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Innovation on Optimization of 5-Fluoruracil SR Tablets for Colon Cancer Treatment

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Abstract

The Oral controlled - release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug - release pattern that are not achieved with traditional immediate (or) sustained - release products Although 5-FU is a widely used antineoplastic agent, the cytotoxicity is not limited to tumor cells. Hematopoietic cells and normal epithelial cells of GI tract are susceptible to 5-FU induced cytotoxicity, which produces sever leucopenia and intestinal toxicity leading to lethal translocation of intestinal microflora. The clinical use of 5-FU is limited by its GI toxicity (stomatitis) and myelotoxicity[1], and oral bioavailability was found to be only 28% in humans. On other hand, severe systemic toxic effects and shorter half life make this drug particularly suitable to be delivered by local delivery system providing continuously sustained release[1]. Targeted delivery of 5-FU not only reduces systemic side effects, but also would provide an effective and safe therapy for colon cancer with reduced dose and duration of therapy.

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Introduction

Oral controlled - release formulations for the small intestine and colon have received considerable attention in the past 25 years for a variety of reasons including pharmaceutical superiority and clinical

benefits derived from the drug - release pattern that are not achieved with traditional immediate (or) sustained - release products[1].By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel disease (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer. Other potential applications of colonic delivery include chronotherapy, prophylaxis of colon cancer and treatment of nicotine addiction[2-3]. It has also gained increased importance not just for the delivery of drugs for the treatment of local diseases[4], but also potential site for the systemic delivery of therapeutic proteins and peptides which are being delivered by injections. These delivery systems when taken orally, allow drugs to release the drug from the delivery system once the delivery system arrives into the colon.

These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are need most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine[4]5-fluorouracil (5-FU) is one of the most widely used agent in the first line chemotherapy of colorectal cancer[i]. Although 5-FU is a widely used antineoplastic agent, the cytotoxicity is not limited to tumor cells. Hematopoietic cells and normal epithelial cells of GI tract are susceptible to 5-FU induced cytotoxicity, which produces sever leucopenia and intestinal toxicity leading to lethal translocation of intestinal microflora. The clinical use of 5-FU is limited by its GI toxicity (stomatitis) and myelotoxicity[ii], and oral bioavailability was found to be only 28% in humans. On other hand, severe systemic toxic effects and shorter half life make this drug particularly suitable to be delivered by local delivery system providing continuously sustained release[iii]. Targeted delivery of 5-FU not only reduces systemic side effects, but also would provide an effective and safe therapy for colon cancer with reduced dose and duration of therapy.

Experimental Work :

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 1 shows the applied full factorial design for core tablet.

Table 1: Full Factorial Design

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

X_1 is the ratio of polymer HPC-M: HPC-H and **X_2** is total weight of polymer in the core tablet. All batches contained 50mg 5- fluoruracil

Preparation of core tablets

The core tablets containing 5-fluoruracil (50 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 2

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 2: 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 3 Composition of core tablets

Batch code	Ingredients (mg)			
	5-fluouracil	HPC-M	HPC-H	Starch 1500
F1	50	10	-	110
F2	50	20	-	100
F3	50	30	-	90
F4	50	5	5	110
F5	50	10	10	100
F6	50	15	15	90
F7	50	-	10	110
F8	50	-	20	100
F9	50	-	30	90

Table 4: 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 1: Dissolution profiles of tablets for first factorial design

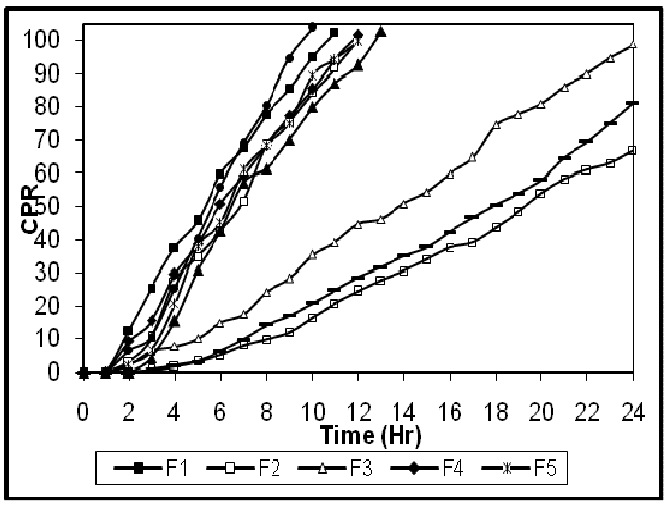


Table 5: Cumulative percentage drug release from tablets for factorial design batches (n = 3)

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.									

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 4.8. 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[iv,v].

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

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

---------- (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 6 : 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 7: Results of dependent variables for factorial design batches

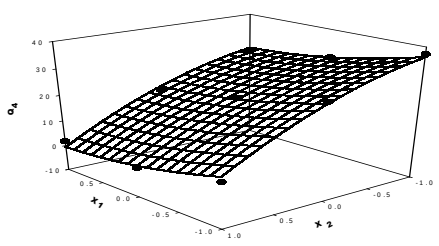
Batch code	Percentage drug release				Release rate constant (*k*)	Diffusion Exponent (n)
	Q_4	Q_6	Q_{12}	Q_{23}		
F1	37.54	59.84	102.46	102.46	0.121	0.791
F2	27.46	42.63	99.86	99.86	0.036	1.235
F3	7.69	14.93	44.56	94.61	0.005	1.760
F4	29.46	50.78	101.48	101.48	0.074	0.961
F5	20.48	45.18	99.48	99.48	0.026	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 8: Results of two way ANOVA for measured response

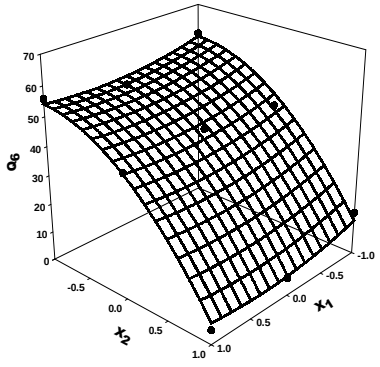
Diffusion Exponent (n)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	0.111	0.055	3.830	0.118
polymer weight	2	1.776	0.888	61.411	<0.001
Residual	4	0.057	0.014		
Total	8	1.945	0.245		
Release rate constant (k)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio 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 2: 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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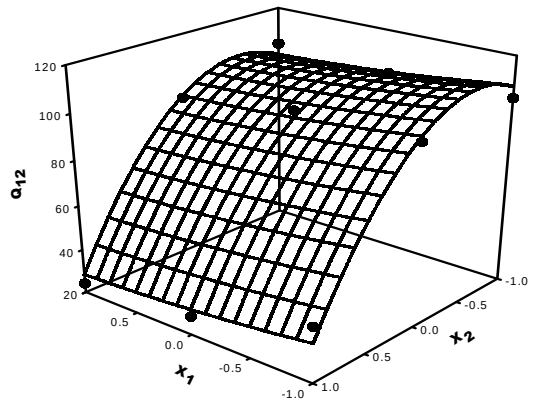
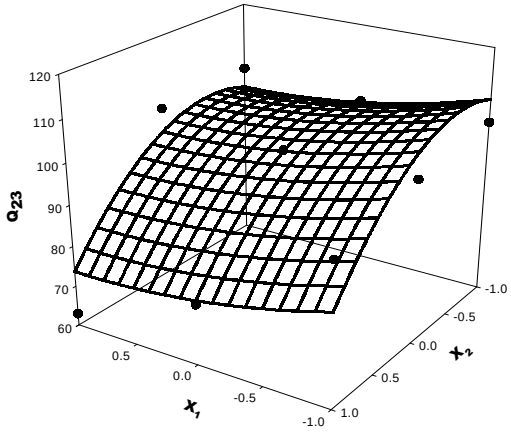


[c]



[d]

DISCUSSION 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 5-FLUORURACIL 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 5-FLUORURACIL 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 5-FLUORURACIL 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 5-FLUORURACIL 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.

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