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Design and Evaluation of Colon Specific Delivery of Budesonide Core in Coat Matrix Tablet Used In Local Ulcerative Colitis

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ABSTRACT

In the present investigation planned to study the less explored sterculia gum as matrix carrier of Budesonide to colon. Developed the formulations from B1 to B4 contains alone sterculia gum and its proportion increased gradually in the formulation. The formulations B5 to B10 contain the sterculia gum in combination with Eudragit S 100 and the hydrophilic, hydrophobic polymer. The budesonide core in coat matrix tablets was prepared by direct compression method. The powder bed of the formulations is evaluated for pre compressional characteristics like bulk density, tapped density, compressibility index and angle of repose. The compressed budesonide core in coat matrix tablets were evaluated for post compressional characteristics like thickness, diameter, hardness, disintegration, friability and to understand the drug release pattern and to correlate the *in vivo* condition, the *in vitro* dissolution performed in three different gastro intestinal pH at 1.2, pH 7.4 and pH 6.8 with and without 4% rat cecal content. The *in vitro* dissolution results of formulations ascertain that sterculia gum alone in formulation uncontrolled the drug release in first 5 hrs and carried lesser amount of drug to colon. The formulations B8 in the first 5 hours released 4.3% and carried the larger amount of drug to colon and in absence of rat cecal content released 90% and in presences of 4% rat cecal content released 99% of drug, indicating the sterculia gum undergoes enzymatic degradation and this formulation is considered as potential in targeting the budesonide to colon in the local ulcerative colitis.

Keywords: Colon, Gastro intestinal tract, Budesonide, Sterculia gum, Rat cecal content.

INTRODUCTION

Ulcerative colitis is the inflammation of colon, the mucous membrane lining the colon became inflamed and causing bloody diarrhoea, pain, gas, bloating, and sometimes hard stools. The ulcerative colitis may be treated by antibiotics, corticosteroids and aminosalicylates. The various research articles report that, budesonide could be certainly beneficial for the treatment of ulcerative colitis and are available in conventional dosage form. [1-3] The conventional dosage forms used to treat the ulcerative colitis are failing to reach the drug at the appropriate site of action and require higher doses and also produce the systemic side effect and give the unreliable therapeutic effect. This can be worked out with colon specific delivery an alternative for site specific delivery and it was beneficial to patients as therapeutic drug concentration reached at the site of action with a reduced dose and lesser adverse effect, giving the safe and effective therapy. Colon is the distal part of the gastrointestinal tract, extends from the ileo cecal to the anus. It is

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suitable to site specific delivery due longer residence time, less hostility of digestive enzyme activity and enhanced absorption responses. Various approaches for colon specific delivery are pH dependent system, Time dependent system, pro drug system and microbial triggered system. [4] The best alternative approach was the microbial degradable system by the action of colonic bacteria. [5] Various natural polysaccharides were investigated as drug carrier in colon targeted system. The natural polysaccharides that are actively investigated as a carrier to the colon are pectin, guar gum, chitosan and chondroitin sulphate. [6] The natural polysaccharides sterculia gum is a complex polysaccharide of high molecular weight of 9,500.000 and appears as white free flowing powder. The pH of 1% solution is 4.6 and the viscosity > 1100 CPS. The gum does not dissolve in water to give a clear solution but rather forms a colloidal sol. Powdered sterculia gum swells in cold water to an extent that a 3% to 4% sol will produce a heavy gel of uniform smoothness and texture moisture .On hydrolysis it yields galactose, rhamnose and galacturonic acid. [7-8] The sterculia gum was less explored as a carrier of drug to the colon. In light of the above information, the present study contemplated to prepare colon targeted matrix tablets of Budesonide core in coat matrix tablets by using the sterculia gum as matrix carrier and evaluated for pre and post compressional characteristics to investigate the carrier is useful in targeting the budesonide to the colon.

Table 1: Formulations of Budesonide core tablets.

Ingredients	Formulation			
	C1(1:0.50)	C2 (1:1)	C3 (1:0.50)	C4 (1:1)
Budesonide	-	-	-	-
Budesonide –β Cyclodextrin	24	24	24	24
Magnesium stearate	1	1	1	1
Talc	2	2	2	2
Mannitol	-	-	-	-
Galen IQ 720	123	123	123	123
Total weight (mg)	150	150	150	150

MATERIALS AND METHODS

The drug Budesonide is received as gift sample from Ajanta Pharma, Mumbai. All the excipients used in the experiment are of analytical grade and are obtained from the commercial suppliers of S. D. Fine Chemicals, Bangalore.

Methodology

Preparation of Budesonide - β Cyclodextrin core tablets

All the ingredients as per formula Table 1 are weighed accurately and uniformly mixed in mortar by using pestle, after thorough mixing, the powder mixture was passed on sieve with mesh number 100. The required quantity of glidant and lubricant was added and then compressed into core tablet by direct compression method in ten station tablet punching machine using 8 mm punch to obtain a tablet of 150 mg weight.

Preparation of core in coat tablet [9]

Preparation of coat powder

All the ingredients as per formula Table 2 are weighed accurately and uniformly mixed in mortar by using pestle, after thorough mixing, the powder mixture was passed on sieve with mesh number 100. The required quantity of glidant and lubricant was added. The 55% of the total weight of coat powder was weighed and placed in the cavity of die, then the core tablet placed exactly center on the powder bed. The remaining 45% of the total coat powder placed above the core tablet and punched the core in coat tablet by direct compression method in ten station tablet punching machine using 10 mm punches to obtain the tablet of 450 mg weight.

Evaluation of pre-compressional characteristics

Phase Solubility Studies [10]

Solubility measurements and the determination of saturation concentrations were carried out by adding excess amount of budesonide to water/cyclodextrin mixtures. Concentrations of these cyclodextrins were selected based on their solubility in water. Solutions with β-CD were prepared at concentrations from 0.5%, 1% and 1.8% (w/w). The budesonide powder was added into glass flasks containing already mentioned percentages of cyclodextrins. The samples were shaken for 24 hours on thermostated shaking bath to reach equilibrium. After reaching equilibrium, the samples were filtered through a 0.2µm pore size membrane filter. The concentrations of dissolved substances in water/ cyclodextrins mixtures were determined by UV-VIS Spectrophotometer (Shimadzu, Japan) at 246 nm.

Angle of repose (°θ) [11]

Angle of repose was determined by measuring the height and radius of the heap of the granule bed. A cylindrical two side open tube of 6 cm length is placed on graph paper. Granules were placed in the tube and slowly removed the tube vertically. With the help of scale the height and radius of the heap were measured and noted. Average of triplicate reading were noted (n = 3).

$$ø = \tan^{-1}(h/r)$$

h = height of heap of granular bed.

r = radius of heap of granular bed.

Bulk density

Bulk density was determined (Konark instruments, India) by placing the granules blend in a measuring cylinder and the total volume was noted. The weight of granule bed was determined in a Dhona 200 D electronic balance. Bulk density was calculated by using the formula. Average of triplicate reading were noted (n = 3).

$$\text{Bulk density} = \frac{\text{Total weight of granules}}{\text{Total volume of granules}}$$

Tapped density

Tapped density was determined (Tapped density apparatus, Konark instruments, India) by taking the dried granules in a measuring cylinder and measuring the volume of granules after 100 tappings and weight

of the total granules. Average of triplicate reading were noted (n = 3).

$$\text{Tapped density} = \frac{\text{Total weight of granules}}{\text{Total volume of granules ater 100 tappings}}$$

Compressibility index [12]

Compressibility index was determined by placing the granules in a measuring cylinder and the volume (V_0) was noted before tapping. After 100 tapings again volume (V) was noted. Average of triplicate compressibility indices of granule readings were taken and tabulated (n = 3).

$$\text{Compressibility index} = (1- V/ V_0) \times 100$$

V_0 = volume of powder/granules before tapping.

V = volume of powder/granules after 100 tapings.

Evaluation of compressional characteristics of the ciprofloxacin tablets

Weight uniformity

Twenty tablets were taken and weighed individually. Average weight was calculated standard deviation and percent coefficient of variance was computed.

Thickness test

The tablets were evaluated for their thickness using a micrometer (Mitutoyo, Japan). Average of thee readings were taken and the results were tabulated (n = 3).

Diameter test

The tablets were evaluated for diameter using a micrometer (Mitutoyo, Japan). Average of thee readings were taken and tabulated (n = 3).

Hardness test

The tablets were evaluated for their hardness using Pfizer hardness tester. Average of thee reading were taken and tabulated (n = 3).

Friability test

The friability of the tablets was determined in Roche Friabilator. Ten tablets were weighed accurately and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. Tablets were taken and again weighed. The percentage weight loss was determined by using formula given below. The experiment was repeated for three times and average was noted.

$$\% \text{ Friability} = \frac{\text{Initial wt of tablets} - \text{Final wt of tablets}}{\text{Initial wt of tablets}} \times 100$$

Swelling study [12]

Accurately weighed tablet was initially placed in a Petridish containing media of 100 ml of 0.1N HCL for 2 h, followed by pH 7.4 buffer for 3 h, later pH 6.8 for 11 h to simulate the GIT system. At regular intervals of time, the tablet was taken out and the excess moisture on the surface of tablet was removed with tissue paper and the tablet was weighed again. The percent of swelling index were calculated by using formula.

$$\% \text{ swelling} = \frac{\text{Final wt of tablet} - \text{Initial wt of tablet}}{\text{Initial wt of tablet}} \times 100$$

Determination of drug content [13]

Five core in coat tablets were crushed into powder in a mortar and powdered equivalent to Budesonide dose was taken in a volumetric flask containing distilled water and kept aside with constant shaking on a rotary shaker for 24 h to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution, at 246 nm against buffer pH 6.8 as blank. Averages of triplicate readings were taken. The content of drug was calculated using slope from calibration curve.

***In vitro* dissolution study** [9]

Drug release study in phosphate buffer of pH 1.2 and Sorenson's phosphate of pH 7.4

To assess the integrity and prevention of drug release in the physiological environment of stomach and small intestine, the drug release study were carried out in pH 1.2 in USP dissolution test apparatus of 900 ml fluid (Apparatus 1, 100 rpm, 37°C) for 2 h and dissolution medium were replaced with Sorenson phosphate buffer of pH 7.4 and continued the drug release study for 3 h, the samples were withdrawn at regular intervals and diluted with respective dissolution medium and estimated the drug release by measuring the absorbance at λ_{max} of 246 nm in UV spectrophotometer.

Drug release study in Sorenson phosphate buffer of pH 6.8

The susceptibility of matrix tablet to colonic enzymatic degradation was assessed by conducting drug release study in modified USP dissolution apparatus. A 150 ml beaker containing 100 ml of 4% w/v rat cecal content was placed and the basket was manipulated to the centre of the beaker. The rat cecal content was prepared by male albino rats. The rats of 3-4 of 150-200 gram were selected and kept for fasting for one day with intermittent administering water before the drug release was conducted. The rats were taken from cage and anesthetized by spinal cord traction before 30 min prior to the experiment. Abdomen of rat was opened and the caecum was ligated at both ends and then suspended in saline phosphate buffer of pH 6.8 with the continuous supply of CO_2, in order to maintain the anaerobic condition. The caecum were opened and the cecal contents were weighed, transferred into 100 ml of Sorenson phosphate buffer of pH 6.8 to make 4% w/v of rat cecal content solution, the cecal enzymes are active in anaerobic condition, to mimic the anaerobic condition, the solution was continuously bubbled with CO_2 and studied the drug release up to 19-20 hours. The sample were withdrawn at regular intervals without pre-filter and replaced with fresh buffer. Absorbance of the sample was measured in UV spectrophotometer at λ_{max} of 246 nm and concentration was calculated by regression equation.

Stability studies [14]

Stability was performed to investigate the influence of temperature and relative humidity on drug content and *in vitro* dissolution of colon specific matrix targeted tablet. Study was performed according to the ICH guidelines at the conditions of temperature 40°C and 75% RH for 90 days. The optimized formulations tablet were wrapped in aluminum foil and packed in amber coloured bottle and kept in stability chamber for 90

days. The samples were withdrawn at the intervals of 0, 15, 45 and 90 days and analyzed the drug content, *in vitro* dissolution release and compared with ambient conditions.

Table 2: Formulations of Budesonide Core in Coat tablet.

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10
Core tablet	C5	C5	C5	C5	C5	C5	C5	C5	C5	C5
Sterculia gum	135	165	195	225	195	195	195	195	195	195
Eudragit s100	-	-	-	-	30	45	30	30	30	30
Xanthan gum	-	-	-	-	-	-	30	45	-	-
$HPMCK_4M$	-					-	-	-	30	45
PVP K90 5% aq	-	-	-	-	-	-	-	-	-	-
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Mg stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
$HPMCK_4M$	-	-	-	-	-	-	-	-	-	-
MCC PH 102	160	130	100	80	69	54	39	24	39	24
Total weight (mg)	450	450	450	450	450	450	450	450	450	450

Table 3: Solubility of Budesonide in different concentration of β – Cyclodextrin

Con %	ABS	Solubility mg/l
0	0	000
0.5	0.29	0.068
0.75	0.36	0.084
1	0.42	0.098
1.5	0.48	0.112
1.8	0.54	0.127

Table 4: *In vitro* release of Budesonide from pure sample, C1, C2 and C4

Time (min)	PC	C1	C2	C4
	C. Amount % Release	C. Amount % Release	C. Amount % Release	C. Amount % Release
0	0	0	0	0
5	0.471	1.882	2.118	0.471
10	1.412	3.765	2.4	1.176
15	1.647	8.00	8.988	1.553
20	3.059	10.82	16.05	8.612
30	5.176	16.94	22.16	14.73
40	9.647	28.71	38.64	18.49
50	12.94	34.82	46.16	24.14
60	16.24	41.41	53.69	28.85
90	20.94	60.24	86.64	42.96
120	24.24	66.35	100.8	50.02

RESULTS AND DISCUSSION

Budesonide is a potent corticosteroid. The solubility of the drug in distilled water and in different pH buffers of pH 1.2, pH 6.8 and pH 7.4 was found to be 0.042 ± 0.16 mg, 0.066 ± 0.18 mg, 0.053 ± 0.24 and 0.42 ± 0.038 mg respectively. The above observation indicates that the solubility of budesonide in water was very less and solubility decreases as the pH of the solution increases hence planned to enhance the solubility of budesonide by solid dispersion inclusion complexation with β-Cyclodextrin. The results in Table 3 conclude that the solubility of budesonide increases with increasing the concentration of β-Cyclodextrin and it increased 3.4 folds more solubility than in distilled water.

The budesonide core formulations powder beds are evaluated for rheological characteristics study. The angle of repose of all formulations before adding glidant was found to be between 30 ± 0.81 and 32 ± 0.8 $^0\theta$ and angle of repose after adding glidant decreased and it was found between 28.2 ± 0.16 and 29.2 ± 0.58$^0\theta$. The bulk density was found in the range of 0.46 ± 00 to 0.47 ± 0.1 g/cc. Tapped density is between 0.51 ± 0.01 and 0.55 ± 0.02 g/cc. The compressibility was found to be 6.4 ± 0.3 to 13.8 ± 0.16%. The above results indicate that the powder beds of all formulations are freely flowable and compressible.

The Budesonide core formulations powder bed are punched in ten station tablet punching using 8 mm punches by direct compression method. The obtained tablets were evaluated for post compressional characteristics. Weight variation of all the formulations was found in the range of 150.4 ± 1.2 to 152 ± 1.63 mg. Thickness of was found between 3.1 ± 0.08 to 3.3 ± 0.16 mm and diameter was found to be 8.03 ± 0.09 to 8.1 ± 0.09. These results confirm that the tablets are uniformly reproducible from batch to batch. The hardness of all formulations was found in the range of 3.3 ± 0.09 to 4.0 ± 0.15 kg/cm^3. Friability of the formulations is in the range of 0.83 ± 0.01 to 0.9 ± 00%. The results show that, they are capable of having sufficient and can withstand during compression coat of the core tablets.

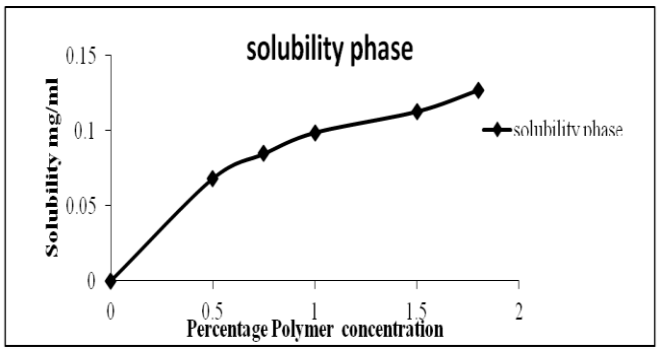

Fig. 1: Solubility phase diagram of Budesonide in different concentration of β-Cyclodextrin.

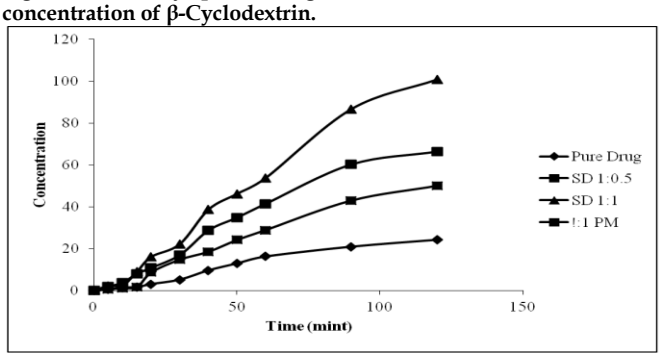

Fig. 2: Comparative *in vitro* release curve of Budesonide from Pure sample, SD (1:0.5), SD (1:1) and PM (1:1).

Table 5: Evaluation of Pre-Compressional and Post-Compressional Characteristics of Budesonide core tablets.

Formulation	Angle of Repose (°θ)		Bulk density g/cc	Tapped density g/cc	CI. Index	Wt. Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness Kg/cm³	Friability %
	B. adding Glidant	A. adding Glidant								
C1	32 ± 0.8	29.8 ± 0.3	0.47 ± 0.1	0.55 ± 0.02	13.8 ± 0.16	150.3 ± 1.2	3.3 ± 0.16	8.1 ± 0.09	3.6 ± 0.25	0.87 ± 0.01
C2	29.5 ± 0.41	28.2 ± 0.16	0.48 ± 0.02	0.53 ± 0.01	9.34 ± 0.14	150.6 ± 0.9	3.2 ± 0.08	8.1 ± 0.08	3.6 ± 0.3	0.9 ± 0.02
C3	30 ± 0.81	29.2 ± 0.58	0.46 ± 00	0.52 ± 00	6.4 ± 0.32	152 ± 1.63	3.3 ± 0.12	8.06 ± 0.09	4.0 ± 0.15	0.83 ± 0.02
C4	31.8 ± 0.49	30.0 ± 0.80	0.46 ± 000	0.51 ± 0.01	11.1 ± 0.15	150 ± 0.81	3.1 ± 0.08	8.03 ± 0.09	3.3 ± 0.09	0.9 ± 00

Table 6: Evaluation of pre–compressional characteristics of coat powder bed

Formulation	Angle of Repose (°θ)		Bulk density g/cc	Tapped density g/cc	Compressibility Index %
	B. adding Glidant	A. adding Glidant			
B1	31.4 ± 0.99	30.0 ± 0.09	0.53 ± 0.02	0.63 ± 0.02	13.8 ± 0.63
B 2	30.4 ± 0.43	29.0 ± 0.71	0.54 ± 0.01	0.59 ± 0.04	8.3 ± 0.37
B 3	31.0 ± 0.81	30.4 ± 0.15	0.53 ± 0.02	0.59 ± 0.01	8.6 ± 0.16
B 4	30.7 ± 0.52	29.4 ± 0.33	0.56 ± 0.00	0.61 ± 0.01	8.3 ± 0.20
B 5	32.2 ± 0.16	30.2 ± 0.16	0.57 ± 0.00	0.65 ± 0.01	10.7 ± 0.12
B 6	31.06 ± 0.52	30.7 ± 0.42	0.56 ± 0.01	0.63 ± 0.02	11.2 ± 0.16
B 7	32.6 ± 0.99	30.4 ± 0.52	0.54 ±0.01	0.63 ± 0.01	14.29 ± 0.24
B 8	30.4 ± 0.56	28.5 ± 0.09	0.54 ± 0.009	0.62 ±0.02	12.3 ± 0.24
B 9	30.4 ± 0.54	28.5 ± 0.09	0.52 ± 0.00	0.59 ± 0.01	8.7 ± 0.18
B 10	30.4 ± 0.56	28.5 ± 0.09	0.51 ± 0.00	0.57 ± 0.02	10.52 ± 0.00

Table 7: Evaluation of Post–compressional characteristics of coat powder bed

Formulation	Weight Variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm³)	Friability %	Drug Content (mg)
B1	451.3 ± 0.94	5.4 ± 0.16	10.20 ± 0.16	6.5 ± 0.08	0.9 ± 0.00	9.0 ± 0.12
B 2	453.3 ± 1.8	5.2 ± 0.25	10.40 ± 0.3	6.6 ± 0.16	0.85 ± 0.04	8.8 ± 0.12
B 3	453.0 ± 1.6	5.4 ± 0.16	10.20 ± 0.16	5.9 ± 0.09	0.76 ± 0.04	9.2 ± 0.16
B 4	452.0 ± 1.6	5.23 ± 0.05	10.13 ± 0.09	6.2 ± 0.16	0.92 ± 0.01	9.0 ± 0.20
B 5	454.0 ± 1.8	5.23 ± 0.05	10.23 ± 0.09	6.4 ± 0.16	0.88 ± 0.1	8.9 ± 0.2
B 6	451.0 ± 0.81	5.3 ± 0.08	10.1 0± 0.12	5.7 ± 0.09	0.92 ± 0.02	9.1 ± 0.18
B 7	454.0 ± 1.63	5.3 ± 0.09	10.20 ± 0.12	5.9 ± 0.08	0.90 ± 0.00	9.0 ± 0.40
B 8	452.6 ± 2.49	5.37 ± 0.05	10.16 ± 0.12	6.4 ± 0.24	0.94 ± 0.01	9.2 ± 0.13
B 9	452.0 ± 0.81	5.2 ± 0.08	10.30 ± 0.08	6.3 ± 0.08	0.95 ± 0.06	9.0 ± 0.16
B 10	450.0 ± 1.24	5.07 ± 0.06	10.10 ± 0.08	6.5 ± .08	0.97 ± 0.08	9.0 ± 0.14

Table 8: Swelling study of colon specific delivery of Budesonide core in coat tablet in different pH.

Buffers	% swelling index									
	pH 1.2			pH 7.4			pH 6.8			
Formulations	0.5 h	1 h	2 h	3 h	5h	6 h	7 h	8 h	12 h	16h
B1	18.2	22	30.2	34.6	48.2	50.2	66.4	74.6	124.4	160.4
B 2	18.4	26.4	36.2	41.2	58.2	60.4	85.6	98.6	174	260
B 3	20.2	28	38.4	56.6	80.2	82.2	120	146.2	220.6	320.6
B 4	23.4	28.6	40.2	42	58.6	66.6	142.2	240	300.2	380.2
B 5	18.8	28.6	32.8	38.6	46.8	88.2	110.6	130.6	236.4	310.2
B 6	18.6	26.6	36.2	40.8	44.8	90.2	120.6	126.4	244	315.6
B 7	23.4	30.2	38.2	41.2	64.2	78.2	130.2	160.4	290.2	390.4
B 8	24.2	31.2	46.6	72.0	100.8	120.6	160.4	240.6	310.2	420.2
B 9	21.4	28.6	36.2	40.6	80.2	114	136.4	210	290	350.6
B 10	22.8	26.	38.4	48.6	90.6	116	148.6	220.6	300.4	370.4

Table 9: *In vitro* release profile of colon specific delivery of Budesonide core in coat matrix tablets of B1 to B4 in GIT fluids.

Time (h)	Formulations							
	B1		B2		B3		B4	
	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.5	2.3 ± 0.2	2.3 ± 0.2	0.9 ± 0.3	2.3 ± 0.2	0.4 ± 0.2	2.3 ± 0.3	0.2 ± 0.3	2.3 ± 0.2
1	5.7 ± 0.2	6.8 ± 0.1	3.8 ± 0.2	5.2 ± 0.3	3.5 ± 0.6	4.9 ± 0.2	2.3 ± 0.4	4.2 ± 0.3
2	10.4 ± 0.2	13.5 ± 0.5	8.0 ± 0.4	8.3 ± 0.4	7.8 ± 0.4	7.6 ± 0.4	5.2 ± 0.6	6.6 ± 0.6
3	12.5 ± 0.2	19.2 ± 0.6	9.0 ± 0.06	10.6 ± 0.3	8.7 ± 0.3	9.9 ± 0.6	7.3 ± 0.2	9.7 ± 0.2
5	14.9 ± 0.4	26.3 ± 0.2	15.2 ± 0.6	15.6 ± 0.3	14.9 ± 0.6	14.9 ± 0.5	13 ± 0.3	13.3 ± 0.2
6	16.6 ± 0.3	33.4 ± 0.3	16.9 ± 0.8	18.1 ± 0.2	16.5 ± 0.3	16.2 ± 0.7	14.1 ± 0.2	14.6 ± 0.4
8	21.9 ± 0.2	51.9 ± 0.4	19.5 ± 0.2	20.8 ± 0.4	19.1 ± 0.2	18.1 ± 0.4	16.7 ± 0.6	17.2 ± 0.3
9	29.8 ± 0.6	73.0 ± 0.4	26.1 ± 0.1	36.6 ± 0.3	23.1 ± 0.9	20.5 ± 0.3	20.7 ± 0.1	20.9 ± 0.2
12	48.3 ± 0.6	99.4 ± 0.2	39.3 ± 0.3	60.4 ± 0.1	24.4 ± 0.6	33.7 ± 0.5	22 ± 0.2	34.1 ± 0.4
15	98.5 ± 0.4		65.7 ± 0.2	97.3 ± 0.2	48.2 ± 0.2	57.4 ± 0.2	37.8 ± 0.6	55.2 ± 0.2
20			100.1 ± 0.6		73.2 ± 0.4	97 ± 0.3	62.9 ± 0.6	76.3 ± 0.3
24					99.6 ± 0.2		90.6 ± 0.3	100 ± 0.2

Table 10: *In vitro* release curve of colon specific delivery of budesonide core in coat matrix tablets of B5 to B10 in GIT fluids with 4% rat cecal.

Time (h)	Formulations											
	B5		B6		B7		B8		B9		B10	
	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%	Wt. Rc Cu. A%	W. Rc Cu. A%
0	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.5	0.2±0.02	2.3±0.02	0.2±0.02	0.2±0.03	0.23±0.2	0.23±0.2	0.23±0.2	0.23±0.1	0.71±0.2	0.23±0.5	0.23±0.2	0.23±0.2
1	1.4±0.03	2.8±0.04	0.7±0.04	1.18±0.2	0.71±0.2	0.71±0.3	0.71±0.1	0.71±0.2	1.9±0.3	0.47±0.4	1.42±0.3	1.18±0.3
2	4.6±0.04	4.9±0.06	3.0±0.06	3.32±0.2	3.08±0.3	3.08±0.5	2.13±0.3	1.42±0.3	4.03±0.4	2.13±0.2	3.08±0.4	3.32±0.4
3	6.65±0.2	9.26±0.2	5.4±0.03	7.60±0.6	4.51±0.1	4.51±0.2	2.85±0.6	2.85±0.4	7.36±0.1	6.41±0.3	4.51±0.6	5.93±0.1
5	13.3±0.2	13.7±0.3	12.1±0.3	12.1±0.1	8.78±0.3	10.78±0.9	4.03±0.2	4.75±0.1	11.6±0.1	11.1±0.2	8.31±0.2	8.31±0.6
6	14.2±0.1	16.4±0.2	13.3±0.2	14.7±0.2	9.97±0.4	11.7±0.2	5.22±0.1	7.39±0.2	12.4±0.3	12.4±0.1	9.50±0.1	10.9±0.4
8	17±0.06	19.0±0.6	14.8±0.4	17.3±0.4	11.5±0.6	14.5±0.3	6.80±0.3	10.8±0.3	13.7±0.5	14.8±0.6	11.8±0.4	13.9±0.5
9	21.7±0.3	34.8±0.3	17.2±0.6	21.3±0.3	13.9±0.7	16.8±0.2	9.18±0.2	16.1±0.1	16.1±0.3	18.2±0.2	13.9±0.2	17.6±0.3
12	25.7±0.2	53.3±0.4	22.5±0.3	30.8±0.0	19.2±0.2	20.2±0.1	14.4±0.1	22.1±0.4	21.4±0.2	26.2±0.4	18.4±0.6	22.7±0.2
15	37.5±0.2	74.4±0.2	30.4±0.5	63.8±0.2	31.0±0.3	34.0±0.3	26.3±0.3	47.2±0.3	31.9±0.6	44.6±0.3	25.0±0.4	38.5±0.5
20	63.9±0.3	98.2±0.3	50.2±0.4	100.8±.3	62.7±0.4	65.7±0.5	58.0±0.4	76.2±0.5	63.6±0.2	81.6±0.5	62.0±0.6	72.8±0.3
24	100.9±.2		92.4±0.3		85.1±0.2	96.1±0.3	80.4±0.6	97.3±0.6	86.0±0.4	100.1±.2	83.1±0.4	99.2±0.3

Table 11: Dissolution profile of B8 formulation of colon specific delivery of Budesonide core in coat matrix tablet after respective days of stability study at 40°C / 75% RH.

	B8				
Days	**0**	**15**	**30**	**45**	**90**
Time (h)	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**
0	0000	0000	0000	0000	0000
0.5	0.230 ± 0.12	0.024 ± 0.12	0.238 ± 0.12	0.238 ± 0.23	0.238 ± 0.12
1	0.710 ± 0.12	0.499 ± 0.14	0.475 ± 0.14	0.475 ± 0.25	0.475 ± 0.15
2	1.420 ± 0.14	1.211 ± 0.16	1.188 ± 0.16	0.95 ± 0.27	0.713 ± 0.17
3	2.850 ± 0.16	2.637 ± 0.4	2.375 ± 0.24	2.138 ± 0.31	1.663 ± 0.25
5	4.750 ± 0.24	4.537 ± 0.42	4.276 ± 0.26	3.8 0 ± 0.33	3.325 ± 0.28
6	7.389 ± 0.25	7.176 ± 0.42	6.915 ± 0.28	6.442 ± 0.35	5.965 ± 0.29
8	10.82 ± 0.28	10.61 ± 0.43	10.35 ± 0.32	9.871 ± 0.42	9.396 ± 0.31
9	16.09 ± 0.32	15.89 ± 0.78	15.62 ± 0.34	15.15 ± 0.44	14.67 ± 0.33
12	22.16 ± 0.36	21.96 ± 0.74	21.69 ± 0.38	21.22 ± 0.46	20.74 ± 0.35
15	47.24 ± 0.38	47.03 ± 0.56	46.77 ± 0.42	46.29 ± 0.48	45.82 ± 0.37
20	76.27 ± 0.42	76.06 ± 0.54	75.8 ± 0.44	75.32 ± 0.12	74.85 ± 0.48
24	97.38 ± 0.13	97.17 ± 0.52	96.91 ± 0.50	96.44 ± 0.09	95.96 ± 0.50

Table 12: Dissolution profile of B10 formulation of colon delivery specific of Budesonide core in coat matrix tablet after respective days of stability study at 40°C / 75% RH.

	B10				
Days	**0**	**15**	**30**	**45**	**90**
Time (h)	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**	**C. Amount % release**
0	0000	0000	0000	0000	0000
0.5	0.238 ± 0.12	0.238 ± 0.25	0.238 ± 0.15	0.238 ± 0.26	0.238 ± 0.32
1	1.188 ± 0.14	0.950± 0.27	0.713 ± 0.17	0.713 ± 0.24	0.713 ±.13
2	3.325 ± 0.16	2.850 ± 0.28	2.375 ± 0.19	2.138 ± 0.20	1.900 ± 0.17
3	5.938 ± 0.24	5.463 ± 0.29	4.988 ± 0.21	4.513 ± 0.30	4.038 ± 0.19
5	8.314 ± 0.26	7.838 ± 0.31	7.363 ± 0.25	6.888 ± 0.36	6.176 ± 0.21
6	10.95 ± 0.45	10.48 ± 0.33	10.23 ± 0.25	9.528 ± 0.42	8.815 ± 0.25
8	13.99 ± 0.48	13.51 ± 0.36	13.04 ± 0.27	12.56 ± 0.44	11.85 ± 0.27
9	17.68 ± 0.52	17.21 ± 0.38	16.73 ± 0.42	16.26 ± 0.48	15.54 ± 0.65
12	22.70 ± 0.56	22.22 ± 0.40	21.75 ± 0.46	21.27 ± 0.50	20.56 ± 0.66
15	38.53 ± 0.32	38.06 ± 0.46	37.58 ± 0.48	37.11 ± 0.23	36.39 ± 0.68
20	72.84 ± 0.34	72.37 ± 0.48	71.89 ± 0.50	71.42 ± 0.28	70.70 ± 0.70
24	99.23 ± 0.31	98.76 ± 0.50	98.28 ± 0.56	97.81 ± 0.12	97.10 ± 0.12

All the formulations are subjected *in vitro* dissolution study. Budesonide released from pure sample at the end of 120 mints was found to be 24.24%. Similarly the dissolution profile of C1 (1:0.5), C2 (1: 1) and C4 (1:1) was found to be 66.35%, 100.8% and 50.02% respectively. The dissolution rate of the formulations are in the order of C2>C1>C3>PC. From the above observation selected C1 (1:1) solid dispersion of budesonide inclusion complexation with β-Cyclodextrin as a core tablet for developing core in coat colon targeted tablet.

All formulations of coat powder bed from B1 to B10 are evaluated for pre- compressional characteristics study. Angle of repose of all formulation before adding glidant was found between 30.4 ± 0.54 and 32.6 ± 0.99$^0\theta$ and after adding glidant the angle of repose reduced and found in the range of 28.5 ± 0.09 to 30.0 ± 0.09$^0\theta$. Bulk density was found between 0.51 ± 00 to 0.57 ± 00

g/cc. Tapped density was found between 0.57 ± 0.02 to 0.65 ± 0.01 g/cc. The compressibility index of the formulations was found in the range of 8.3 ± 0.20 to 14.29 ± 0.24%. The above observations inform that the coat powder beds are freely flowable and compressible. Powder bed of coat formulations equivalent to 55% of the total weight were placed in die cavity and the selected core tablet is at the center on powder bed and the remaining % of the coat powder were placed on the core tablet and punched in tablet punching machine using 10 mm punches. The obtained tablets were evaluated for post compressional characteristics study. All formulations of core in coat tablet, weight variation was found between 450 ± 1.24 to 454 ± 1.63 mg. Thickness was in the range of 5.0 ± 0.08 to 5.4 ± 0.16 mm and diameter was in the range of 10.1 ± 0.12 to 10.4 ± 0.3 mm. The results confirm that they are uniform and reproducible from batch to batch. The hardness of all the formulation was in the range of 5.7 ± 0.09 to 6.6 kg/cm^3 and friability was found between 0.85 ± 0.04 to 0.99 ± 0.08%. The above observations show that tablets of all formulations are having sufficient mechanical strength and they can withstand wear and tear while handling. The drug content of all the formulations was to be 8.9 ± 0.02 to 9.2 ± 0.13 mg, indicating the drug is uniformly and fairly distributed through the tablet.

The core in coat tablets from formulations B1 to B10 were studied for swelling study in different pH buffers of pH 1.2, pH 6.8 and pH 7.4 for a period of 16 h. The swelling index from formulation B1 to B4 was in the range of 160.4 to 380.2%, indicating the swelling increases with increasing the polymer concentration. Swelling index from formulation B5 and B6 was found to be 310.2% and 315% respectively, indicating slight decrease in swelling index due to presence Eudragit S 100 polymer, which get dissolved in intestine pH. The swelling index from formulation B7 and B8 was found to be 390.4% and 420.2%, indicating the increased swelling index due to synergetic effect of swelling contributed by xanthan gum polymer. The swelling index of formulation B9 and B10 was found to be 350.6% and 370.4% respectively, indicating the swelling index is lower than formulation containing the xanthan gum due to lesser synergetic effect contributed to swelling of tablet by HPMC polymer.

To derive the dissolution profile and to understand the drug release, the *in vitro* dissolution study performed in the absence and presence of 4% w/v rat cecal content up to period of 24 hr. Formulations of core in coat tablets of B 1, B 2, B 3 and B 4 at the initial first 5 hr the drug release is 16.6%, 15.2%, 14.96% and 13.06% respectively and at the end of 15 h, 20 h, 24 h and 24 h the drug release was 100.0%, 100% , 97.04% and 99.68% respectively . The same formulations subjected *in vitro* dissolution study in presence of 4% w/v rat cecal content at the end 12 h, 15 h, 20 h and 24 h the drug release was found to be 100.0%, 97.36 %, 97.04% and 100.0%. The results indicates that the alone sterculia gum in formulation of increasing concentration, unable to control the drug release in the physiological environment of stomach and small intestine and carried lesser proportion of drug to colon. The drug release rate is higher in presence of 4% rat cecal content than in control dissolution study.

Table 13: Drug content of the optimized formulations after 90 days of stability study at 40°C/75 % RH.

Days	B8 DC (mg)	B10 DC (mg)
0	9.00 ± 0.12	9.0 ± 0.09
3	9.00 ± 0.18	8.98 ± 0.06
5	8.94 ± 0.20	8.94 ± 0.14
10	8.92 ± 0.42	8.90 ± 0.28
15	8.90 ± 0.16	8.88 ± 0.07
30	8.8 6 ± 0.06	8.85 ± 0.03
45	8.80 ± 0.08	8.8 2± 0.09
90	8.78 ± 0.16	8.74 ± 0.14

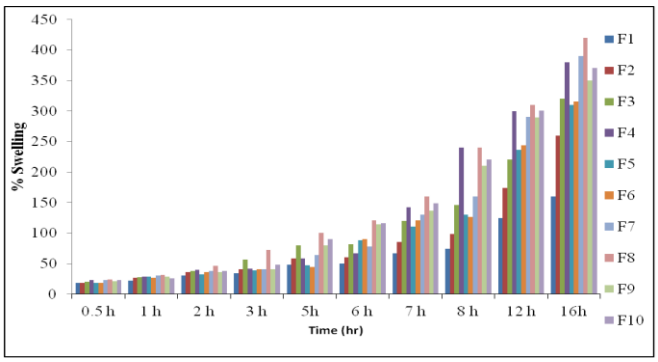

Fig. 3: Comparative swelling index curve of respective formulations from B1-B10.

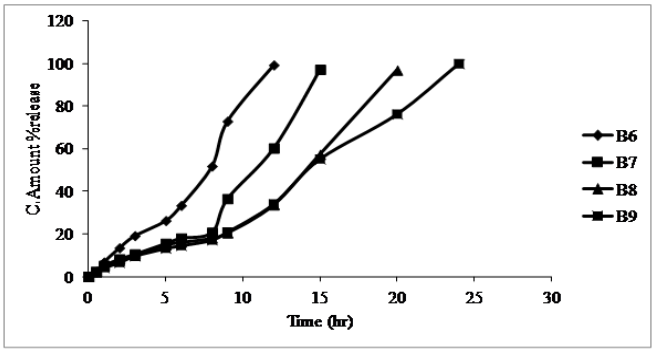

Fig. 4. *In vitro* release curve of colon specific delivery of budesonide core in coat matrix tablets of B1 to B4 in GIT fluid with 4% rat cecal content.

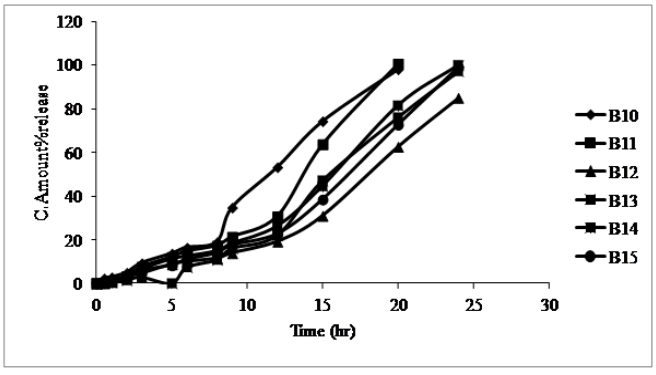

Fig. 5 *In vitro* release curve of colon specific delivery of budesonide core in coat matrix tablets of B5 to B10 in GIT fluid with 4% rat cecal content.

Further formulations B5 and B6 developed by incorporating the Eudragit S 100 a pH dependent soluble polymer, at the initial first 5 h the drug release is 12.6% and 11.4 % respectively and at the end of 24 h the drug release was 100.0% and 92.48% respectively. The same formulations subjected *in vitro* dissolution study in presence of 4% w/v rat cecal content at the end of 20 h the drug release was found to be 98.23% and 100.8% respectively. The results indicates that the incorporating of Eudragit S 100 in formulation slightly prevented drug release in stomach pH and get dissolved in the small intestine pH and failed to control the drug release in first 5 h and carried lesser amount of drug to colon, the drug release rate is higher in presence of rat cecal content than control dissolution study.

Formulations of core in coat tablets of B7, B 8, B9 and B 10 at the initial first 5 h the drug release is 6%, 3%, 10% and 7% respectively and at the end of 24 h drug release was 85%, 80.44% , 88% and 83% respectively . The same formulations subjected *in vitro* dissolution study in presence of 4% w/v rat cecal content at the end of 24 h the drug release was found to be 100.4%, 98.39%, 100.1% and 99.23%. The results indicates that the sterculia gum in combination with xanthan gum released the minimum amount of drug in physiological environment of stomach and small intestine and carried the maximum drug to colon, the drug release rate is higher in presence of rat cecal content than control dissolution study. The drug release preventing in first 5 hr is in order B8 > B6 >B10 > B9 respectively. In all the formulations, the polymer gets hydrated and viscous gel layer is formed and that slows down further seeping of dissolution fluid towards the core of tablet and controls the drug release and the release takes place by diffusion through this matrix in control study, where in presence of rat cecal content the bacterial enzymes degrade the sterculia gum and higher release rate takes place in the dissolution medium.

In view of potential utility of formulation B8 & B10 for targeting the drug to colon, stability study was carried at the condition of 40°C / 75% RH for 3 months. During the storage period the tablets were observed for physical appearance and studied the assay and *in vitro* dissolution study. The obtained data's are mentioned in Table 10, 11 and 12. The results indicates that the there is no change in physical appearance and negligible change in drug content and the dissolution profile remains similar to the dissolution profile before storage. Hence the above optimized potential colon targeted formulations remains stable for minimum of 2 years in ambient condition.

Budesonide is a potent corticosteroid and very less soluble in water. The solubility of budesonide is enhanced by solid dispersion inclusion complexation with β-Cyclodextrin at drug: carrier (1:1). The powder bed of core formulations rheological studies indicates, the powder bed is freely flowable and compressible. The core in coat tablet of all the post compressional studies shows that the tablets are uniform and reproducible from batch to batch and have sufficient hardness to with stand the compression pressure while preparing the core in coat. Formulations on subjecting to dissolution study, the Formulation B8 and B10 are potential in targeting the drug to colon. The optimized formulations stability according to ICH guidelines, indicates negligible change in drug content and similar *in vitro* dissolution profile during storage and before storage, hence the formulations can remains stable for period of 2 years in ambient condition.

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