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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF PULSATILE RELEASE TABLET OF BUDESONIDE

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ABSTRACT

The objective of this study was to develop a ileo caecal targeted drug delivery of budesonide for the treatment of IBD. Budesonide were selected as model standard drugs to treat IBD. Budesonide is a potent, synthetic non-halogenated corticosteroid with high topical anti-inflammatory effect and little systemic effects. Tablets were prepared by using Crospovidone and Eudragit L30D coating for the burst release in the ileo caecal region. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated were within the acceptable limits. Formulation F11 was proved to be good drug content, dimensional stability, lag time and drug release in the ileo caecal region as compared to the other formulations. Stability studies were carried out on the optimized formulation F11 for period of 3 months at 40^0c/75 %RH. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months.

KEYWORDS: Budesonide. ileo caecal, Lag time, Stability study.

INTRODUCTION

Colon specific drug delivery system (CSDDS) refers to targeting of drugs into the lower GIT, which occurs primarily in the large intestine or also referred as colon. The delivery of drugs to the colon has number of therapeutic implications in the field of drug delivery. CSDDS is considered to be beneficial in the local and systemic treatment of ileo caecal and colon related diseases and disorders. These include the topical treatment of diseases associated with

the colon like inflammatory bowel disease (IBD) and inflammatory bowel syndrome (IBS), colon cancer, diverticula and amebiasis. Also it may be used for the oral delivery of proteins and peptides. Colon is rich in lymphoid tissue, uptake of antigens into the mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.[1] CSDDS is of importance when delay in absorption is desired from therapeutic point of view in treatment of diseases showing peak symptoms in early morning i.e. chronotherapy that are sensitive to circadian rhythms e.g. nocturnal asthma, rheumatic disease, ischemic heart disease (IHD) and angina attack. As dosage forms remains longer in the colon rather than in the small intestine, hence colon specific formulations could be used to prolong drug delivery.[2-3]

Colonic delivery is considered to be better than rectal delivery of dosage form (suppositories and enemas) due to lack of efficacy and a high variability in distribution of drugs, e.g. suppositories are effective only in rectum due to their confined use, while enemas can offer only topical treatment only to the sigmoid and descending colon. Thus, oral route is preferred but absorption and degradation in upper GIT is major obstacle and must be circumvented for successful colonic delivery.[4-5]

Treatment might be more effective if the drug substances were targeted directly on the site of action in the colon. Lower doses might be adequate and if so systemic side effects may be reduced. This region of the colon is recognized as having a somewhat less hostile environment with less diversity and intensity of activity than in the stomach and small intestine. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs. As colon is relatively free of peptidases such special delivery systems will have a fair chance for oral administration undigested, unchanged and fully active peptide drugs. The simplest method for targeting of drugs to the colon is to obtain slower release for longer period of time or immediate release in abundant quantity. The special placement of drugs into selected locations in the GIT is quite difficult due to physiological constraints, namely, motility and mucus turnover. In some cases drugs may be unstable in upper GIT and are generally not well absorbed from the lumen of the GIT due to their relatively large molecular size and high peptidase activity. Protecting drugs from hydrolysis in GIT and subsequently releasing these drugs in the ileum or colon may result in better systemic bioavailability. Specific systemic absorption in the colonic region offers interesting possibilities for the treatment of disease susceptible to circadian rhythms.[6-9]

Budesonide were selected as model standard drugs to treat IBD. Budesonide is a potent, synthetic non-halogenated corticosteroid with high topical anti-inflammatory effect and little systemic effects. Additionally, budesonide has low incidence of adverse effects and high topical effects and has important suggestions in the pharmacotherapy of IBD, both in treatment of UC and CD. It was found that less than 5% of drug was available beyond the ileum and caecum, and hence, colonic delivery still needs to be optimized by a more reliable targeted system. The objective of the study is to develop budesonide loaded tablets with Crospovidone and based on coating with Eudragit L30D Presently in the market there is no immediate release Budesonide formulation to target ileo caecal region. Most common site for the occurrence of Crohn's disease is ileo caecal region; hence it is necessary to target Budesonide in this region without being release in stomach or small intestine for effective treatment.[10-12]

MATERIAL AND METHODS

Material

Budesonide was a kind gift from Ethypharma Pvt. Ltd. (Mumbai, India). Eudragit L30D was purchased from the Research-Lab Fine Chem Industries (Mumbai, India). Polyethylene Glycol was purchased from Clariant Pvt. Ltd. (Mumbai, India). Magnesium Stearate, lactose, polyvinyl pyrolidone (PVP K30), Methylene chloride were purchased from Signet India Pvt. Ltd, Mumbai. Crospovidone and Isopropyl alcohol (IPA) were purchased from Loba Chemicals (Mumbai, India). Other excipients used were of standard pharmaceutical grade

Methods

Preparation of budesonide pulsatile release tablets

The granules were prepared by wet granulation method. The drug budesonide, crospovidone and lactose were passed through sieve 40# separately and blended thoroughly. After proper mixing then slowly added the binding solution containing PVP K-30 in IPA till fine uniform granules were obtained. The wet mass was passed through sieve 16# and dried at 50°C for 30 minutes to get the moisture content less than one. Then lubricate the dried granules with magnesium stearate which were already passed through sieve 40#. Then lubricated granules were compressed on cadmach tablet punch machine for all formulations.[13] Granules were evaluated for micromeritic properties such as bulk density, tapped density, angle of repose and hausner ratio.

Coating of Eudragit L30D over drug containing tablets

Eudragit L30D coating dispersion requires addition of glycol as plasticizer and stirred the solution for few minutes with a magnetic stirrer. This solution was sprayed over the above processed tablets up to 5, 10, 15, 20, 25, 30 and 35% weight gain.

Table 1: Composition of budesonide preliminary experimental batch F1-F8 (all quantities in mg)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Budesonide	9	9	9	9	9	9	9	9
Crospovidone	15	20	25	25	20	25	20	25
PVP K30	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10
Lactose	136	131	126	126	131	126	131	126
Eudragit L30D Weight gain	5%	5%	5%	10%	10%	15%	15%	20%

Table 2: Composition of budesonide preliminary experimental batch F9-F15 (all quantities in mg)

Formulation code	F9	F10	F11	F12	F13	F14	F15
Budesonide	9	9	9	9	9	9	9
Crospovidone	20	25	20	25	20	25	20
PVP K30	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10
Lactose	131	126	131	126	131	126	131
Eudragit L30D Weight gain	20%	25%	25%	30%	30%	35%	35%

Evaluation of granules

Angle of repose: Granules flowability was determined by calculating angle of repose by funnel technique. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm above the platform. About 20 g of granules was slowly passed along the wall of funnel till the tip of the pile produced and touches the stem of the funnel. A rough circle was drawn about the pile base and the radius of the sample cone was measured.[14] Angle of repose was calculated from average radius using formula:

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose

h = height of the pile

r = average radius of the powder cone.

Bulk Density

Apparent bulk density of granules was determined by the graduated cylinder and measuring the volume and weight "as it is".[15] Bulk density was calculated by using following formula:

$$\text{Bulk density (g/mL)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

Tapped Density

Tapped density was determined with the aid of tapped density tester apparatus. In this method 20 gm of sample was poured gently through a glass funnel in to a 100mL graduated cylinder. The cylinder was then placed in the apparatus and parameters were set to carry out the test. [15] Volume occupied by the sample after tapping were recorded and tapped density was calculated by following formula:

$$\text{Tapped density (g/mL)} = \frac{\text{Weight of sample in grams}}{\text{After tapping volume occupied by the sample}}$$

Hausner ratio

It provides an indication of the degree of densification which could result from vibration of the feed hopper. Hausner ratio closer of less than 1.25 indicates good flow, while greater than 1.5 indicates poor flow materials.[16]

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's index or % compressibility

Carr's index or % compressibility [16] was calculated by using following equations:

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Tablet thickness and diameter

Tablet Thickness and diameter were accurately measured by using digital vernier caliper in mm.[17]

Hardness and Friability

Hardness of tablet was determined by Monsanto hardness tester. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets

at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de dusted and reweighed. [18] The percentage friability was calculated.

$$F = \frac{W1 - W2}{W1} \times 100$$

Where F represents the percentage weight loss, and W1 and W2 are the initial and final tablet weights, respectively.

Weight variation

Twenty tablets were selected at random and average weight was determined. Then individual tablets were compared with the average weight.[18]

Drug content uniformity

For determination of drug content, weighed and powder 5 tablets, then weighed accurately a quantity of the powder equivalent to 9mg of budesonide were transferred to the conical flask and suitably diluted with 10mL phosphate buffer (pH 7.4) respectively. The solution was filtered through Whatman filter paper (no.41), and assayed at 245nm, using a JASCO V630, Japan UV- spectrophotometer.[19]

In vitro drug release study

The test was carried out in a rotating basket method specified in the USP XXIII dissolution tester (Electrolab, TDT-08L, India) at a rotation speed of 100 rpm in 900 ml dissolution medium at 37 ± 0.5 °C in media with pH 1.2 (HCl 0.1 N), pH 7.4 and pH 6.8 (phosphate buffer) for 2 h, 3 h, and till the end of the test, respectively. 5 ml aliquots of the dissolution fluid were removed at specified time intervals and replaced with fresh dissolution medium and assayed for the amount of budesonide by spectrophotometer (JASCO V630, Japan) at wavelength 245 nm. The dissolution data was analyzed to calculate % drug released at different time intervals.[20-21]

Stability study

Stability Study was carried out for formulations to assess its stability, as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber (6CHM-GMP, Remi Instrument Ltd., Mumbai) at elevated temperature and humidity conditions of 40^0C/ 75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. At the end of study, samples were

analyzed for the drug content, *in vitro* drug release and other physicochemical parameters.[22-23]

RESULT AND DISCUSSION

Granules evaluation

The physical characteristics of the granules (F1 to F15) such as bulk density, tapped density, carr's index, hausner ratio, angle of repose were determined. The results are given in Table 3. The bulk densities were ranged from 0.704-0.885 gm/ml. The tapped densities were ranged from 0.886-0.981 gm/ml. The carr's compressibility index were ranged from 7.04-20.45%. The hausners rations were found to be in the limit 1.07-1.25. The angles of repose of all formulation were found to be between the limit 22.19°-26.61°. All the formulation shows excellent flow properties. So, the granules passes the evaluated tests and subjected to next stage of work compression.

Table 3: Evaluation of budesonide pulsatile release tablets granules (F1-F15)

Formulation code	Bulk density gm/ml	Tapped density gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose (°)
F1	0.731±0.03	0.870±0.02	15.97±0.21	1.19±0.04	23.68±1.41
F2	0.724±0.04	0.866±0.05	16.39±0.12	1.19±0.03	23.30±1.63
F3	0.715±0.03	0.871±0.01	17.91±0.14	1.21±0.03	25.15±1.52
F4	0.820±0.05	0.960±0.04	14.58±0.08	1.17±0.06	24.68±2.53
F5	0.785±0.05	0.876±0.04	10.38±0.09	1.11±0.04	26.39±2.67
F6	0.885±0.03	0.963±0.03	8.09±0.11	1.08±0.05	23.16±0.98
F7	0.704±0.04	0.885±0.02	20.45±0.12	1.25±0.02	22.19±1.41
F8	0.711±0.06	0.881±0.03	19.29±0.14	1.23±0.04	26.61±1.36
F9	0.845±0.04	0.909±0.04	7.04±0.05	1.07±0.06	25.43±1.76
F10	0.817±0.03	0.981±0.05	16.71±0.15	1.20±0.07	22.61±1.34
F11	0.746±0.02	0.885±0.08	15.70±0.17	1.18±0.02	23.68±1.53
F12	0.715±0.05	0.878±0.04	18.56±0.14	1.22±0.01	25.72±2.04
F13	0.736±0.07	0.888±0.02	17.11±0.13	1.20±0.03	24.14±2.68
F14	0.716±0.02	0.869±0.06	17.60±0.10	1.21±0.02	23.71±0.97
F15	0.713±0.01	0.873±0.03	18.32±0.16	1.22±0.02	24.05±2.65

All value represents mean ± SD (n=3)

Tablet thickness and diameter: The thickness of the tablets range from 3.41-3.66 mm respectively. The diameter of the tablet in the range of 5.97-6.03mm.There is no variation in tablet thickness and diameter between the formulations. The results are given in Table 4.

Hardness, friability and weight uniformity of tablets: The hardness of the tablets was within the range and optimum for burst release, and ranging from 7.4-8.2 Kg/cm^2 for all F1-F15 formulations. The friability of all formulations was ranging from 0.093-0.219 % w/w and passes as per IP limit should not be more than 1 % w/w. The weight uniformity of tablet in all formulation was observed to be within the IP limit 10 %. All formulations were complying with the official test. The values were mentioned in Table 4 and Table 5.

Drug content: The assays of all formulation from F1-F15 were found to be between 99.19-99.71 %. The result shows that all formulation containing drug were within the limit (99-101 %). The values were mentioned in Table 5.

Table 4: Evaluation of budesonide pulsatile release tablets (F1-F15)

Formulation code	Thickness in mm	Diameter in mm	Hardness in Kg/cm^2	Friability in % w/w
F1	3.63±0.01	6.03±0.02	7.6±0.04	0.120±0.03
F2	3.45±0.02	6.01±0.01	7.4±0.12	0.138±0.03
F3	3.56±0.01	6.00±0.03	7.7±0.06	0.098±0.03
F4	3.55±0.02	5.99±0.01	7.5±0.03	0.219±0.04
F5	3.41±0.02	5.98±0.01	7.9±0.11	0.154±0.06
F6	3.48±0.01	6.00±0.02	7.5±0.05	0.135±0.02
F7	3.57±0.03	6.03±0.03	8.0±0.04	0.103±0.04
F8	3.66±0.03	6.01±0.02	7.8±0.06	0.189±0.03
F9	3.61±0.02	6.02±0.01	7.4±0.12	0.141±0.04
F10	3.64±0.02	6.00±0.03	7.9±0.04	0.084±0.03
F11	3.43±0.03	5.99±0.02	7.8±0.09	0.093±0.03
F12	3.56±0.02	5.97±0.02	7.9±0.07	0.128±0.04
F13	3.51±0.01	5.99±0.02	8.1±0.06	0.138±0.02
F14	3.61±0.02	5.98±0.01	8.2±0.08	0.098±0.02
F15	3.49±0.01	5.98±0.03	8.0±0.12	0.104±0.04

All value represents mean ± SD (n=3)

Table 5: Evaluation of budesonide pulsatile release tablets (F1-F15)

Formulation code	Weight variation in mg	Drug content (%)
F1	179.20±1.75	99.31±0.03
F2	182.71±2.67	99.39±0.02
F3	185.32±2.52	99.49±0.02
F4	176.05±2.14	99.20±0.13
F5	179.02±1.93	99.27±0.03
F6	180.53±3.86	99.59±0.02
F7	176.78±2.02	99.24±0.04
F8	178.44±3.54	99.56±0.12
F9	180.05±2.82	99.39±0.13

F10	183.71±3.74	99.19±0.07
F11	185.40±2.53	99.52±0.11
F12	181.82±1.85	99.37±0.06
F13	175.73±1.25	99.43±0.06
F14	183.66±3.07	99.62±0.17
F15	184.91±1.18	99.71±0.06

All value represents mean ± SD (n=3)

***In vitro* drug release study of budesonide experimental trial batches**

In vitro drug release study was conducted in pH 1.2, 7.4 and 6.8 simulated to stomach, small intestine and colon respectively.

Table 6: % drug release of experimental trial batch F1-F8

Media	Time (min)	% Cumulative drug release							
		F1	F2	F3	F4	F5	F6	F7	F8
pH 1.2	0	0	0	0	0	0	0	0	0
	30	72.35	18.63	3.19	5.39	0.03	0	0	0
	60	77.60	37.63	12.30	11.07	0.17	0.014	0	0
	90		71.38	18.98	12.50	0.63	15.87	0	0
	120		84.88	41.54	37.01	0.94	39.20	0	0
pH 7.4	150			75.97	63.88	0.96	54.8	0	0
	180			91.74	69.64	1.39	62.25	0	0.28
	210				93.87	33.34	80.32	0.57	0.68
	240					86.43	93.79	0.94	1.43
	270					94.38		6.27	3.49
	300							47.57	23.96
pH 6.8	330							86.93	52.76
	360							93.28	77.81
	390								89.47
	420								

Table 7: % drug release of experimental trial batch F9-F15

Media	Time (min)	% Cumulative drug release						
		F9	F10	F11	F12	F13	F14	F15
pH 1.2	0	0	0	0	0	0	0	0
	30	0	0	0	0	0	0	0
	60	0	0	0	0	0	0	0
	90	0	0	0	0	0	0	0
	120	0	0	0	0	0	0	0
pH 7.4	150	0	0	0	0	0	0	0
	180	1.76	0.32	0	0	0	0	0
	210	4.89	0.92	0	0	0	0	0
	240	3.42	1.44	0.17	0	0	0	0
	270	23.91	5.48	1.97	0.40	0	0	0
	300	63.52	9.83	3.49	1.81	6.483	2.27	2.277
pH 6.8	330	93.47	56.39	93.98	26.18	94.38	8.32	19.757

	360		92.68		91.74		93.79	86.936
	390							93.283
	420							

Accelerated stability study

Budesonide optimized formulation F11 was found to be stable during accelerated stability studies for drug content 99.52, 99.46, 99.32 and 99.27% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. *In vitro* drug release studied and found to be 93.98, 93.18, 93.09 and 91.25% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. Results obtained were shown in Table 8. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months. It may be inferred that there was no degradation of physical properties and change in the matrix system of the formulation.

Table 8: Results of Accelerated stability study of optimized formulations

	Optimized formulation	
	Drug content (%)	**% drug release**
Initial	99.52	93.98
One month		
Ambient	99.50	93.29
40^0c / 75%RH	99.46	93.18
Two month		
Ambient	99.41	93.14
40^0c / 75%RH	99.32	93.09
Three month		
Ambient	99.39	91.89
40^0c / 75%RH	99.27	91.25

CONCLUSION

UC and CD are two features of IBD. They are recognized by chronic relapsing inflammation in the whole GI tract from mouth to anus, but are two distinct entities. Recently researchers have shown an increased interest in investigating the effect of different anti-inflammatory drugs used for the treatment of IBD. Hence budesonide a first line therapy drug for long term treatment of CD and for effective short term remedy to treat UC, was selected in this research work.

In the formulation after budesonide mixed with crospovidone in order to bring rupture of the outer functional Eudragit L30D coat. When crosspovidone comes in contact of aqueous medium in GIT get swelled due to absorbing water, creates pressure thus leads to rupturing of

outer coat. It was observed that the process parameters and solution composition used in Eudragit L30D coating worked with good efficiency. Increasing level of crosspovidone creats more pressure over outer Eudragit L30D coat due to its wicking and swelling ability of disintegrant is best utilized and thus releases drug immediately by rupturing the outer membrane. Which confirms that the formulation have ability to target drug release in ileo caecal region.

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