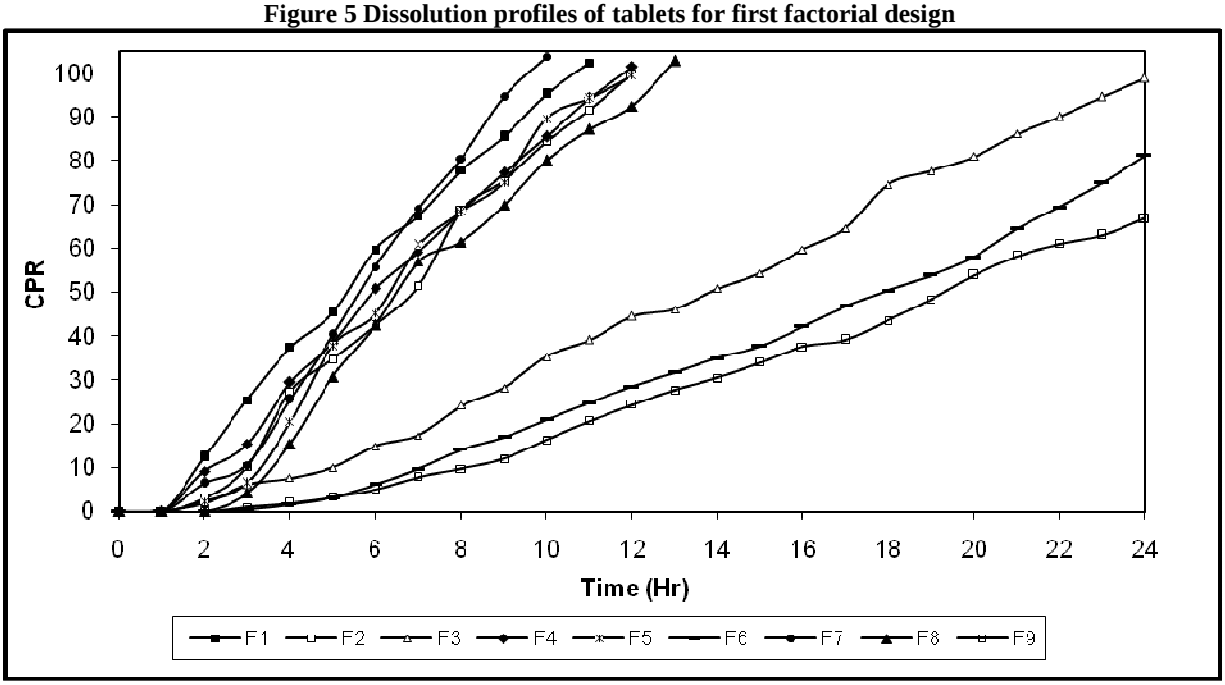


Table7 Cumulative percentage drug release from tablets for factorial design batches (n = 3)

Time (hr)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.19	0.00	0.00	0.00	0.00	0.00	0.00
2	12.46	3.12	1.96	9.24	2.37	0.00	6.48	0.00	0.00
3	25.43	10.26	6.15	15.36	6.48	0.55	10.61	4.26	0.98
4	37.54	27.46	7.69	29.46	20.48	1.72	25.49	15.46	1.91
5	45.49	34.72	10.04	38.47	37.89	3.21	40.26	30.78	3.40
6	59.84	42.63	14.93	50.78	45.18	6.24	55.86	42.53	5.09
7	67.48	51.61	17.48	59.19	60.75	9.74	69.12	57.12	7.96
8	77.86	68.79	24.15	68.49	68.49	14.20	80.49	61.48	9.70
9	85.48	75.48	28.27	77.26	75.18	16.98	94.63	69.94	12.01
10	95.12	84.34	35.37	85.46	89.60	20.96	103.75	80.07	16.37
11	102.46	91.64	39.18	94.26	91.48	24.80	-	87.20	20.77
12	-	99.86	44.56	101.48	99.48	28.56	-	92.43	24.42
13	-	-	46.13	-	-	31.74	-	102.84	27.74
14	-	-	50.84	-	-	35.08	-	-	30.49
15	-	-	54.37	-	-	37.78	-	-	34.12
16	-	-	59.78	-	-	42.27	-	-	37.60
17	-	-	64.68	-	-	46.82	-	-	39.16
18	-	-	74.53	-	-	50.37	-	-	43.61
23	-	-	94.61	-	-	75.02	-	-	63.05
24	-	-	98.83	-	-	81.29	-	-	66.87

Standard deviation values of all batches are within the limit of ±5.

Figure 6 Influence of polymer weight on drug release using HPC-M in core tablet

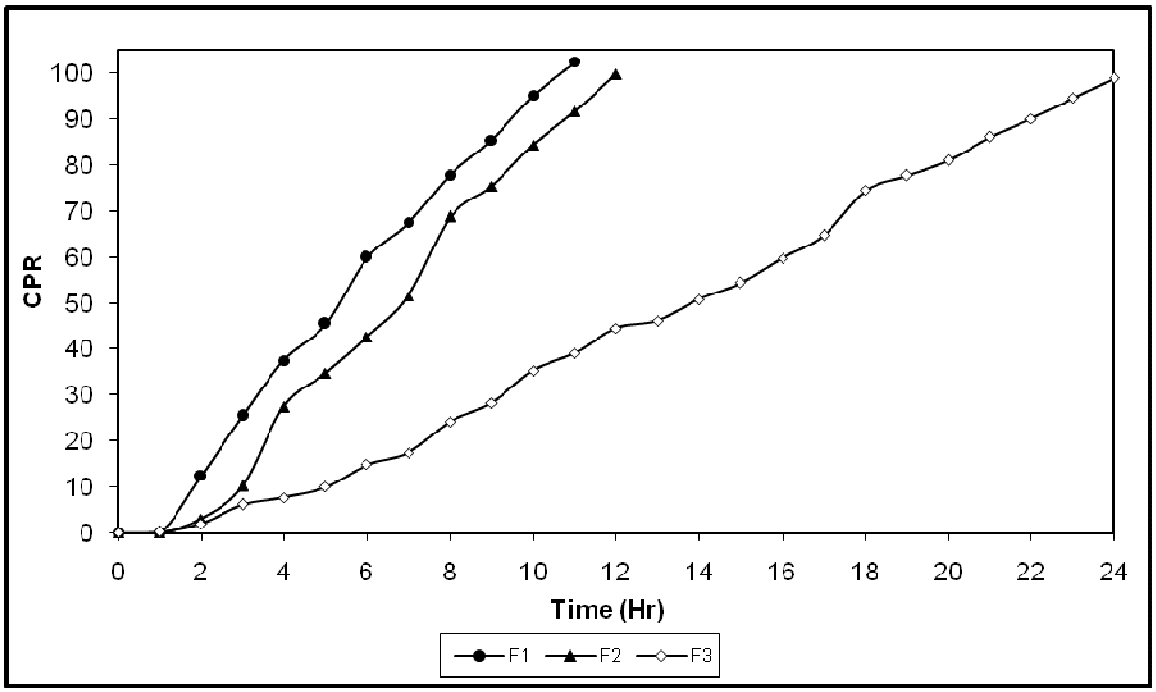


Figure 7 Influence of change in polymer weight on drug release using HPC-M and HPC-H (50:50%) in core tablet

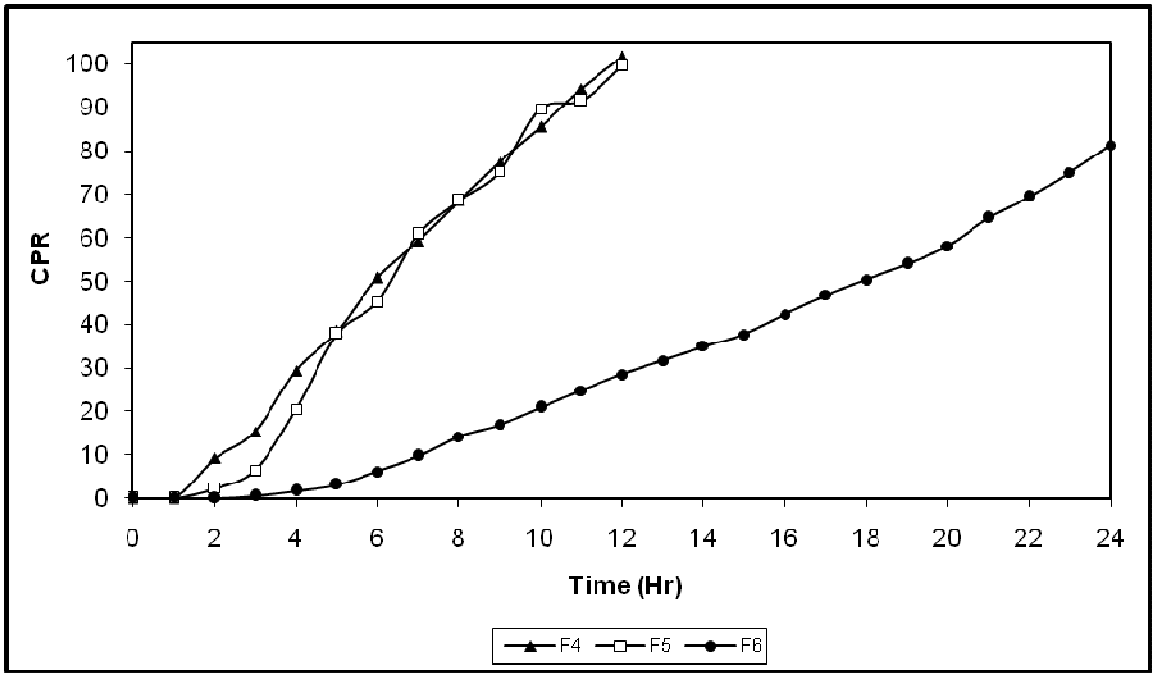


Figure 8 Influence of change in polymer weight on drug release using HPC-H in core tablet

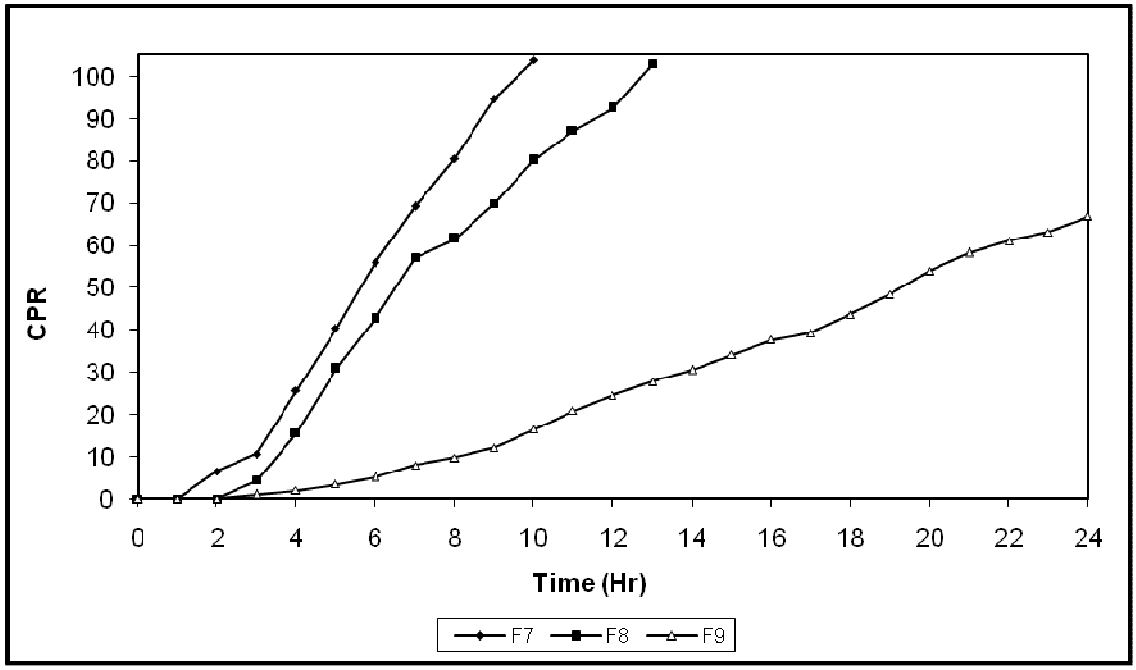


Figure 9 Influence of polymer grade (HPC-M & HPC-H) on drug release at total polymer weight of 10 mg.

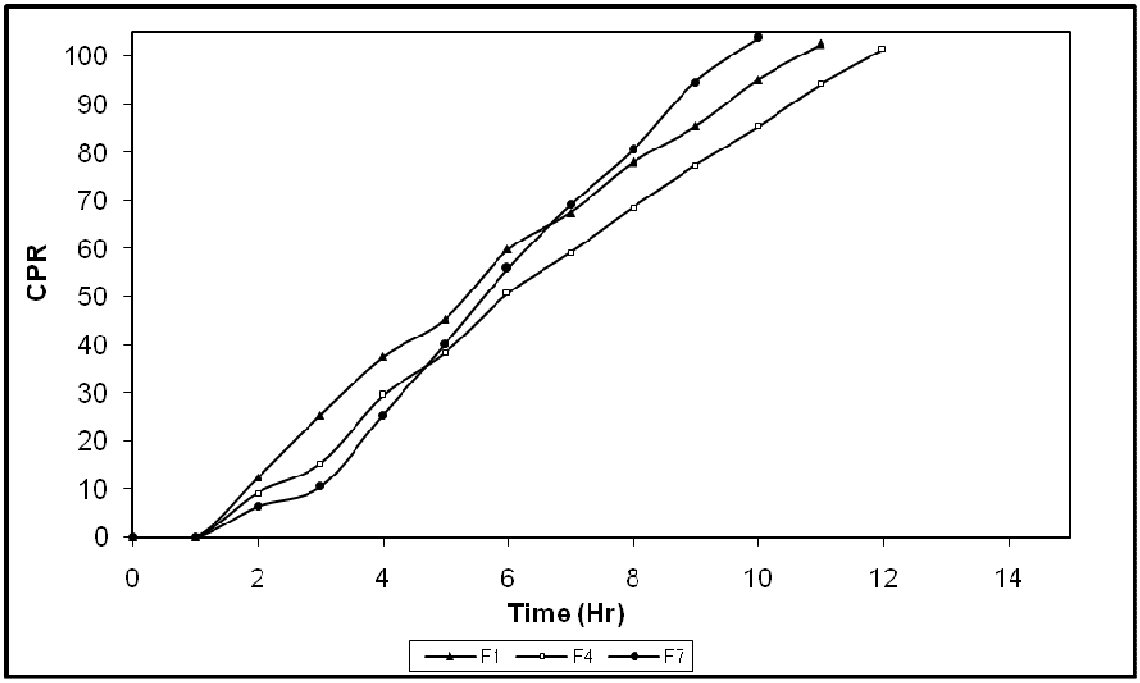


Figure 10 Influence of change in polymer grade (HPC-M & HPC-H) on drug release at total polymer weight of 20 mg.

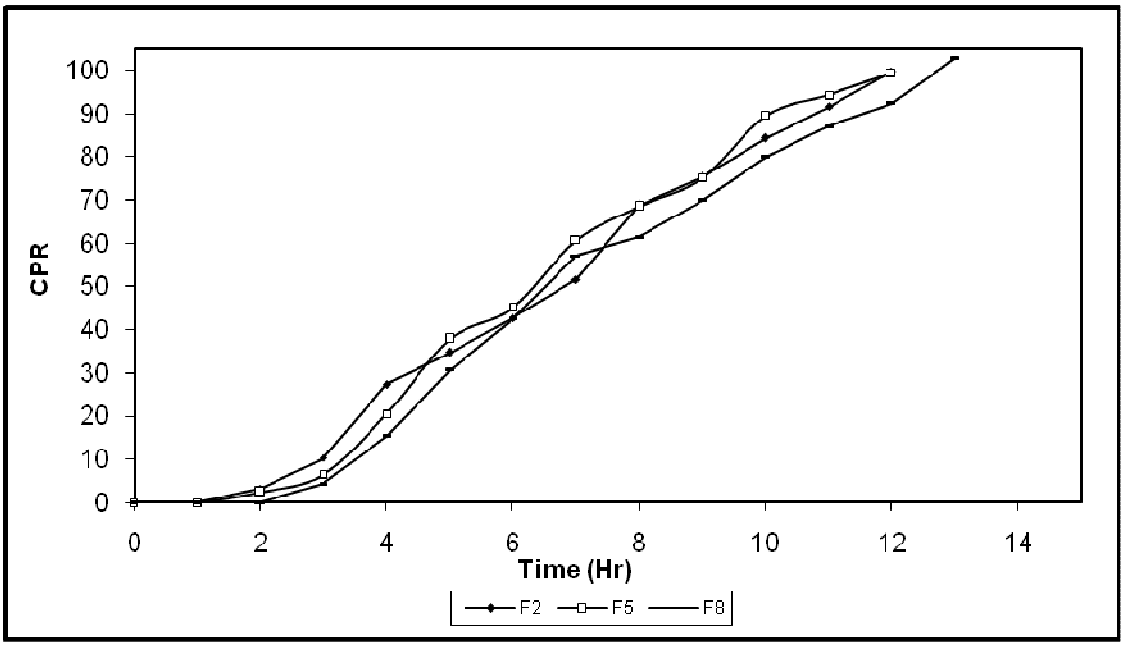
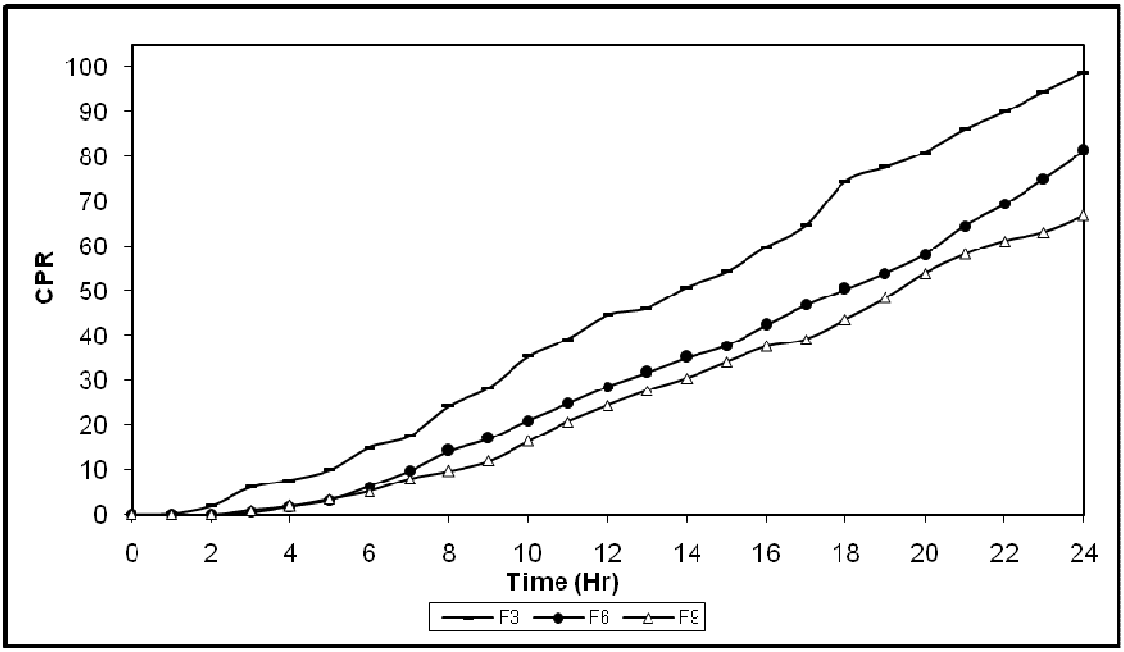


Figure 11 Influence of change in polymer grade (HPC-M & HPC-H) on drug release at total polymer weight of 30 mg.



Statistical analysis

The statistical analysis of the factorial design batches were performed by multiple regression analysis using Microsoft Excel®. The results of multiple regression analysis for factorial design batches are depicted in Table.8. To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, USA). The results of ANOVA for factorial design batches are depicted in Table 4.10. To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Sigma Plot software (Sigma Plot Software 8.0, SPSS, USA). The response surface plots for factorial are depicted as Figure 4.13. The value of $P<0.05$ was considered to be significant.

For evaluation and comparison of dissolution profiles, the dissolution profiles were analyzed using dissimilarity factor f_1 and similarity factor f_2. Dissimilarity factor f_1 and similarity factor f_2 were determined using the equation 2 and 3 as given below[5,6].

$$f_1 = \{\sum_{t=1}^{n} |R_t - T_t| \div \sum_{t=1}^{n} R_t\} \times 100 \quad \text{---------- (2)}$$

$$f_2 = 50 \log\{[1 + 1/n \sum_{t=1}^{n} w_t (R_t - T_t)^2]^{-0.5} \times 100\} \quad \text{---------- (3)}$$

Where,

n is the number of time points,

w_t is an optional weight factor,

R_t is the reference assay at time point t and
T_t is the test assay at time point t.
The f_2 value between 50 and 100 suggests that dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases. The f_1 describes the relative error between two dissolution profiles. The percent error is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles.

Table 8 Multiple regression analysis for dependent variables

Parameters	Coefficient of regression parameters							
	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	r^2	P
Q_4	19.77	-4.97	-13.52	2.03*	-3.83	1.57*	0.9982	0.0007
Q_6	41.61	-2.32	-23.37	2.74*	-11.32	-1.46*	0.9934	0.005
Q_{12}	96.31	-4.38	-35.02	1.40	-29.71	-5.35	0.9984	0.0006
Q_{23}	99.10	-4.54*	-12.50	2.43*	-10.66	08.21*	0.9663	0.0543
k	0.025	-0.012*	-0.040	0.008	0.011*	0.015*	0.9856	0.0159
n	1.392	0.101*	0.532	-0.156*	0.191*	-0.004*	0.9850	0.0169

* Indicate the value is insignificant at P = 0.05.

Table 9 Results of dependent variables for factorial design batches

Batch code	Percentage drug release				Release rate constant (*k*)	Diffusion Exponent (n)
	Q_4	Q_6	Q_{12}	Q_{23}		
F1	37.54	59.84	102.46	102.46	0.121	0.791
F2	27.46	42.63	99.86	99.86	0.036	1.235
F3	7.69	14.93	44.56	94.61	0.005	1.760
F4	29.46	50.78	101.48	101.48	0.074	0.961
F5	20.48	45.18	99.48	99.48	0.026	1.360
F6	1.72	6.24	28.56	75.02	0.001	2.239
F7	25.49	55.86	103.75	103.75	0.057	1.089
F8	15.46	42.53	92.43	102.84	0.032	1.268
F9	1.91	5.09	24.42	63.05	0.1098	2.038

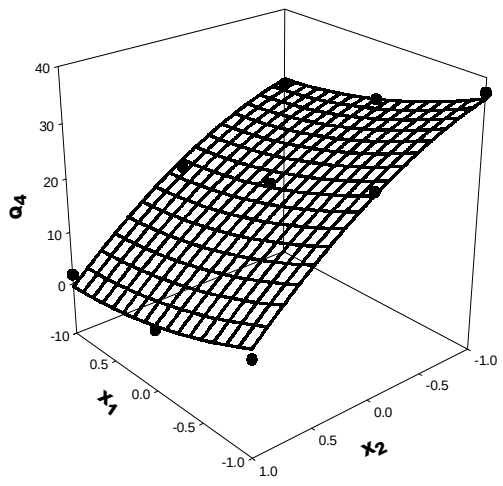
Table 10 Results of two way ANOVA for measured response

Diffusion Exponent (n)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	0.111	0.055	3.830	0.118
polymer weight	2	1.776	0.888	61.411	<0.001
Residual	4	0.057	0.014		
Total	8	1.945	0.245		
Release rate constant (k)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	0.0009	0.0005	1.565	0.315
polymer weight	2	0.0103	0.0052	16.062	0.012
Residual	4	0.0012	0.0003		
Total	8	0.012	0.001		
Q_4					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**

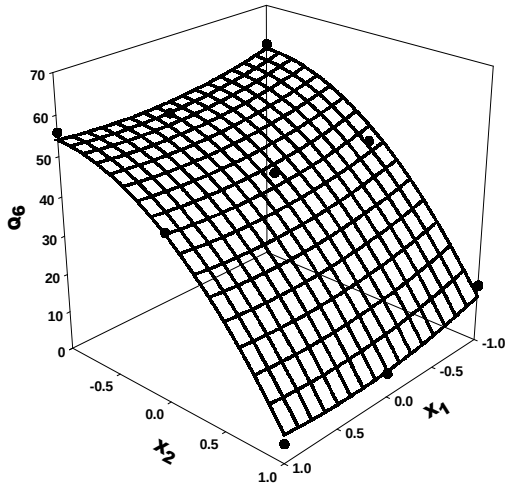
Ratio of polymer	2	156.614	78.30	21.645	0.007
polymer weight	2	1127.45	563.72	155.82	<0.001
Residual	4	14.47	3.618		
Total	8	1298.54	162.31		
		Q_6			
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	47.38	23.691	1.684	0.295
polymer weight	2	3533.37	1766.68	125.608	<0.001
Residual	4	56.26	14.06		
Total	8	3637.02	454.62		
		Q_{12}			
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	119.06	59.53	1.645	0.301
polymer weight	2	9126.86	4563.43	126.063	<0.001
Residual	4	144.79	36.200		
Total	8	9390.72	1173.841		
		Q_{23}			
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	135.98	67.99	0.714	0.543
polymer weight	2	1165.23	582.61	6.116	0.061
Residual	4	381.07	95.269		
Total	8	1682.29	210.28		

DF is degree of freedom, SS is sum of square, MS is mean sum of square and F is Fischer's ratio.

Figure 12 Surface response plot to depict the ratio of polymer (X_1) and polymer weight (X_2) on [a] Q_4 [b] Q_6 [c] Q_{12}[d] Q_{23}



[a]



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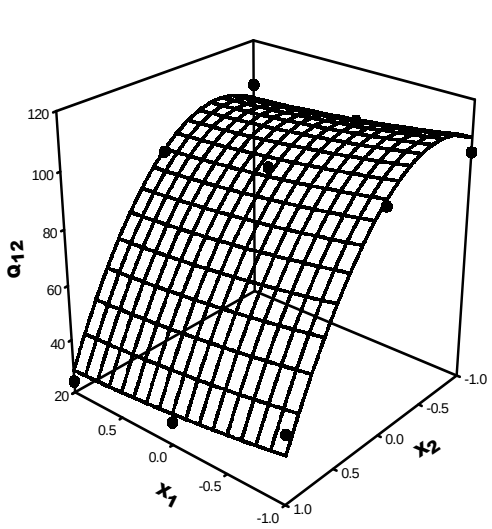
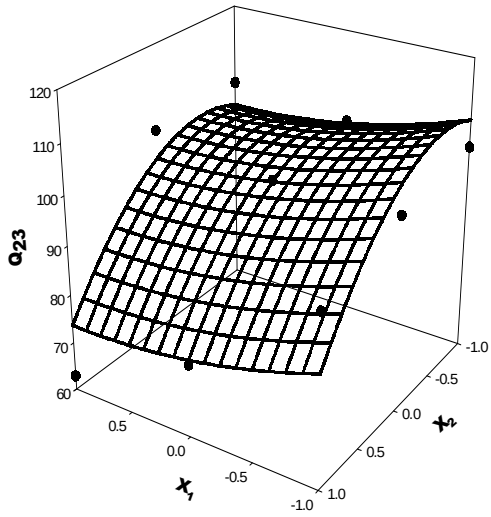


[c]



[d]

Optimization of polymer in coating material using full factorial design

The amount of HPC-H (X_1) and ratio of MCC: Tablettose 80 (X_2) in the compression coat were selected as independent variables. Percentage drug release at 4 h (Q_4), 6 h (Q_6), 12 h (Q_{12}) and 18 h (Q_{18}) release rate constant (k) and diffusion exponent (n) were selected as dependent variables. The amount of HPC-H was evaluated at 40, 80 and 120 mg of the total coating weight and ratio of MCC: Tablettose 80 was evaluated at 25:75, 50:50 and 75:25. The core tablets containing MTX (30 mg), Starch 1500 and HPC-M were prepared by direct compression using 8 mm flat punch. The total weight of core tablet was kept 150 mg. In second factorial design composition of core tablet was kept constant as per optimized batch from first factorial design. The composition of core tablet is given in Table 4.11. Total weight of polymer and ratio of Excipient (MCC and lactose) in coating material were optimized in second factorial design**.** The Composition of coating material for all batches is given in Table 4.13. The weight of coating material was kept 200 mg for all batches.

Compression coating of core tablets

The core tablets were coated by compression coating using 10 mm standard flat punch in the Rimek rotary press. Half of the coating material was placed in the die cavity over which the 8 mm core tablet was placed precisely in the centre of the cavity. Other half of the coating material was layered uniformly over the tablet. The tablets were compressed to obtain hardness of 6-7 Kg/cm^3. The weight of all tablets was kept 350 mg.

Table 11 Composition of core tablets for all batches in second factorial design

Ingredient	Quantity (mg)/ Tablet
Methotrexate	30
HPC-M	30
Starch (Starch – 1500)	90
Total weight of core tablet was kept 150 mg	

Table 12 Full factorial design for coating material in second factorial design

Batch code	Coded level		Actual value (mg)	Actual value (%)
			X_1	X_2
	X_1	X_2	HPC-H	MCC:Lactose
S1	-1	-1	40	25:75
S2	-1	0	40	50:50
S3	-1	+1	40	75:25
S4	0	-1	80	25:75
S5	0	0	80	50:50
S6	0	+1	80	75:25
S7	+1	-1	120	25:75
S8	+1	0	120	50:50
S9	+1	+1	120	75:25

Table 13 Composition of coating material for all batches in second factorial design

Batch code	Ingredients (mg)		
	HPC-H	MCC	Lactose
S1	40	40	120
S2	40	80	80
S3	40	120	40
S4	80	30	90
S5	80	60	60
S6	80	90	30
S7	120	20	60
S8	120	40	40
S9	120	60	20

Statistical analysis

The results of ANOVA for factorial design batches are depicted in Table 8. The results of Tukey test are depicted in Table 4.19. To demonstrate graphically the influence of each factor on responses, the response surface plots were generated using Sigma Plot software (Sigma Plot Software 8.0, SPSS, USA). The response surface plots for factorial are depicted as Figure 5.13. The value of $P<0.05$ was considered to be significant.

Kinetic treatment of dissolution profiles

Swellable polymer hydrogels have several important characteristics that play an essential role in drug diffusion including swelling ratio and specific mesh or pore size. Swelling ratio describes

the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure, hydrophilicity and ionization of the functional groups. The pore size is the space available for drug transport. The drug characteristics are as important as those of the gel. The size, shape and ionization of the drug affect its diffusion through the gel layer[7].

The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion, but other processes in addition to diffusion are also important. There is also a relaxation of the polymer chains, which influences the drug release mechanism. This process is described as non-Fickian or anomalous diffusion. Release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chains. The thermodynamic state of the polymer and the penetrant concentration are responsible for the different types of the diffusion. A third class of the diffusion is Case II diffusion, which is a special case of non-Fickian diffusion[8]. A simple, semi-empirical equation given by Korsmeyer and Peppas[9] (Eq. 4) was used to analyze data of controlled release of drugs from polymer matrices.

$$M_t/M_\infty = kt^n \text{ ---------- (4)}$$

Where,

M_t is amount of drug release at time t,
M_∞ is total amount of drug present in formulation,
k is release rate constant depend on geometry of dosage form and
n is diffusion exponent indicating the mechanism of drug release.
If the value of n is 0.45 indicate fickian diffusion, between 0.45 and 0.85 indicate anomalous transport and 0.85 or more indicates case-II transport.

Table 14Results of evaluation of tablets for factorial design batches

Batch Code	Assay (%) (n = 20)	Average weight (mg) (n =20)	Friability (%)
S1	101.43	342 (1.7)	0.48
S2	103.36	359 (2.9)	0.28
S3	102.54	353 (2.2)	0.42
S4	101.67	344(3.6)	0.38
S5	102.23	340 (1.8)	0.23
S6	102.12	359(2.9)	0.39
S7	99.87	360 (2.3)	0.24
S8	102.48	347 (1.3)	0.41
S9	99.29	362 (3.2)	0.36

Table 15mulative percentage drug release from tablets for factorial design batches (n = 3).

Time (hr)	Batch code								
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	8.95	5.52	1.38	0.00	0.00	0.00	0.00	0.00	0.00
2	12.60	9.70	3.88	0.00	0.00	0.00	0.00	0.00	0.00
3	19.10	13.44	6.14	0.36	0.48	0.00	0.00	0.00	0.00
4	26.54	17.51	8.77	4.32	1.71	0.29	0.00	0.00	0.58
5	34.05	26.02	13.22	6.18	3.07	1.57	4.90	1.78	0.77
6	40.17	32.43	15.99	9.17	7.01	1.59	6.73	3.33	1.33
7	46.48	37.74	20.76	13.43	8.05	3.02	10.17	4.10	3.67
8	51.94	44.02	25.21	16.32	9.43	3.60	13.22	6.35	5.18
9	57.64	49.70	28.54	18.52	12.04	4.19	14.77	6.78	6.46
10	61.10	54.88	32.28	21.07	15.72	5.34	16.71	7.53	8.73
11	63.40	57.30	36.78	25.68	19.26	8.46	20.50	10.98	11.16
12	68.40	62.30	41.21	30.62	23.26	9.22	23.41	13.30	13.97
13	72.00	64.60	44.10	34.56	26.51	13.12	27.58	15.89	17.49
14	75.60	70.60	48.29	38.68	30.53	15.96	32.40	20.35	20.56
15	82.35	74.84	51.98	42.07	33.06	18.33	36.48	23.14	24.27
16	91.15	82.34	56.31	48.38	36.47	20.67	40.36	26.44	26.06
17	97.60	89.92	58.98	55.23	38.63	23.89	47.64	32.91	31.05
18	98.59	93.29	65.21	62.48	44.66	29.59	48.82	38.77	35.17
24	103.45	101.59	81.19	94.82	62.09	47.05	64.21	54.18	53.23

Standard deviation values of all batches are within the limit of ± 5.

Figure13 Dissolution profiles of tablets for second factorial design

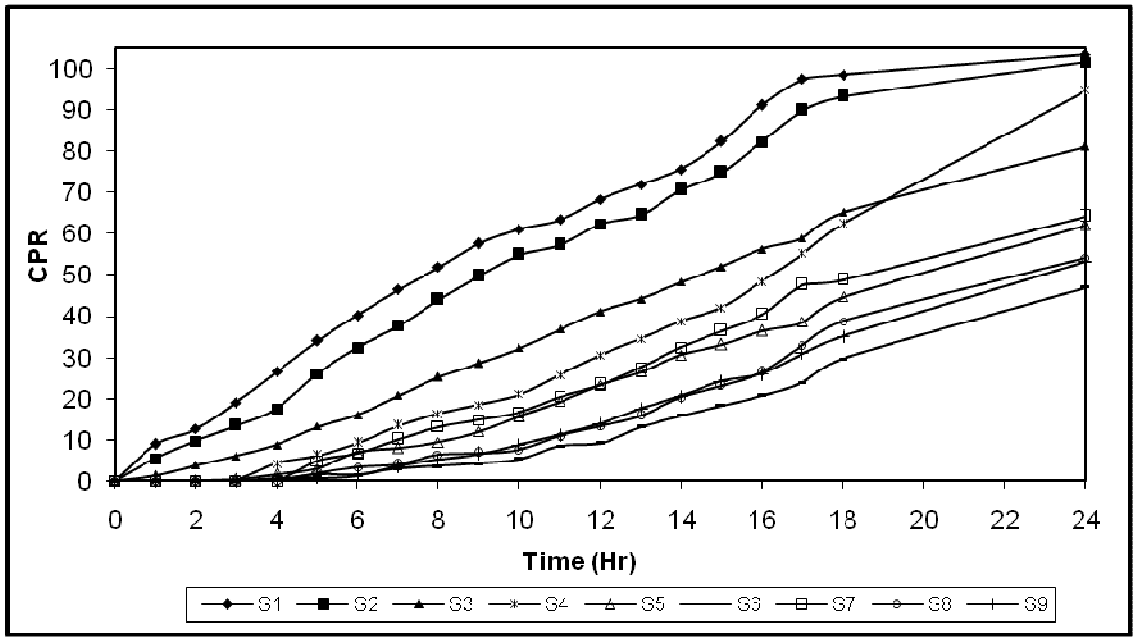


Figure 14 Influence of ratio of excipient on drug release using HPC-H (40 mg) in coating material

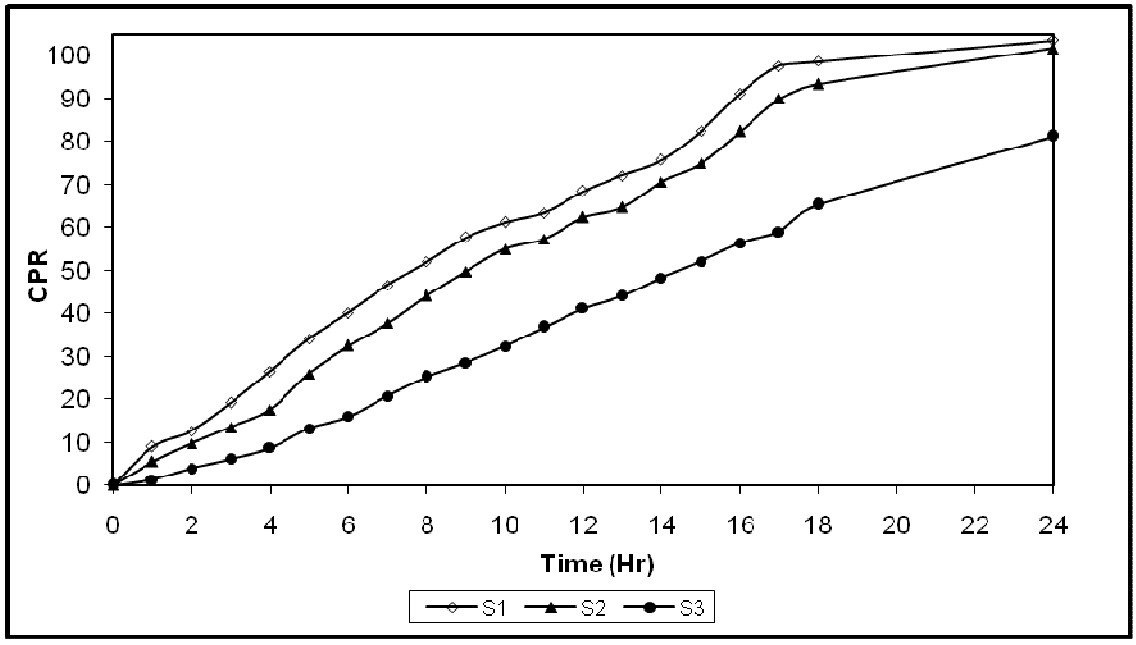


Figure 15 Influence of change in ratio of excipient on drug release using HPC-H (80 mg) in coating material

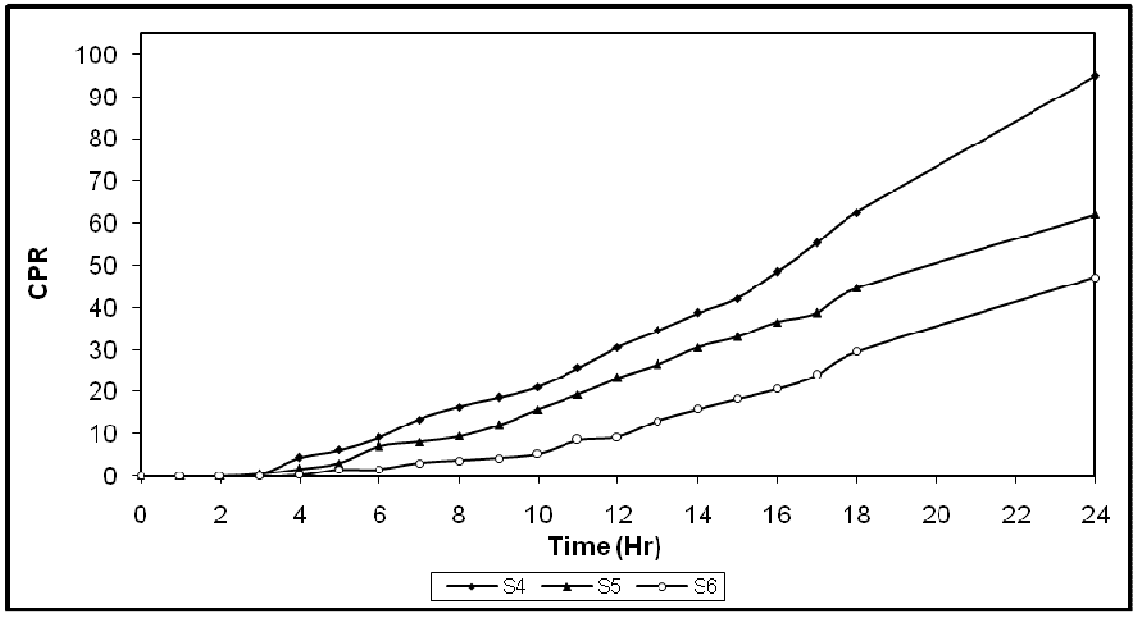


Figure 7 Influence of change in ratio of excipient on drug release using HPC-H (120 mg) in coating material

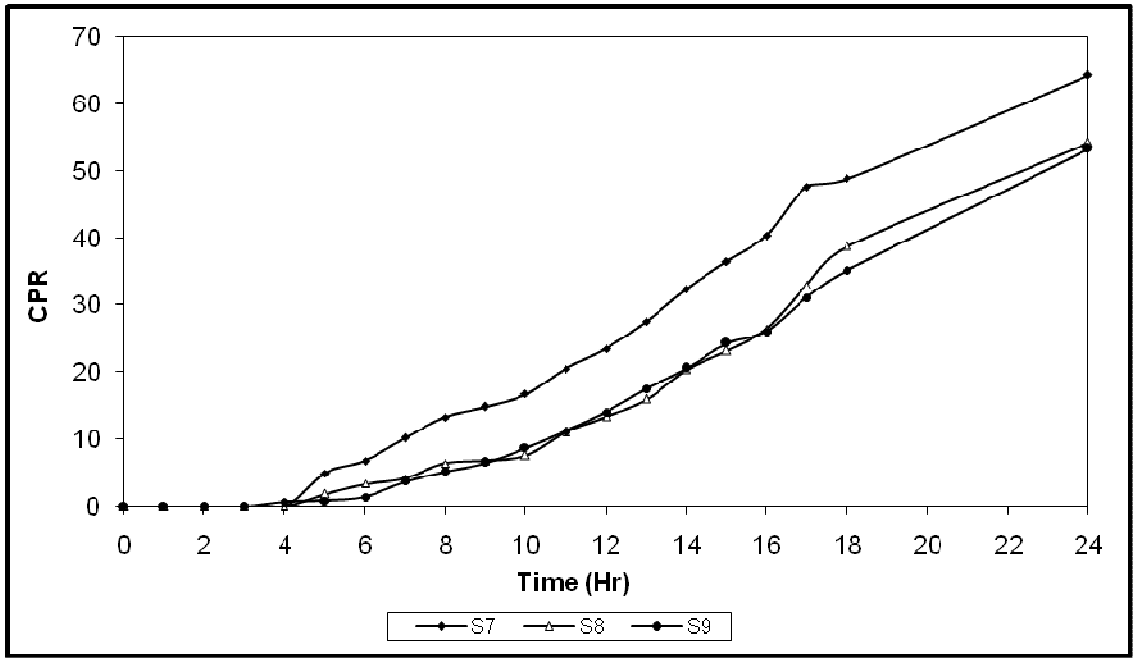


Figure 16 Influence of polymer weight (HPC-H) in coating material on drug release from tablet containing MCC and lactose in ratio of 25:75%.

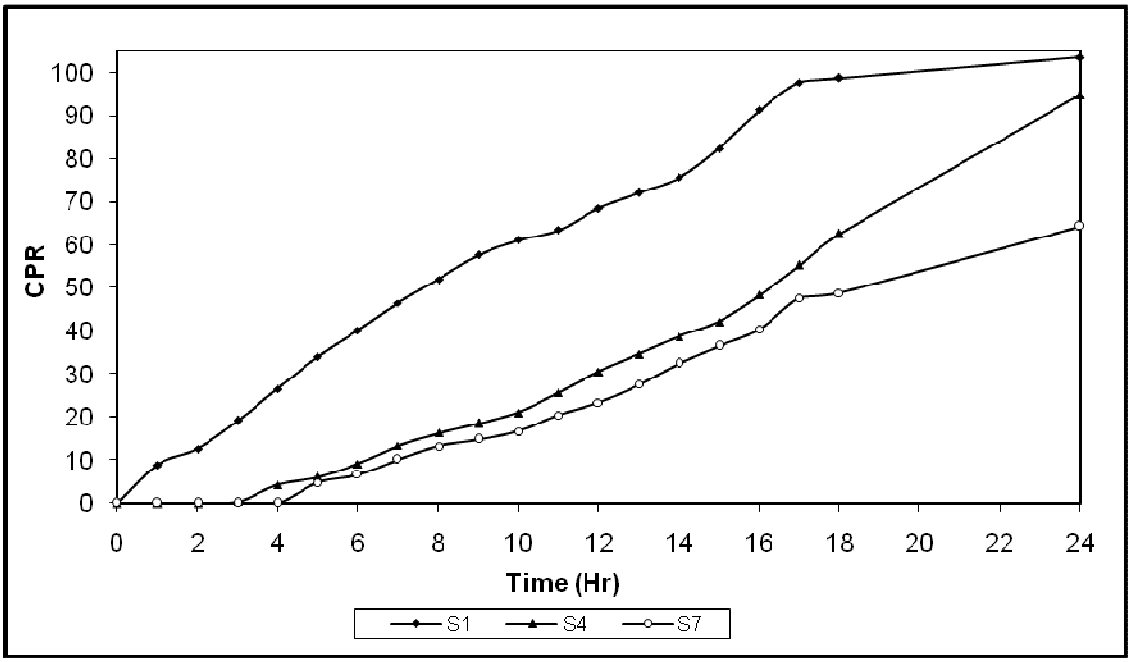


Figure 17 Influence of polymer weight (HPC-H) in coating material on drug release from tablet containing MCC and lactose in ratio of 50:50%.

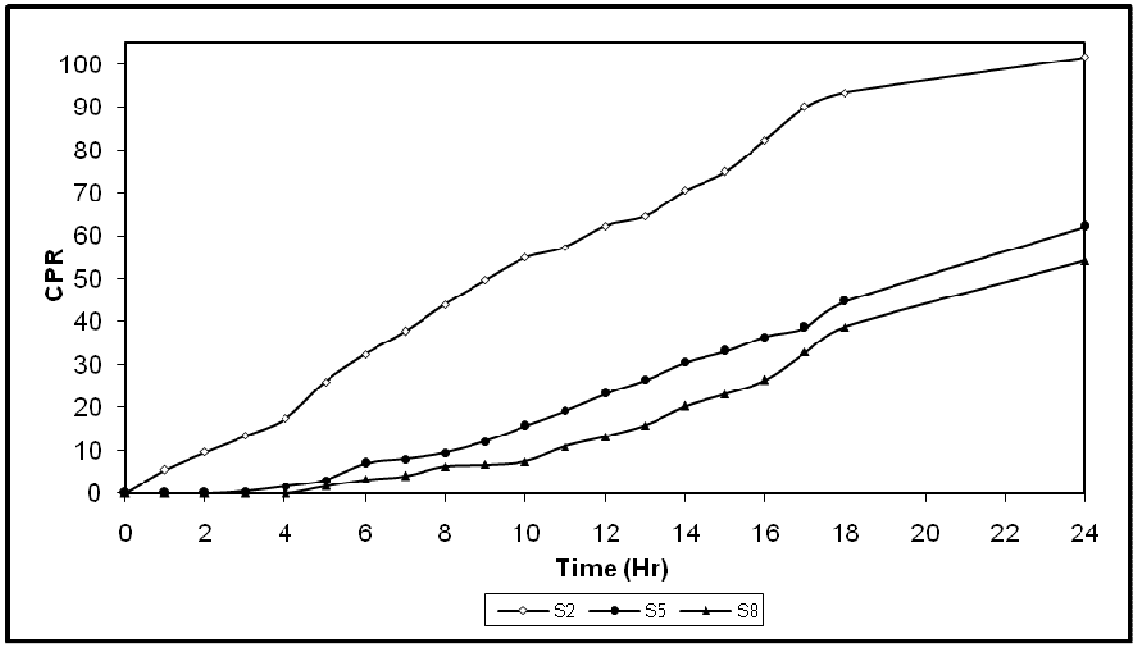


Figure 18 Influence of polymer weight (HPC-H) in coating material on drug release from tablet containing MCC and lactose in ratio of 75:25%.

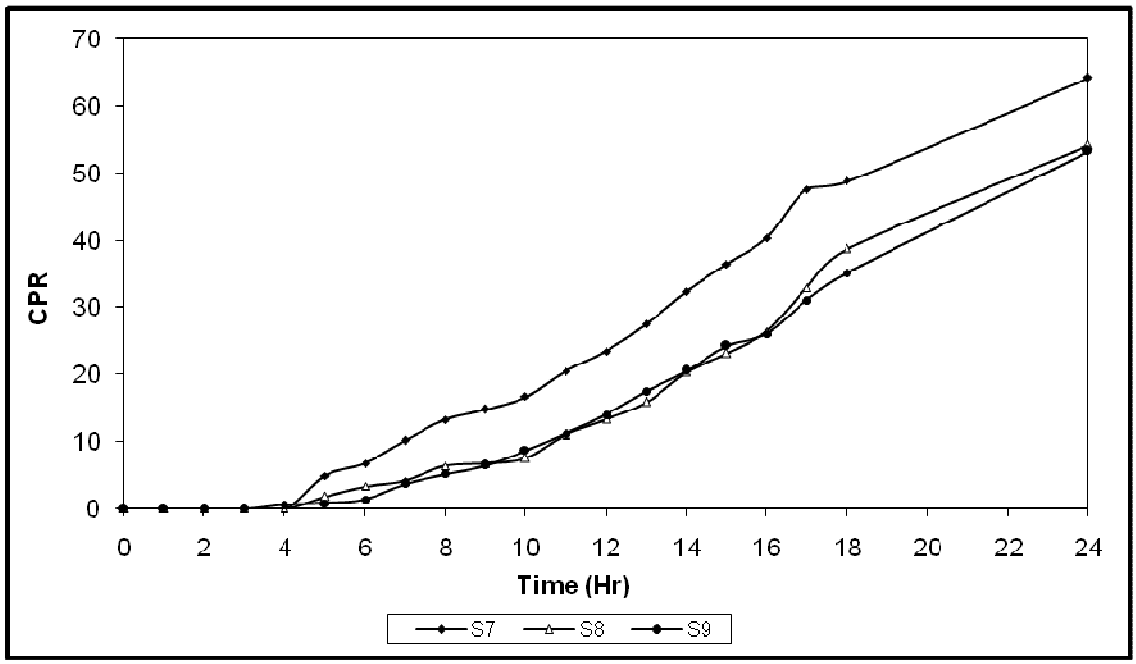


Table 16 Results of dependent variables for factorial design batches

Batch code	Percentage drug release				Release rate constant (*k*)	Diffusion Exponent (n)
	Q_4	Q_6	Q_{12}	Q_{18}		
S1	26.54	40.17	68.40	98.59	0.0827	0.851
S2	17.51	32.43	62.30	93.29	0.0513	0.996
S3	8.77	15.99	41.21	65.21	0.0152	1.307
S4	4.32	9.17	30.62	62.48	0.0012	2.182
S5	1.71	7.01	23.26	44.66	0.0008	2.214
S6	0.29	1.59	9.22	29.59	0.0001	2.632
S7	0.00	6.73	23.41	48.82	0.0034	1.706
S8	0.00	3.33	13.30	38.77	0.0005	2.221
S9	0.58	1.33	13.97	35.17	0.0001	2.733

Table 17 Multiple regression analysis for dependent variables

Parameters	Coefficient of regression parameters							
	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	r^2	P
Q_4	1.87*	-8.70	-3.53	6.79	-0.34*	4.58	0.9950	0.0032
Q_6	7.09	-12.86	-6.19	10.74	-1.75*	-4.69	0.9917	0.0070
Q_{12}	22.24	-20.20	-9.67	16.06	-1.81*	-4.43*	0.9916	0.0071
Q_{18}	47.37	-22.17	-13.31	17.94	-2.68	4.93*	0.9891	0.0105
K	0.001*	-0.024	-0.012*	0.024	-0.0004*	0.016*	0.9714	0.0431
n	2.28	0.584	0.322	-0.707	0.091*	0.142*	0.9945	0.0037

** Indicate the value is insignificant at P = 0.05.*

Table 18 Results of two way ANOVA for measured response

Diffusion Exponent (n)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
polymer weight	2	3.049	1.524	49.775	0.001
Ratio of excipient	2	0.640	0.320	10.443	0.026
Residual	4	0.123	0.030		
Total	8	3.811	0.476		
Release rate constant (k)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
polymer weight	2	0.0047	0.00237	6.642	0.054
Ratio of excipient	2	0.00086	0.00043	1.210	0.338
Residual	4	0.00143	0.00035		
Total	8	0.0704	0.00088		
Q_4					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
polymer weight	2	547.135	273.568	11.999	0.020
Ratio of excipient	2	75.284	37.642	1.651	0.300
Residual	4	91.197	22.799		
Total	8	713.616	89.202		
Q_6					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**

polymer weight	2	1224.00	612.001	21.470	0.007
Ratio of excipient	2	236.339	118.170	4.146	0.106
Residual	4	114.018	28.504		
Total	8	1574.35	196.795		

Q_{12}

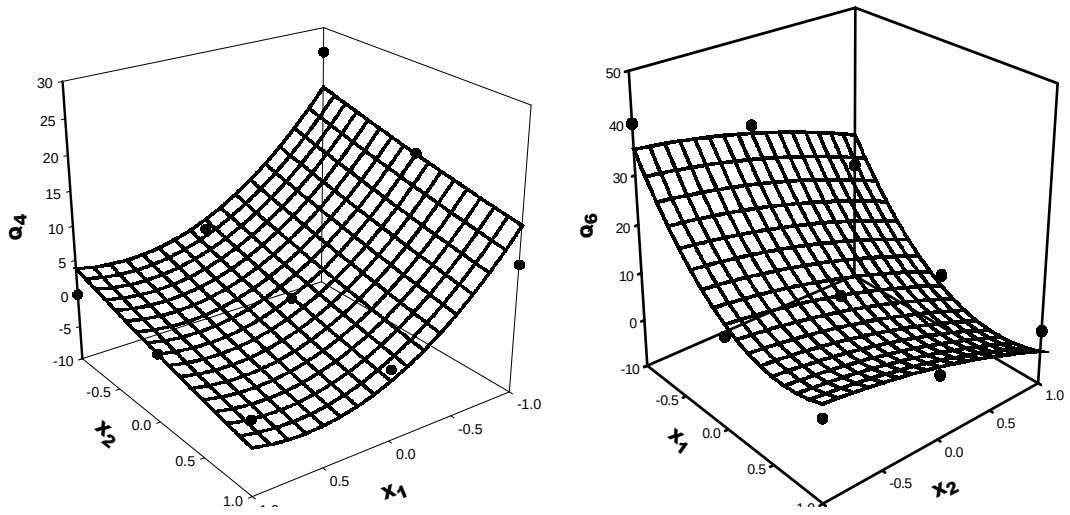
Source of variation	DF	SS	MS	F	P
polymer weight	2	2965.621	1482.81	42.486	0.002
Ratio of excipient	2	567.835	283.91	8.135	0.039
Residual	4	139.605	34.90		
Total	8	363.061	459.13		

Q_{18}

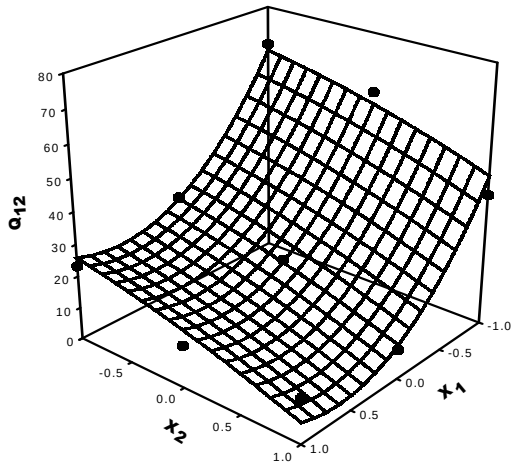
Source of variation	DF	SS	MS	F	P
polymer weight	2	3594.43	1797.215	35.516	0.003
Ratio of excipient	2	1079.007	539.503	10.661	0.025
Residual	4	202.413	50.603		
Total	8	485.85	609.48		

DF is degree of freedom, SS is sum of square, MS is mean sum of square and F is Fischer's ratio.

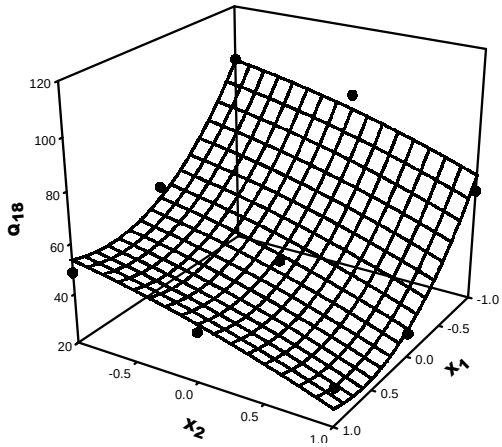
Figure 19 Surface response plot to depict the polymer weight (X_1) and the ratio of excipient (X_2) on [a] Q_4 [b] Q_6 [c] Q_{12} [d] Q_{18}



[a] [b]



[c]



[d]

Comparison of optimized batch between First and second factorial design.

The optimized batch from first factorial design used for optimizing polymer in core tablet was compared with optimized batch of second factorial design applied to optimize coating material in terms of dissolution profiles. Table 4.20 and figure 4.22 shows the release profile of batch F3 of first factorial design and S4 of second factorial design.

Table19 Cumulative percent drug release from batch F3 (first factorial) and F4 (second factorial).

Time (Hr)	S4 (Second Factorial)	F3 (First Factorial)
0	0.00	0.00
1	0.00	0.19
2	0.00	1.96
3	0.36	6.15
4	4.32	7.69
5	6.18	10.04
6	9.17	14.93
7	13.43	17.48
8	16.32	24.15
9	18.52	28.27
10	21.07	35.37
11	25.68	39.18
12	30.62	44.56
13	34.56	46.13
14	38.68	50.84
15	42.07	54.37
16	48.38	59.78
17	55.23	64.68
18	62.48	74.53
24	94.82	98.83
f_1 value	**Reference**	**30.13**
f_2 value	**Reference**	**51.31**

Figure 20 Comparative dissolution profile of F3 (First Factorial design) and S4 (Second Factorial design)

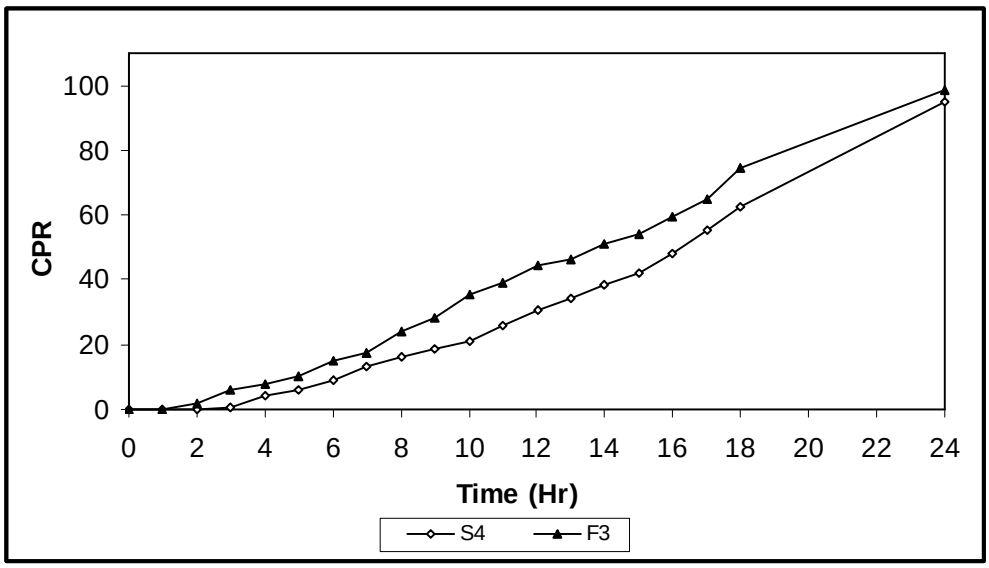


Table 20 Dissolution profiles of batches evaluated for stability study

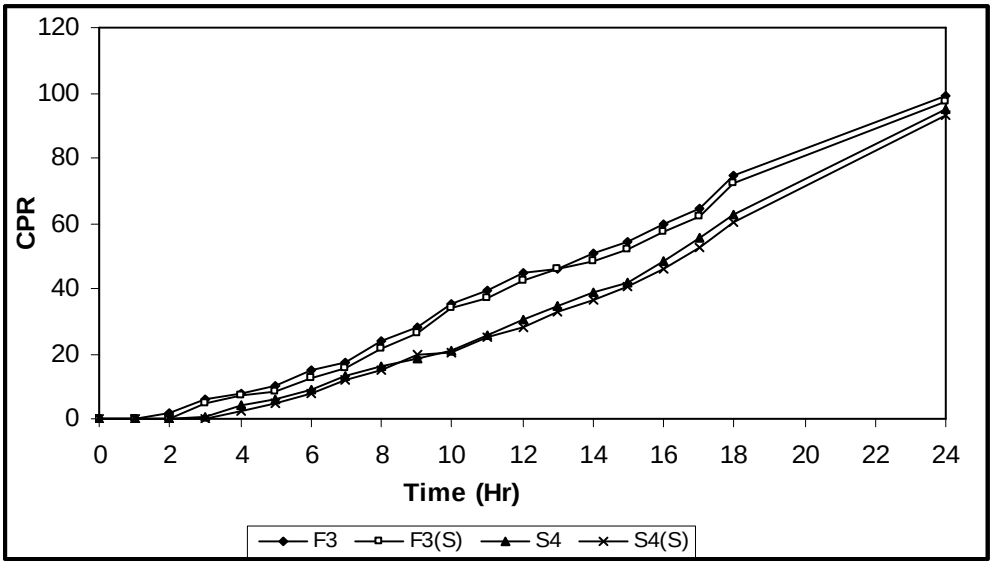
Time (hr)	Cumulative Percentage Drug Release (CPR)			
	F3	F3 (S)	S4	S4 (S)
0	0.00	0.00	0.00	0.00
1	0.19	0.24	0.00	0.00
2	1.96	0.23	0.00	0.00
3	6.15	4.85	0.36	0.00
4	7.69	6.97	4.32	2.32
5	10.04	8.12	6.18	4.57
6	14.93	12.34	9.17	7.65
7	17.48	15.23	13.43	11.93
8	24.15	21.39	16.32	14.65
9	28.27	26.48	18.52	19.84
10	35.37	33.94	21.07	20.32
11	39.18	37.08	25.68	24.87
12	44.56	42.38	30.62	28.32
13	46.13	45.97	34.56	33.04
14	50.84	48.63	38.68	36.19
15	54.37	52.20	42.07	40.43
16	59.78	57.38	48.38	45.82
17	64.68	62.28	55.23	52.45
18	74.53	71.98	62.48	60.43
24	98.83	97.04	94.82	93.43
f_1 value	Ref.	4.963	Ref.	5.416
f_2 value	Ref.	83.082	Ref.	85.394

F3(S), and F4(S) represents the respective stability batches

Stability study of optimized batch

In order to determine the change in performance of dosage form on storage, stability study of batch F3 of first factorial and batch F4 of second factorial design was carried out at 40^{o} C in a humidity jar having 75 % RH according to ICH[10]. Samples were withdrawn after three month and evaluated for change in drug release pattern. The similarity (f_2) and dissimilarity (f_1) factor was applied to study the effect of storage on batch F3 and S4. The release profile of sample put on stability study was depicted in Table 4.21and Figure 4.23.

Figure 21 Dissolution profiles of batch F3 (first factorial) and F4 (second factorial) evaluated for stability study



SUMMARY AND CONCLUSION

The use of polymeric matrix devices to control the release of variety of therapeutic agents has become increasingly important in development of the modified release dosage forms. The device may be a swellable, hydrophilic monolithic systems, an erosion controlled monolithic system or a non erodible system. The initial burst release of MTX from such matrix tablet surface can be controlled by compression coating technology. Appropriate combination of hydrophilic polymer in upper and lower layer of tablet can govern the release of MTX as well as lag time to deliver it in effective concentration to the colon with reduced toxicity. The lag time can be controlled by appropriate combination of polymer and excipients in coating layer. The release mechanism of MTX from the compression coated tablets was controlled by the rate of water uptake into the core tablet, which in turn was dependent upon the channeling agent used, the type and concentration of polymer. The hydration and swelling of these polymers results in the formation of gel which control the release of MTX from tablet. The hydrophilic lactose forms channels within the coating layer and thus increase the drug release, whereas MCC swell in initial period and atlast erodes along with polymer.

The type of polymer, the type of channeling agent and swellable inert excipients in core as well as compression coat was statistically optimized using factorial design. The tablets of the promising batches were found to be stable for three months under accelerated stability studies. The optimized batches from both factorial design were compared using similarity and dissimilarity factor. The batches F3 (First factorial design) and S4 (Second factorial design) were found to be similar displayed the zero order release kinetics after lag time of 6 hr.

Thus the colon targeted tablet of MTX can be formulated by optimized proportion of HPC and excipients in coating layer as well as in core tablet.

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