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COLONIC DELIVERY OF COMPRESSION COATED BUDESONIDE TABLETS USING ETHYL CELLULOSE AND EUDRAGIT RLPO POLYMER MIXTURE

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ABSTRACT

Budesonide containing ethyl cellulose /eudragit RLPO compression coated tablets were prepared and there in vitro behavior tested for colonic delivery. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineral corticoid activity. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in ulcerative colitis, crohn's disease and inflammatory bowel disease. In this study, each 150 mg core tablet of budesonide was compression coated with 60% ethyl cellulose and 40% eudragit RLPO, 70% ethyl cellulose and 30% eudragit RLPO and 80% ethyl cellulose and 20% eudragit RLPO at a coat weight of 200 mg, 250 mg and 300 mg respectively. Drug release studies were carried out in pH 6.8 phosphate buffer IP solution. The Eudragit RLPO/Ethyl cellulose envelope was found to be a good delivery system for budesonide to be delivered to the colon.

KEY-WORDS: **Budesonide, CDDS, compression coated tablet.**

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INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs [1-3]. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is thought to be the most significant absorption site for peptides and protein drugs because of limited diversity and intensity of digestive enzymes, beside this proteolytictivity shown by the colon is much lesser than that of the small intestine. CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability[4] and finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers [5]. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis[6-8].Budesonide is a glucocorticoid steroid for the treatment of asthma and non-infectious rhinitis (including hay fever and other allergies), and for treatment and prevention of nasal polyposis. In addition, it is used for Crohn's disease (inflammatory bowel disease). Budesonide has a high first-pass metabolism. It has efficacy in the terminal ileum and the right colon. Budesonide in comparison with prednisolone has been associated with fewer bone density losses, and, unlike other corticosteroids, has little influence on the hypothalamic-pituitary-adrenal axis, which also limits the need of tapering before discontinuation. Overall, it has a lower incidence of systemic manifestations than similar medications [9-10].

MATERIALS AND METHODS

Materials

Budesonide was obtained from Glenmark Pharmaceuticals Ltd., Nasik. Eudragit L100 and Eudragit S100 were obtained from Colorcon Ltd., Goa. Eudragit RLPO and Eudragit RSPO were obtained from Lupin Pharmaceuticals, Pune. Ethyl Cellulose was obtained as gift sample Alkem Pharmaceuticals Ltd., Mumbai. Other materials used were of AR Grade and were purchased from Modern Scientifics, Nashik.

Methods

Preparation of fast disintegrating Budesonide core tablets

Rapidly disintegrating Budesonide core tablets (average weight 150 mg) were prepared by direct compression technique. The composition of core tablets was given in table 1. Quantity weighing 150 mg was taken and compressed into tablets using 7 mm round; concave punches on a single station tablet punching machine (Remek, India).The quality control tests such as thickness, weight variation, hardness, friability and disintegration were performed on the core tablets. Based on disintegration time the best formulation was selected among all six formulations for further study[11-12].

Table 1
Composition of trial batches of Core tablets (M1-M6)

Ingredients(mg)	Formulation code					
	M1	M2	M3	M4	M5	M6
Budesonide	9	9		9	9	9
Lactose	129	90	100	110	115	115
Microcrystalline cellulose	-----	40	30	20	-----	-----
PVP K30	-----	-----	-----	-----	15	-----
HPMC E3LV	-----	-----	-----	-----	-----	15
Acdisol	7.5	7.5	7.5	7.5	7.5	7.5
Talc	3	3	3	3	3	3
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Total	150	150	150	150	150	150

Physical characterization of core tablets
The developed core tablet formulations were studied for their physical properties like thickness, hardness, friability and assay as follows:

Thickness
The thickness of tablets was determined using micrometer screw gauge (Japan)

Hardness
The hardness of tablets was measured using the Monsanto hardness tester (Cadmach, Ahmadabad, India).

Friability
For each formulation the friability of 6 tablets was determined using Roche Friabilator. (Remi equipments).

Assay
Five tablets were weighed and powdered. Weigh accurately a quantity of the powder equivalent to 0.09 g of Budesonide shake with 50 ml of 6.8 pH phosphate buffer + 1% Tween 20 for10 minutes, and add sufficient buffer to produce 100.0 ml and filter. After suitable dilution with solvent measure the absorbance of the resulting solution at the maximum at about 247 nm. Calculate the content of $C_{25}H_{34}O_{6,\ at}$ the maximum at about 247 nm.

Preparation of press coated tablets of Budesonide
Before selection of final polymers different formulation containing Ethyl cellulose in combination with different methacrylic acid polymer selected from Eudragit L100, Eudragit S100, Eudragit RLPO, and Eudragit RSPO were prepared. The formulated / optimized core tablets were compresed-coated with the different coat formulation containing EC and different methacrylic acid polymers (Eudragit L100/S100/RLPO/RSPO) in 70:30 ratios with a coat weight of 250mg. The composition of compression-coat material was shown in table no.02. For compression coating about 50% (125mg) of coat weight material was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manually, which was then filled with the remainder 50% (125mg) of the coat material. The coating material was then compressed around the core tablet by using 9.9 mm round, concave punches with compression force 7 kg/cm^2 using rotary press (Rimek, India) [13-14].

Physical characterization of press coated tablets of Budesonide
The developed formulation of press coated tablets were studied for their physical properties like thickness, hardness, friability and Assay and Dissolution test as described in section

Stability study
The optimized formulation was wrapped in aluminum foil and subjected to 40 ±0.5°C temperature in oven for the period of one month. The formulation was analyzed for organoleptic characteristics, thickness, hardness, assay and dissolution.

RESULTS AND DISCUSSION

Table 2
Evaluation of core tablets

Sr. No.	Formulation Code	Hardness (kg/cm^2)	Friability (%)	Assay (%)	Thickness (mm)	Disintegration Time(min)
1.	M1	3.2	0.53	98.4	3.6	3.22
2.	M2	3.3	0.37	97.8	3.8	5.11
3.	M3	3.2	0.43	99.6	3.6	5.40
4.	M4	3.2	0.45	96.9	3.5	6.32
5.	M5	3.3	0.42	99.2	3.7	5.38
6.	M6	3.2	0.48	98.5	3.5	4.43

Table 3
Formulations of preliminary trials of press coated tablets

Formulation code	Coat weight(mg)	Polymer (%) in Coat weight				
		Ethyl cellulose	Eudragit L100	Eudragit S100	Eudragit RLPO	Eudragit RSPO
P1	250	70	30	-----	-----	-----
P2	250	70	-----	30	-----	-----
P3	250	70	-----	-----	30	-----
P4	250	70	-----	-----	-----	30

Table 4
Evaluation of powder blend used for preliminary press coated tablets

Polymers	Bulk density (gm/ml)	Tap density (gm/ml)	Compressibility (Carr's index)	Hausner ratio	Angle of repose(°)
EC: Eudragit L100	0.467	0.532	12.3	1.139	19.98
EC: Eudragit S100	0.485	0.548	11.5	1.129	21.06
EC: Eudragit RLPO	0.473	0.538	12.1	1.137	23.66
EC: Eudragit RSP	0.495	0.558	11.3	1.27	19.31

Table 5
Evaluation of preliminary press coated tablets

Sr. No.	Formulation Code	Weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
1.	P1	250±5	6.9	6.5	0.15	99.1
2.	P2	250±5	7.2	6.6	0.23	98.3
3.	P3	250±5	6.8	6.5	0.17	100.8
4.	P4	250±5	6.8	6.6	0.14	97.4

Dissolution Study

The Budesonide tablets were evaluated for in vitro drug release using USP Type I Dissolution Apparatus at of 37±0.5°C temperature with constant stirring rate of 100 rpm. The dissolution studies were carried out in a pH progression media containing 1% v/v Tween 20 to maintain sink conditions. pH 1.2 acid buffer IP (900 ml) was used for 2 hr followed by pH 6.8 phosphate buffer IP (900 ml) for remaining time . Aliquots (5 ml) were withdrawn at predetermined intervals and immediately analyzed for Budesonide using UV 2501PC spectrophotometer. An equal volume of respective media containing 1% v/v Tween 20) was replaced after each sampling [15-17].

Table 6
% drug release from Preliminary batches of press coated tablets

Time(hrs)	% drug release			
	P1	P2	P3	P4
1	0	0	0	0
2	0	0	0	0
2.5	0	0	0	0
3	0	0	0	0
3.5	78.53	0	0	0
4	99.7	83.42	0	0
4.5	98.83	97.65	0	0
5		99.97	0	0
5.5		99.08	0	0
6			74.94	0
6.5			99.73	0
7			99.47	0
7.5				0
8				0
8.5				0
9				0
9.5				0
10				0
10.5				0
11				0
11.5				0
12				0
13				85.43
14				99.62
15				99.07

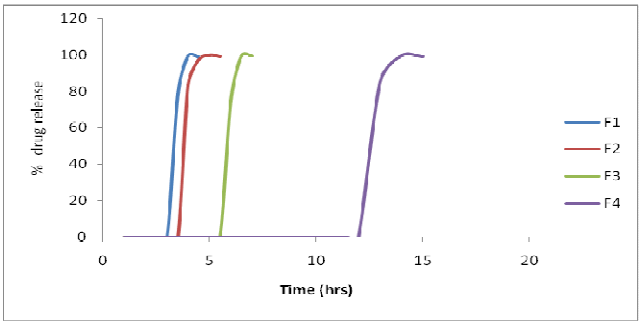

Figure 1
% drug release from preliminary press coated tablets.

Factorial design

Based on the results obtained with preliminary formulations, 3^2 randomized full factorial designs were applied in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed in all 9 possible combinations. The Ratio of release rate modifying polymer ethyl cellulose: Eudragit RLPO (X_1), and the amount of coat weight (X_2), were selected as independent variables. Time required for 90% drug release (t_{90}), was selected as dependent variables. The probable formulations using 3^2 randomized full factorial designs are as shown in Table 09.

Table 7
Coded formulation

Variables	F1	F2	F3	F4	F5	F6	F7	F8	F9
X_1	-1	-1	-1	0	0	0	1	1	1
X_2	-1	0	1	-1	0	1	-1	0	1

Table 8
Coded Level

Coded levels	-1	0	1
X_1(Ethyl Cellulose: Eudragit RLPO) % in coat weight	60:40	70:30	80:20
X_2 (Coat Weight) in mg	200	250	300

Table 9
Formulations by Factorial design

Polymer in coat	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose	120	150	180	140	175	210	160	200	240
Eudragit RLPO	80	100	120	60	75	90	40	50	60

From the result of preliminary trial of press coated tablets as shown in fig 8.13 it was observed that P1 and P2 formulation shows premature drug release before intestinal transit time i.e. before 5 hrs. P3 formulation shows desirable the lag time of 5 hrs with burst release within 6 hrs. P4 formulation shows unexpected lag time of 10 hrs.

Factorial design

Among preliminary formulations P3 formulation shows desirable lag time. So it is selected for factorial design to optimize the effect of variables on formulation. Thereafter further studies with 3^2 factorial designs were carried out using Coating ratio of Ethyl cellulose: Eudragit RLPO (X_1) and Coat weight(X_2) as independent variables.

Evaluation of formulation

The formulations developed as per 3^2 factorial design were evaluated for Hardness, Friability, Thickness, Assay according to standard pharmacopoeial procedures.

Table 10
Evaluation Parameters of Different formulation

Formulation	Tablet weight(mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Assay (%)
F1	350	6.9	0.11	6.04	99.35
F2	350	7.2	0.23	6.01	100.67
F3	350	7.3	0.15	6.03	101.22
F4	400	6.8	0.12	6.67	99.76
F5	400	7.2	0.18	6.62	97.92
F6	400	7.1	0.15	6.61	99.11
F7	450	7.3	0.21	7.24	102.45
F8	450	7.3	0.17	7.29	98.65
F9	450	6.9	0.11	7.22	99.47

Hardness of tablets was in the range of 6 .8 -7.3 kg/cm^2. Thickness of tablets was in the range 6.01 -7.29 mm. Percent weight loss in the friabilty test was found to be less than 0.25% of all the cases. The assay was found within 100 ± 3%. All results obtained were complies with the official standards.

Table 11
% Drug release of optimized formulations

Time(hrs)	% drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
2.5	0	0	0	0	0	0	75.91	0	0
3	0	0	0	0	0	0	99.28	0	0
3.5	0	0	0	0	0	0	98.22	79.92	0
4	0	0	0	81.52	0	0		91.45	0
4.5	0	0	0	98.23	0	0		99.83	71.16
5	75.16	0	0	97.78	0	0		99.03	91.55
5.5	96.83	0	0		73.84	0			99.61
6	99.37	0	0		95.88	0			99.45
6.5	99.18	0	0		99.07	0			
7		0	0		99.23	79.76			
7.5		0	0			96.91			
8		0	0			99.56			
8.5		0	0			97.34			
9		77.45	0						
9.5		99.19	0						
10		99.32	0						
10.5			84.99						
11			97.26						
11.5			98.44						

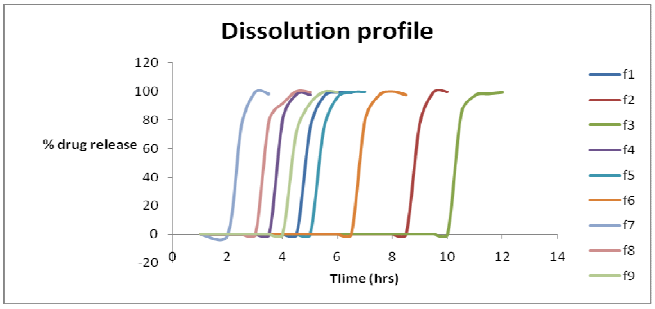

Figure 2
% drug release of press coated tablets

In vitro drug release study reveals that as the proportion of Ethyl cellulose: Eudragit RLPO in tablets was increased by 10% there was a remarkable change on the retardation of the release of Budesonide from the formulation F1 to F9.Also the increment of coat weight of this polymer mixture

by 50mg showed significant effect on the controlling of Budesonide release from the formulation F1 to F9.

Optimization

A 3^2 full factorial design was constructed to study the effect of the ratio of coating material (X_1) and the amount of polymer in the coating ($X_{2)}$ on the drug release from the tablets. The one dependent variable chosen was selected i.e. at least 90 % drug release. The resulting compiled in the table

Table 11
Layout of Actual Design in Design Expert software

Std	Run	A : Proportion of Ethyl cellulose :Eudragit RLPO (%)	B:Coat weight (mg)	Response 1 T_{90} (hrs)
1	1	60:40	200	3
2	2	70:30	200	4.5
3	6	80:20	200	5.5
4	5	60:40	250	4
5	3	70:30	250	6
6	9	80:20	250	9.5
7	8	60:40	300	5
8	4	70:30	300	7.5
9	7	80:20	300	11

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices. Based on the principle of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms.

The various computations for the current optimization study were performed using Design Expert software (Design expert trial version 8.0.1; state ease inc., Minneapolis, MN, USA). A two- factor three level full factorial design was used for systematic study of the ratio of coating material and the amount of polymer in the coating. Various RSM computations for the current optimization study were performed employing Design Expert software. A 3^2 full factorial design was constructed where the ratio of coating material (Ethyl cellulose: Eudragit RLPO) (X_1) and the amount of polymer in the coating ($X_{2)}$ were selected as the independent variables i.e. factors The level of this factors is selected on the basis of initial studies and observations . All the other formulation aspects and processing variables were kept invariant throughout the study period.Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as Equation below

$$Y= \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_1X_2 + \beta_4X_1^2+ \beta_5X_2^2$$

where, β0 is the intercept representing the arithmetic average of all quantitative outcomes of 9 runs; β_1 to β_5 are the coefficients computed from the observed experimental values of Y; and X_1 and X_2 are the coded levels of the independent variable(s). The terms X_1X_2 shows how the response values change when two factors are simultaneously changed.The polynomial terms are included to investigate the nonlinearity. The polynomial equations

can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). In the equation represents that by making a minor change in the setting of that factor one may obtain a significant change in the dependent variables. Statistical validity of polynomials was established on the basis of analysis of variance (ANOVA) provision in the Design Expert software level of significance was considered significant at P>0.005.The best-fitting mathematical model was selected based on the comparison of several statistical parameters including the coefficient of variation (CV),The multiple correlation coefficient (R^2),the adjusted multiple correlation coefficient (adjusted R^2)and the predicted residual sum of squares (PRESS) provided by the software. PRESS indicates how well the model fits the data and for the chosen model it should be small relative to the other model under consideration. The 3D response surface plot is very useful to see interaction effects of responses.

Full and reduced model assessment for the dependent variable:
A) Model for t_{90} Full model equation
T90% = +6.48+2.28A+1.85B+0.88AB

Table 12
Analysis of Variance for Response t90

Source	Sum of squares	df	Mean Square	F value	P- Value prob>F	Significance
Model	54.11	3	18.04	62.56	0.0002	S
A-ethyl cellulose: Eudragit ratio	32.50	1	32.50	62.56	0.0002	S
B-coat weight	*20.15*	1	*20.15*	*69.88*	*0.0004*	S
AB	*3.24*	1	*3.24*	*11.24*	*0.0203*	S
Recidual	1.44	5	0.29			
Cor Total	55.56	8				

The model F-value of 62.56 implies the model is significant. There is only a 0.02% chance that a "model F value" this large could occur due to noise .Value of "prob >F" less than 0.0500 indicate model term are significant. In this case A, B, AB is the significant model terms.Value greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve the model.

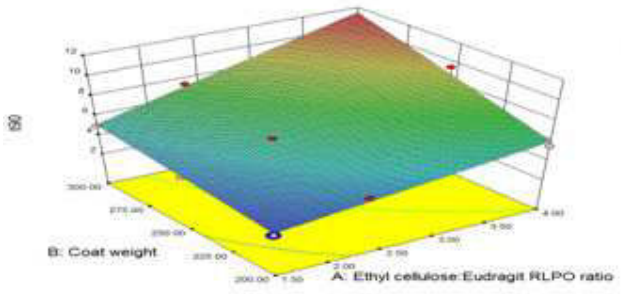

Figure 3: ***Response plot of t_{90}***

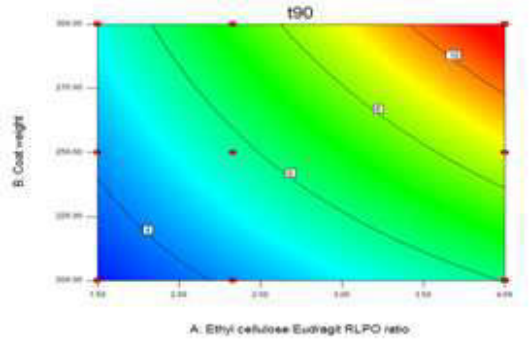

Figure 4: ***Contour plot of t_{90}***

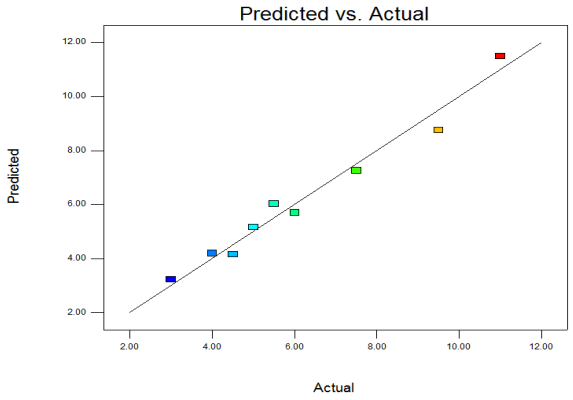

Figure 5
Predicted vs. actual values of t_{90}

From the figure of the response curve of t90 it was observed that higher the ratio of Ethyl cellulose: Eudragit RLPO higher the value of t90 indicated by positive signs in equation. Similarly more the coat weight, higher the value of t90 and it is indicated by positive signs in equation.

Optimization Result

The optimization was performed on the basis of response surface modeling by using the numerical and graphical optimization method. Desirability is an objective function that ranges from zero outside of the limits to one at the goal. The numerical optimization finds a point that maximizes the desirability function. The characteristics of a goal may be altered by adjusting the weight or importance. For several responses and factors, all goals get combined into one desirability function. The goal of optimization is to find a good set of conditions that will meet all the goals.

Table 13
Proposed optimized formulation by Design Expert software

Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A:Ethyl cellulose:Eudragit RLPO ratio	is in range	1.5	4	1	1	3
B:Coat weight	is in range	200	300	1	1	3
t90	is target = 6	3	11	1	1	3

Solutions

Number	Ethyl cellulos	Coat weight	t90	Desirability	
1	2.36	257.63	5.99999	1.000	Selected

Table 14
Composition of optimized formulation

Optimized formulation	Quantity (mg)
Budesonide	9
Lactose	129
Acdisol	7.5
Talc	3
Magnesium Stearate	1.5
Core Tablet total	150
Polymer (Ethyl cellulose: Eudragit RLPO) ratio in coat weight	68.84:29.16
Coat weight	257.63
Total Weight	407.63

Tablets were compressed with hardness 7 kg/cm^2. Thickness of tablets was found to be 6.9 ± 0.6 mm. Tablet weight was found to be 407.63 mg. Assay was found to be 99.92±2%. All results obtained were complies with the official standards. The comparison between predicted values and experimental values was carried out.

Table 15
Predicted and experimental values obtained for different responses of optimised formulation.

Responses	Predicted values	Experimental values
T_{90} (hrs)	6	6

Stability Study

Hardness was found to be 7 kg/cm^2. Thickness of tablets was found to be 6.9 ± 0.5 mm. Tablet weight was found to be 400 mg. The assay was found to be 98.92±3%. Short term stability testing was carried out for the optimized formulation (OF). The results for the dissolution profile are as depicted in the graph. Short-term accelerated stability data obtained for optimized formulation revealed that drug content, thickness, hardness, in-vitro dissolution were within the acceptable limit. Thus the formulation can be said to be stable. All results obtained were complying with the official standards.

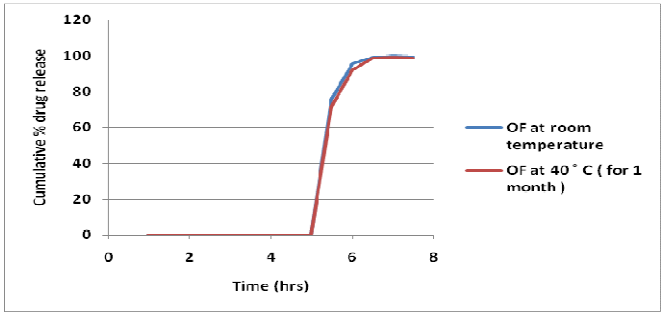

Figure 6
Dissolution profiles of OF at room temperature and OF at 40^{0}c

CONCLUSION

Colon targeted tablets of Budesonide were prepared using tablet core which comprises drug with directly compressible lactose, Cross carmellose sodium, Talc and Magnesium stearate which was further coated with a combination of Ethyl cellulose and Eudragit RLPO polymer. As the concentration of Ethyl cellulose: Eudragit RLPO polymer increases in coat weight, drug release decreases. As the amount of Ethyl cellulose: Eudragit RLPO polymer increases in coat, drug release decreases. Various tablet evaluation parameters like thickness, hardness, friability and assay of all formulations were found to be satisfactory. The dissolution study revealed that formulations F5 shows desirable drug release after 6 hrs which is optimum time required for entry of drug into colon without premature drug release into stomach and upper intestinal tract. Optimized formulation is stable at 40° C for one month. It can be concluded that colon targeted drug delivery can be formulated by using compression coated tablets of Budesonide. Such formulation delivers the drug directly in contact with distal small intestinal parts and colonic part for in local treatment of inflammatory bowel disease and crown's disease.

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