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Research Article

DEVELOPMENT AND CHARACTERIZATION OF COLON TARGETED ENTERIC COATED MATRIX TABLET OF TEGASEROD MALEATE

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ABSTRACT

The various pharmaceutical approaches which have been used for targeting drugs to the colon are mainly based on pH-dependent, time dependent and/or bacterially degradable polymers[1]. Among the various experimented approaches, pH-sensitive and time-controlled delivery systems are most widely used[2,3,4]. The strategy of using pH as a trigger to achieve specific drug release in colon is based on pH variation along gastrointestinal tract. However, the pH dependent methods often do not have sufficient site specificity, owing to the high intra/inter- subject variability in physiological values of gastrointestinal pH[5]. On other hand time dependent drug delivery systems are based on the principle of delaying drug release until its estimated arrival in the colon. However, the colon arrival time cannot be accurately predicted, despite the relative consistency of transit time in small intestine, because of the potentially large variation in gastric emptying time[6].

Tegaserod maleate (TM) is the first selective 5-hydroxytryptamine type-4 (5-HT_4) receptor partial agonist used for the treatment of constipation predominant irritable bowel syndrome (IBS), a complex gastrointestinal disorder characterized by a combination of abdominal pain, discomfort, diarrhea, and/or constipation[7]. The aim of the study was to develop and evaluate enteric-coated matrix tablet of Tegaserod maleate (TM) for colonic delivery by exploiting prolonged release characteristics of Eudragit RSPO and Eudragit RLPO with pH dependent solubility property of a Eudragit S100. Extended release matrix tablet were prepared by combination of freely permeable and less permeable polymers like Eudragit RLPO and Eudragit RSPO respectively. The pH dependent release was achieved by coating matrix tablet with Eudragit S 100, a methacrylic acid co-polymer soluble at pH .

Keywords: Tegaserod maleate, Enteric coating, Matrix tablet.

INTRODUCTION

The various pharmaceutical approaches which have been used for targeting drugs to the colon are mainly based on pH-dependent, time dependent and/or bacterially degradable polymers[8]. Among the various experimented approaches, pH-sensitive and time-controlled delivery systems are most widely used[9,10,11]. The strategy of using pH as a trigger to achieve specific drug release in colon is based on pH variation along gastrointestinal tract. However, the pH dependent methods often do not have sufficient site specificity, owing to the high intra/inter- subject variability in physiological values of gastrointestinal pH[12]. On other hand time dependent drug delivery systems are based on the principle of delaying drug release until its estimated arrival in the colon. However, the colon arrival time cannot be accurately predicted, despite the relative consistency of transit time in small intestine, because of the potentially large variation in gastric emptying time[13]. Therefore, the appropriate integration of pH-sensitive and time-dependent functions in a single dosage form should improve colon targeting, by suppressing drug release in the stomach and thus reducing the effect of variation in gastric residence time.

Tegaserod maleate (TM) is the first selective 5-hydroxytryptamine type-4 (5-HT_4) receptor partial agonist used for the treatment of constipation predominant irritable bowel syndrome (IBS), a complex gastrointestinal disorder characterized by a combination of abdominal pain, discomfort, diarrhea, and/or constipation[14]. TM is insoluble in water and has pH dependent solubility. Below pH 3, TM is rapidly degraded through hydrolytic breakdown. TM is readily absorbed following oral administration under fasted condition, and the peak plasma concentration occurs after 1.0-1.3 hr. Absolute bioavailability is about 10 %, and terminal elimination half-life is close to 11 hr[15]. To improve the oral bioavailability and prevent rapid hydrolysis of TM in gastric milieu, a dosage form containing TM is coated with pH-dependent materials which dissolve at a higher pH.

The aim of the study was to develop and evaluate enteric-coated matrix tablet of Tegaserod maleate (TM) for colonic delivery by exploiting prolonged release characteristics of Eudragit RSPO and Eudragit RLPO with pH dependent solubility property of a Eudragit S100. Extended release matrix tablet were prepared by combination of freely permeable and less permeable polymers like Eudragit RLPO and Eudragit RSPO respectively. The pH dependent release was achieved by coating matrix tablet with Eudragit S 100, a methacrylic acid co-polymer soluble at pH 7.

EXPERIMENTAL

Preliminary screening of formulation variables

In preliminary study, matrix tablet containing tegaserod maleate (TM) along with Eudragit RLPO and Eudragit RSPO were prepared to evaluate the effect of Eudragit RSPO and Eudragit RLPO on drug release. The tablets containing 20 mg of tegaserod maleate were prepared by direct compression of physical mixture of the drug and excipients. The homogenously mixed blend was compressed using 8 mm standard concave punch in the Rimek rotary press. The tablets were compressed to obtain hardness of 5-6 Kg/cm^3. Table 6.1 shows the composition of all batches in preliminary study. Tablettose 80 was added as filler in all batches to make a constant weight of tablet (150 mg).

Table 1: Composition for matrix tablets

Batch code	Ingredients (mg)			
	Drug	Eudragit RLPO	Eudragit RSPO	Tablettose 80
P1	20	75	--	55
P2	20	100	--	30
P3	20	125	--	5
P4	20	--	75	55
P5	20	--	100	30
P6	20	--	125	5
P7	20	50	25	55
P8	20	50	50	30
P9	20	25	100	5

Evaluation of prepared tablets

Compressed tablets were evaluated for assay, weight variation[16] and friability[17] according USP 28. For assay, the 20 tablets were crushed and the powder equivalent of 20 mg of tegaserod maleate was transferred to 1000 ml of 0.1 N HCl in volumetric flask. The solution was analyzed at 312 nm using double beam UV/VIS spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve.

***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 10 h study at 6.8 pH by adding 200 ml of 0.2 mol/L trisodium phosphate in dissolution media. Temperature was maintained constant at 37 + 0.5^0. 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 312 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.

Preparation of matrix tablet

The matrix tablets containing tegaserod maleate (20 mg) along with Eudragit RSPO, Eudragit RLPO and lactose were prepared by direct compression method. The weight of polymer in each tablet was kept constant upto 80 mg using different concentration of Eudragit RSPO and Eudragit RLPO. The final weight of tablets was adjusted upto 150 mg with addition of lactose (Tablettose 80). Table 6.4 depicts the composition of the factorial design batches in terms of the actual and transformed values.

Table 2: Cumulative percentage drug release from tablets for preliminary screening

Batch code	Time (hr)								
	0	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**
P1	0.00	28.64	41.39	50.45	58.84	75.32	89.28	98.48	102.76
P2	0.00	25.37	37.58	46.12	52.94	63.86	78.64	90.46	99.86
P3	0.00	22.57	29.31	35.48	45.78	54.08	67.48	79.33	84.67
P4	0.00	26.87	39.41	44.69	51.64	62.13	70.85	76.32	84.43
P5	0.00	23.48	33.17	39.53	44.32	52.76	60.38	68.87	75.08
P6	0.00	22.67	28.41	31.68	39.86	45.21	56.81	60.12	66.19
P7	0.00	30.42	41.78	48.28	56.87	64.49	72.34	87.53	95.17
P8	0.00	25.73	35.97	43.48	50.22	61.80	67.11	74.64	84.79
P9	0.00	20.48	28.61	32.08	42.33	48.19	59.34	66.29	71.48

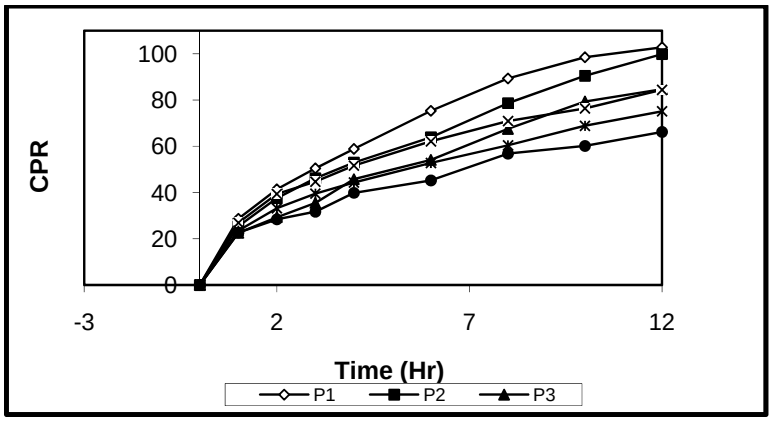


Fig. 2: Comparative dissolution profile of tablets prepared using Eudragit RLPO and Eudragit RSPO

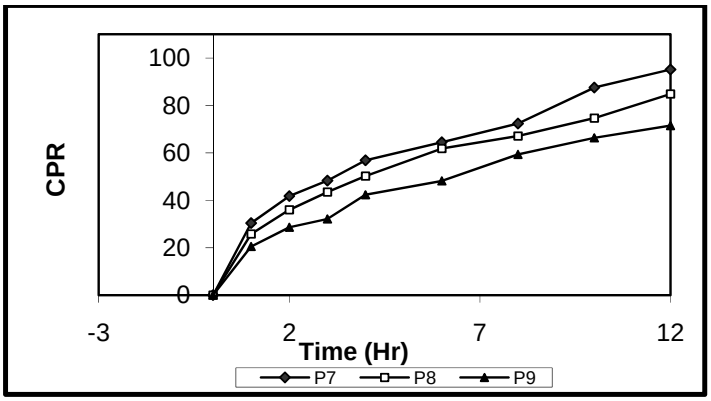


Fig. 3: Dissolution profiles of matrix tablets containing Eudragit RLPO and Eudragit RSPO in different ratio

Enteric coating of matrix tablet

The enteric coating solution was prepared by dissolving Eudragit S 100 in acetone at 12 % w/v using 1.5% PEG 400 as plasticizer. This solvent was selected because it allowed the dissolution of enteric polymer while maintaining the integrity of matrix tablet. Coating of tablet was carried out by immersion of tablet in coating solution followed by evaporation of solvent. The process was repeated until the desired amount of coating per tablet was achieved. The matrix tablets were coated at three different levels, 5, 15 and 25 % (w/w) as total solid applied.

Table 3: Full factorial design for all batches

Batch code	Coded level		Actual value (%)	
	X_1	X_2	X_1	X_2
F1	-1	-1	25:75	5
F2	-1	0	25:75	15
F3	-1	+1	25:75	25
F4	0	-1	50:50	5
F5	0	0	50:50	15
F6	0	+1	50:50	25
F7	+1	-1	75:25	5
F8	+1	0	75:25	15
F9	+1	+1	75:25	25

X_1 is the ratio of Eudragit RLPO: Eudragit RSPO and X_2 is the percentage weight of coating (12% w/v Eudragit S100). All batches contained 20 mg tegaserod maleate, and 50 mg tablettose 80 to make the total tablet weight of 150 mg.

Table 4: Composition of enteric coated matrix tablet for all factorial batches

Batch	Eudragit (mg)		Eudragit S 100 (mg)
	RLPO	RSPO	
F1	20	60	7.5
F2	20	60	22.5
F3	20	60	37.5
F4	40	40	7.5
F5	40	40	22.5
F6	40	40	37.5
F7	60	20	7.5
F8	60	20	22.5
F9	60	20	37.5

All batches contain 20 mg tegaserod maleate and 50 mg tablettose in matrix tablet. The total weight of uncoated tablet was kept 150 mg.

Table 5: Results of evaluation of matrix tablets for factorial design batches

Batch code	Assay (%) (n = 20)	Average weight (mg) (n =20)	Friability (%)
F1	100.87	150 (3.1)	0.54
F2	101.62	150 (2.8)	0.37
F3	99.36	150 (1.5)	0.43
F4	101.34	150 (2.5)	0.59
F5	99.41	150 (1.2)	0.35
F6	100.29	150 (1.7)	0.48
F7	99.74	150 (1.8)	0.56
F8	101.85	150 (1.5)	0.49
F9	99.69	150 (2.1)	0.55

Table 6: Dissolution profiles of tablets for factorial design batches (n = 3)

Time (Hr)	Cumulative percent drug release								
	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	14.46	2.85	0.75	16.42	3.26	1.23	19.35	2.38	1.54
2	26.76	5.34	2.18	24.18	6.08	3.31	29.46	7.48	2.96
3	29.73	9.37	4.47	30.23	10.27	4.97	35.87	10.64	4.73
4	32.87	13.48	7.84	34.87	18.48	8.38	42.79	14.69	7.45
5	35.52	25.71	10.09	39.69	29.86	12.21	48.61	25.75	14.47
6	39.94	31.48	17.64	46.67	37.25	24.43	55.97	33.76	31.48
7	43.36	36.87	27.94	52.31	42.89	30.97	61.71	45.24	40.64
8	48.74	44.69	35.76	58.29	47.42	37.64	70.39	53.82	46.78
9	53.12	49.24	40.61	66.08	55.21	43.56	81.12	66.79	52.17
10	58.85	55.86	44.26	71.44	62.34	50.49	88.04	78.83	58.34
11	62.26	59.70	50.88	76.67	69.71	56.34	94.33	89.78	64.57
12	67.62	63.38	54.78	81.75	75.29	61.54	100.89	96.48	70.34

Standard deviation values of all batches are within the limit of + 5

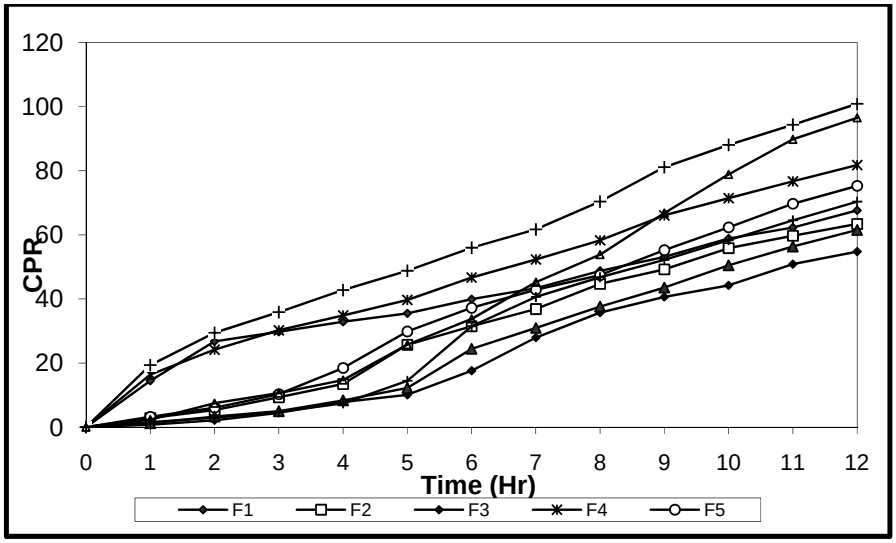


Fig. 4: Dissolution profiles of tablets for factorial design batches

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 6.8. To evaluate contribution of each factor with different levels on responses, two way analysis of variance (ANOVA) followed by Tukey test was performed using Sigma Stat software (Sigma Stat 2.03, SPSS, USA). The results of Tukey test are depicted in Table 6.9 and Table 6.10. 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 6.11. The value of P< 0.05 was considered to be significant.

Roentgenographic studies of optimized batch

The roentgenographic study was carried out on placebo tablet for which drug was replaced from tablet of optimized batch (F8) with 20 mg barium sulphate in matrix tablet and 5 mg barium sulphate was added in enteric coating material to visualize tablet in gastrointestinal tract. Study was carried out on 28 year old healthy female human volunteer.

The volunteer was required to fast for 10 hours before the study. The volunteer was given tablet and subjected to X-ray photograph at different time interval of 2, 4, 6, and 8 hours to observe shape, integrity and position of tablet. The images of X-ray photograph were displayed in Figure 6.12.

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_8	Q_{10}		
F1	32.87	39.94	48.74	58.85	0.154	0.568
F2	13.48	31.48	44.69	55.86	0.025	1.352
F3	7.84	17.64	35.76	44.26	0.007	1.827
F4	34.87	46.67	58.29	71.44	0.151	0.655
F5	18.48	37.25	47.42	62.34	0.029	1.348
F6	8.38	24.43	37.64	50.49	0.010	1.678
F7	42.79	55.97	70.39	88.04	0.179	0.669
F8	14.69	33.76	53.82	78.83	0.023	1.518
F9	7.45	31.48	46.78	58.34	0.010	1.739

Table 8: Multiple regression analysis for dependent variables

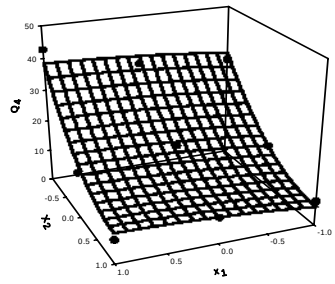
Parameters	Coefficient of regression parameters							
	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	r^2	P
Q_4	16.03	1.791	-14.478*	-0.721*	6.818*	-2.58*	0.9921	0.0065
Q_6	34.87	5.358*	-11.506	-1.068*	1.856	-0.547*	0.9676	0.0515
Q_8	47.14	6.966	-9.45	2.246*	0.956*	-2.657*	0.9891	0.0105
Q_{10}	63.938	11.04	-10.873	2.606	-3.773	-3.777	0.9977	0.0009
k	0.0233	0.004*	-0.076	0.002*	0.059	-0.005*	0.9970	0.001
n	1.371	0.029*	0.558	0.051*	-0.216	-0.047*	0.9958	0.0025

* Indicate the value is insignificant at P = 0.05.

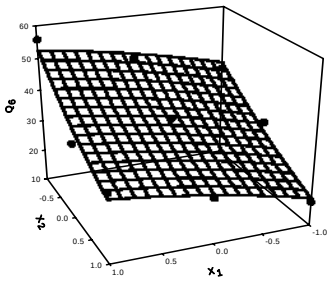
Table 9: Results of two way ANOVA for measured response

Diffusion Exponent (n)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	0.0107	0.00536	0.846	0.494
coating weight	2	1.967	0.983	155..328	<0.001
Residual	4	0.0253	0.00633		
Total	8	2.003	0.250		
Release rate constant (k)					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	0.000131	0.000065	0.713	0.544
coating weight	2	0.0419	0.0209	228.484	<0.001
Residual	4	0.000367	0.000091		
Total	8	0.424	0.00530		
Q_4					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	20.302	10.151	0.830	0.499
coating weight	2	1350.712	675.356	55.236	0.001
Residual	4	48.907	12.227		
Total	8	1419.921	177.490		
Q_6					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	174.553	87.277	5.156	0.078
coating weight	2	801.315	400.657	23.671	0.006
Residual	4	67.705	16.926		
Total	8	1043.572	130.447		
Q_8					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	301.302	150.651	12.667	0.019
coating weight	2	547.900	273.950	23.035	0.006
Residual	4	47.571	11.893		
Total	8	896.773	112.097		
Q_{10}					
Source of variation	**DF**	**SS**	**MS**	**F**	**P**
Ratio of polymer	2	744.879	372.440	23.314	0.006
coating weight	2	737.852	368.926	23.094	0.006
Residual	4	63.900	15.975		
Total	8	1546.631	193.329		

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



[a]



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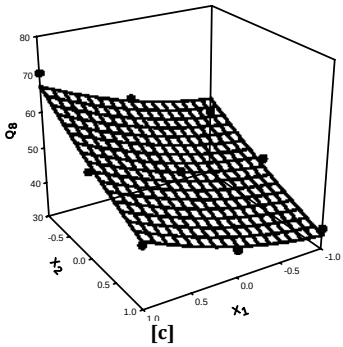

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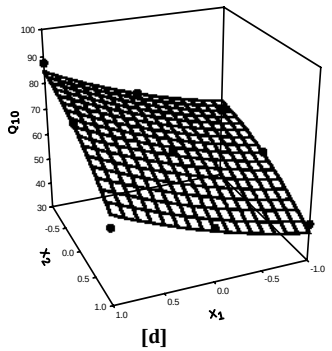

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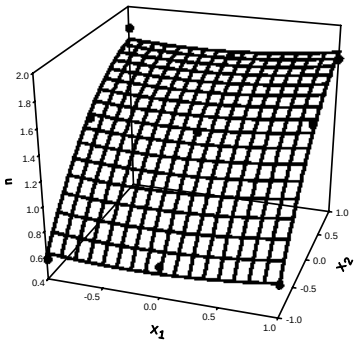

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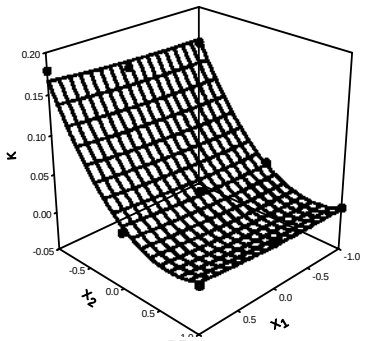
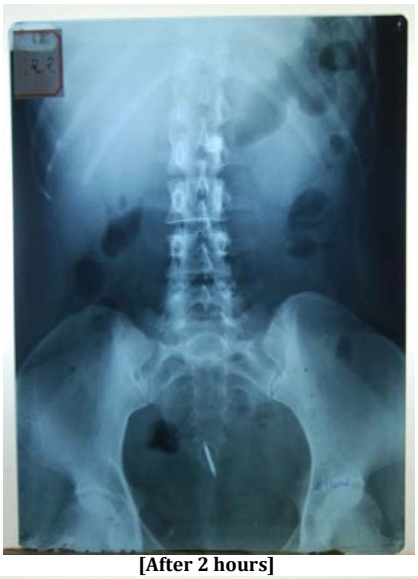
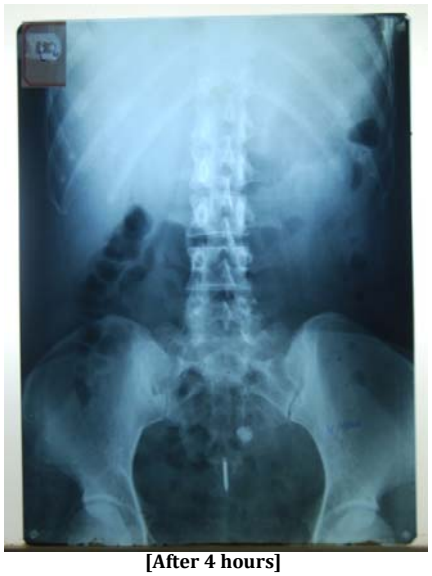


[f]

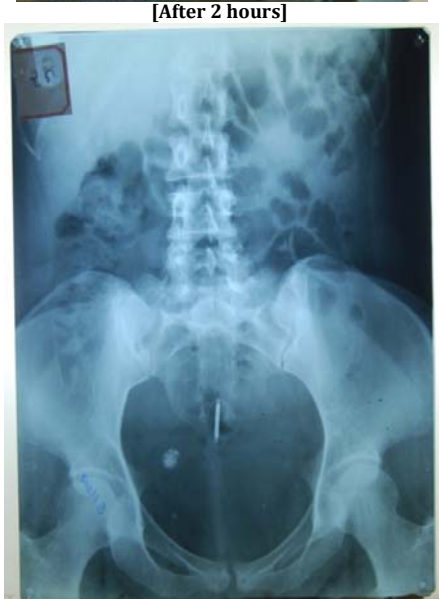
Fig. 11: Surface response plot to depict the influence of ratio of polymer (X_1) and coating weight (X_2) on [a] Q_4 [b] Q_6 [c] Q_8 [d] Q_{10} and [e] n [f] K



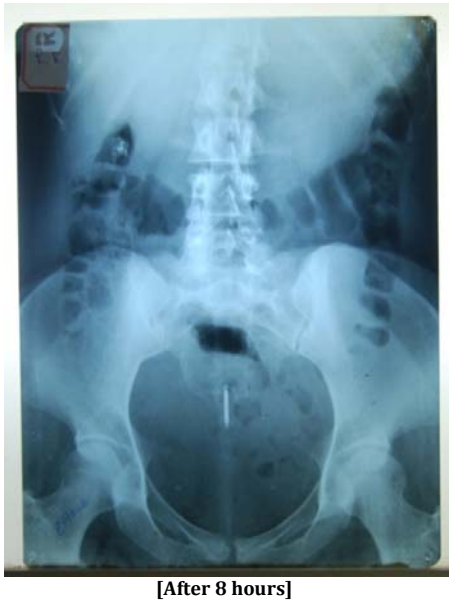
[After 2 hours]



[After 4 hours]



[After 6 hours]



[After 8 hours]

Fig. 12: X-ray photographs of Roentgenographic studies

Stability study of optimized batch

An ethical drug manufacturer is committed to provide to his consumers drug products, which are efficacious and safe. Only instituting a sound programme to study the stability of a product during its various phases of development and to arrive at the proper storage conditions and the expiry period under those conditions can ensure this objective. This is a requirement in most of the countries and is stipulated by the regulatory agencies of those countries. These studies would very quickly identify the need, if any, to stabilize the active substance or the formulation, and save invaluable time and effort from being spend on an unmarketable formulation. With the recent trend towards globalization of manufacturing operation, it is imperative that the final product be sufficiently rugged for marketing world wide under various climatic conditions including tropical, subtropical and temperate.

In order to determine the change in performance of dosage form on storage, stability study of batch F8 was carried out at 40°C in a humidity jar having 75 % RH according to ICH[18].

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 F8. The release profile of sample put on stability study was depicted in Table 6.11 and Figure 6.13.

Table 11 Dissolution profiles of batch F8 evaluated for stability study

Time (hr)	Cumulative percentage drug release	
	Fresh Sample	**After 3 month**
0	0.00	0.00
1	2.38	1.47
2	7.48	6.12
3	10.64	8.35
4	14.69	12.84
5	25.75	22.73
6	33.76	31.07
7	45.24	43.87
8	53.82	50.76
9	66.79	64.37
10	78.83	76.51
11	89.78	86.29
12	96.48	94.17
f_1 value	**Reference**	**5.153**
f_2 value	**Reference**	**80.586**

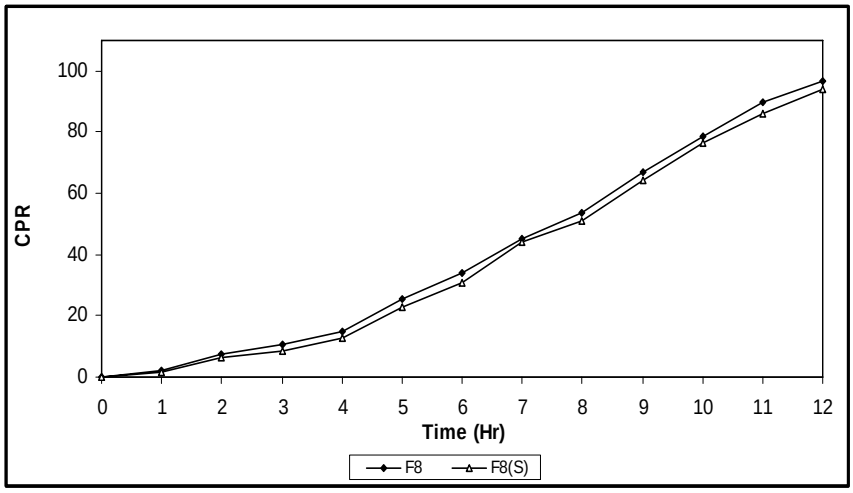


Fig. 13: Dissolution profiles of batch F8 evaluated for stability study

CONCLUSION

The present study was aimed to formulate and evaluate enteric coated matrix tablet for drug targeting to colon. The result of *in vitro* dissolution studies demonstrated that the enteric coating of Eudragit S 100 to the matrix tablet containing Eudragit RLPO and Eudragit RSPO can be used successfully to achieve gastric resistance and timed release of tegaserod maleate. The enteric coating level emerged as the critical factor in determining the duration of the lag phase, whereas the release rate mainly depended on the ratio of Eudragit RLPO and Eudragit RSPO in matrix tablet. Therefore, the duration of the lag time and the rate of drug release after lag time can be modified by adequately adjusting the enteric coating level and the polymeric matrix composition respectively.

Among all the batches, the batch F8 contain Eudragit RLPO and Eudragit RSPO in ratio of 3:1 in matrix tablet coated with Eudragit S 100 solution(12% w/v), total polymer weight 15 %w/w shows most promising drug release pattern over 12 hr *in vitro* dissolution study.

REFERENCES

1. Watts P and Illium L., Colonic drug delivery, **Drug Dev Ind Pharm.,** 23, 1997, 893-913.
2. Ueda S and Hata T., Development of novel drug delivery system. Time controlled explosion system. I. Concept and design**, J Drug Target.,** 2, 1993, 35-44.
3. Hu Z and Shimokawa T., Characterization of norfloxacine release from tablet coatedwith a new pH sensitive polymers, **J Drug Target.,** 7, 1999, 223-232.

4. Khan M and Prebeg Z., A pH dependent colon targeted oral drug delivery system using methacrylic acid copolymers, **J Cont Rel.,** 58, 1999, 215-222.
5. Ashaford M and Fell J., An *in vitro* investigation into suitability of pH dependent polymers for colonic targeting, **Int J Pharm.,** 91, 1993, 241-245.
6. Yang L and Chu J., Colon-specific drug delivery: new approaches and *in vitro*-in vivo evaluation, **Int J Pharm.,** 235, 2002, 1-15.
7. Rivkin A., tegaserod maleate in treatment of irritable bowel syndrome: A clinical review, **Clin Ther.,** 25, 2003, 1952-1974.
8. Novaritis pharmaceutical corporation, East Hanover, NJ, USA, ZelmacTM (tegaserod) Advisory Commettee Breafing Document, 2000.
9. US Pharmacopoeia 28, United State Pharmacopoeial Convention, Rockville, M.D., USA, Asian edition, 2005, 2509.
10. US Pharmacopoeia 28, United State Pharmacopoeial Convention, Rockville, M.D., USA, Asian edition, 2005, 2745.
11. Carstensen J., Drug stability: Principle and practices, Marcel Dekker, New York, USA, 2nd Edn., 1995, 538-550.