CHINESE JOURNAL OF MEDICAL GENETICS
ISSN: 1003-9406 Vol. 31 Iss. 3 2022

DEVELOPMENT OF DUAL MATRIX BASED COLON TARGETED DELAYED RELEASE BUDESONIDE TABLETS FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASES

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ABSTRACT

Current work was aimed to develop and assess colon-targeted delayed release dual matrix formulations and microcapsules of anti-inflammatory drugs Budesonide and Mesalamine as a novel avenue for the treatment of inflammatory bowel diseases. Eight different dual matrix core tablet formulations (B1-B8) containing 9 mg of Budesonide were prepared using different concentration of Eudragit® L100, PolyoxTM WSR303 and Carbopol® 971 based on factorial design with three factors and two levels (23). Coating the prepared matrix core was done with a 10% w/w Eudragit® L30D solution. The developed formulations were tested for product attributes like weight variation, thickness/ hardness, percent friability, content-uniformity, swelling index, mucoadhesion strength, and in-vitro drug dissolution in dissolution media simulating gastrointestinal conditions. Studies of the stability and in-vitro release kinetics of the tablets were also conducted.

IR spectral analysis shows that a drug and polymer physical mixture was safe and did not react chemically with one another. All Budesonide tablet formulations (B1–B8) with a dual matrix had pre-compression values that were within the allowed range. Tablet thickness, weight fluctuation, friability, and content uniformity were all within acceptable ranges after compression, as defined by the Pharmacopeia. Formulation B5 (100 mg of Eudragit® L100 and 120 mg of PolyoxTM WSR303 was shown to have the highest tablet swelling index and mucoadhesive strength. Stability experiments confirmed that formulation B5 was stable and that it provided the best in-vitro drug release.

Keywords: Dual matrix tablets; Targeted drug delivery system; Inflammatory bowel disease; Roentgenographic study

INTRODUCTION

Oral dosage forms are the most popular choice for patients because of their versatility, accessibility of consumption, high patient compliance, and lack of sterility restrictions.1,2 When a drug is administered orally, it gets absorbed into the body after dissolving in stomach or intestinal fluid. When drugs need to be administered locally in the colon, or when they need to be shielded from the stomach and duodenum, the limitations of the typical oral dose form become apparent.3

Management of colon diseases like ulcerative colitis, Crohn's disease and irritable bowel syndrome often relies on oral delivery of drugs directly to the colon, as this provides high local

concentration while minimizing side effects caused by drug release in the upper GIT or unnecessary systemic absorption.2,3 Colonic administration may also be used for various purposes, such as chronotherapy, colon cancer prevention, and nicotine addiction therapy. It has also acquired prominence as a potential venue for the systemic distribution of curative proteins and peptides that are rendered inactive by gastric circumstances, in addition to its role as a delivery mechanism for drugs used to treat local ailments.

Drug targeting, in particular colon targeting, is being explored from many different angles. Microbially driven drug release, pH-dependent polymer coating, and redox-sensitive polymer timed-release dosage forms are some of the examples that target drug delivery to colon. Among the different methods of drug targeting the colon, coating the formulation with pH-dependent polymers is the most common. The pH changes that occur from the stomach to the colon motivate the usage of polymers that are pH-dependent. After eating, the stomach's pH rises to 1–2, the proximal small intestine's is 6.5–7.5, and the distal is 5.5–8.5.In the transition from the ileum to the colon, the pH level drops dramatically. pH in the ascending colon is 7.0, while it is 6.6 in the transverse colon4.

When it comes to colon-targeted drug administration, the pH-dependent polymers described as insoluble at low pH become progressively soluble at higher pH. While a pH dependent polymeric system shields the drug from stomach and first part of the small intestine; it may degrade in its inferior part. For colon-targeted formulations, Eudragits especially Eudragit® L & S are the polymers of choice because of their anionic nature and resistance to water at low pH. Both Eudragit® L100 and S100 have carboxyl-to-ester ratios close to 1:1. In an alkaline environment, polymers are converted into salts. Copolymers of methacrylic acid and methyl methacrylate, Eudragit® L100 and S100 are commercially available. A copolymer of methacrylic acid and ethyl acrylate, Eudragit® L100-55 has a carboxyl-to-ester ratio of 1:1 and dissolves at pH greater than 5.5. This polymer can be used as a coating without the need for organic solvents because it disperses in water to produce latex. The aqueous dispersion known as Eudragit® L 30D-55 is composed of the methacrylic acid copolymer Eudragit® L100, S100, & L100-55, which are all listed in USP/NF 23 as methacrylic acid copolymer A, B, & C respectively. Carbopol can potentially be used as a supplemental strategy for colon targeting. When the drug is granulated with Carbopol, the resulting tablets have a semi-permeable membrane that lets water in. Carbopol starts to swell at about a neutral pH (colon pH), causing the coating to burst and the drug to be released.

The anti-inflammatory properties of budesonide, a synthetic non-halogenated corticosteroid, are most noticeable when used topically, whereas its systemic effects are minimal. Budesonide is a popular option for treating colon disease because of low incidence of adverse effects from corticosteroids and high topical effect. Budesonide is used to treat Crohn's disease, and it is currently available in a variety of different forms, such as enemas and controlled-release capsules. Budesonide, included within Entocort® capsules, is released almost immediately after oral administration and is absorbed more rapidly and at more distal places in the small intestine than Budenofalk®. Another pH-dependent controlled-release capsule version of Budesonide is

available under the brand name Budenofalk®. Budenofalk® has the potential to transport more Budesonide to the terminal ileum than Entocort®, and it also has a slightly larger systemic exposure. Drugs for ulcerative colitis don't seem to get to the distal colon and rectum well enough from these formulations. Drugs for various diseased conditions of the colon are extra effectual when given directly to the affected area.

Chronic inflammatory disorders of the small intestine embrace ulcerative colitis and Crohn's disease. One therapy tactic for these conditions is administering the drug directly to inflammatory target. Thus, it was postulated that Budesonide and Mesalamine administered via colon-targeted extended-release drug delivery systems could aid to treat such diseases and disorders. As a result of the foregoing, it was decided to prepare and assess colon-targeted extended-release dual matrix tablets containing Budesonide and Mesalamine employing polymers such as Eudragit® L100, Eudragit® S100, Eudragit® RL-30D, PolyoxTM WSR303, Carbopol® 971 etc.

MATERIAL AND METHODS

Chemicals

Budesonide was obtained from Cipla Ltd, Goa, Eudragit® S100, Eudragit® L100 were obtained from Evonik India, Mumbai, Eudragit® L 30D and PolyoxTM WSR303 from Dr Reddys Lab, Hyderabad, Carbopol® 971 and Avicel PH-101 from Wockhardt Pharma, Aurangabad while Aerosil 200 was obtained from Flamingo Pharma, Nanded.

Animals

The tablets were put through a Roentgenographic investigation using healthy New Zealand white rabbits weighing 2-2.5 kg. Shelters for the animals were standard environmental conditions with no prior drug treatment and provided with a regular rodent feed and free access to water. Committee for the Ethical Treatment of Animals in Research Institutions (IAEC) permission letter 484/F-34/2017-18 attests to the experiment's compliance with the CPCSEA criteria for the control and supervision of experiments involving animals.

Study of Drug-Excipient Compatibility

Each sample of the powder mixture was prepared in a separate, sterile mortar and pestle to ensure a consistent consistency. These samples were placed in amber glass vials with polypropylene closures and subjected to ICH accelerated stability conditions for four weeks at temperature of 40°C and humidity levels of 75%RH. Fourier transform infrared spectroscopy was utilized to determine if there were any interactions or incompatibilities after visual inspection of the samples for physical changes.

Samples were packed in a 10 ml sample amber glass vials for interaction studies as per specifications given in table 1.

Table 1: Sample specifications for drug-excipient interaction studies

Condition	Pack	Orientation	Sample Quantity/Station
40°C/75% RH	With perforated Lid	Upright	3 Glass Bottles

	With Closed Lid		3 Glass Bottles
25°C/60% RH	With perforated Lid	Upright	3 Glass Bottles
	With Closed Lid		3 Glass Bottles

Design of Experiments for Optimization of dual matrix tablets

Prototype trials suggest that formulations made up of the desired drug release profile may be impossible to achieve with just one polymer. To achieve this goal, it was decided to use varying concentrations of the polymers Eudragit® L100, PolyoxTM WSR303, and Carbopol® 971 in the core matrix tablets. Minitab-18® software was used to examine the relationship between the independent variable (the concentration of Eudragit® L100, PolyoxTM WSR303, and Carbopol® 971) and the dependent factors (the swelling characteristics, mucoadhesion, and the percentage of drug release).

Table 2: Combinations for trial batches

Batch	**Eudragit® L100** (mg)	**Polyox™ WSR303** (mg)	**Carbopol® 971** (mg)
B1	80	120	30
B2	100	100	25
B3	100	120	25
B4	80	100	25
B5	100	120	30
B6	100	100	30
B7	80	120	25
B8	80	100	30

To find the optimal dosage of Budesonide for the dual matrix core tablets, a 23-level full factorial design with three components was employed. Optimal dissolution profiles of core matrix tablets were sought by selecting varying concentrations of the Eudragit® L100 (X1), PolyoxTM WSR303 (X2), and Carbopol® 971 (X3) polymers as independent variables or factors. Each polymer was studied at two different levels of concentrations and trials were conducted to understand the response all possible eight combinations. Following factorial regression equation was used for this purpose;

$$y = \beta_o + \beta_1 X1 + \beta_2 X2 + \beta_3 X3 + \beta_4 X1X2 + \beta_5 X1X3 + \beta_6 X2X3 + \beta_7 X1X2X3$$

Equation 1: Factorial Regression Equation

Where Y represents the dependent variable, β0 represents geometric mean of the response, and β1 through β7 represent the estimated coefficients for X1, X2, and X3, respectively. The average impact of shifting each variable from its minimum to maximum value is represented by the primary effects (X1, X2, and X3). A response's sensitivity to simultaneous changes in two or more independent variables is revealed by the interaction effects (X1X2, X1X3, X2X3, and X1X2X3). The potential non-linearity of the polynomial terms (X1, X2, and X3) was explored.

Total eight Formulations (B1-B8) of delayed release matrix tablets of Budesonide were prepared through combination of a hydrophilic polymer (PolyoxTM WSR303), a mucoadhesive polymer (Carbopol® 971) and a hydrophobic pH dependent polymer (Eudragit® L100) using Avicel® PH101 as diluent. The composition of optimization batches of Budesonide dual matrix tablet core is represented in Table 3.

Table 3: Composition of optimization batches of Budesonide dual matrix tablet core

Ingredients	Formulations							
(Quantity in mg)	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**
Budesonide	9	9	9	9	9	9	9	9
Eudragit® L100	80	100	100	80	100	100	80	80
Polyox™ WSR303	120	100	120	100	120	100	120	100
Carbopol® 971	30	25	25	25	30	30	25	30
Avicel® PH101	85	90	70	110	65	85	90	105
Magnesium Stearate	6	6	6	6	6	6	6	6
Total Weight (mg)	330	330	330	330	330	330	330	330

Budesonide and excipients were accurately weighed for a batch of 100 tablets. Weights equivalent to 330 mg per tablets were taken as per table 3. Budesonide, Polyox™ WSR303, Eudragit® L100, Carbopol® 971 and Avicel PH101 were screened through # 20 sieve while Magnesium stearate was passed through # 60 sieve. Tablet compression was completed by using 12-station Karnavati Rimek Minipress MT-II compression machine.

Blending and lubrication of formulation composition

All sifted ingredients were loaded in Hugopharm Uniblender double cone blender of 2 liter capacity with below sequence; Drug Premix-I, Polyox™ WSR 303, Eudragit® L100, Carbopol® 971. All the above ingredients were mixed for 15 minutes at 24 RPM in double cone blender to get Drug Premix-II. Magnesium stearate was sifted through #60 sieve separately & mixed into Drug Premix-II blend and lubrication was performed for 5 minutes at 24 RPM in double cone blender (Final Blend). Finally the lubricated blend was collected in aluminum bags and sealed.

Evaluation of Pre-Compression Parameters

The prepared powder mixture was subjected to evaluation precompression parameters such as bulk density, tapped density, Carr's index, Hausner ratio and angle of repose as per previously published protocol5,6.

Compression Core Matrix Tablets

Compression of the lubricated blend was done using Karnavati Rimek Minipress MT-II compression machine, fitted with B tooling, round shaped, flat with bevel edge, no embossing punches and round shaped dies. The compressed core matrix tablets were evaluated for weight variation, thickness, hardness and friability as per previously published protocols. The tablets were also evaluated for content of active ingredients, assay of tablet blend, and drug content in tablets.

Coating of core matrix tablets

Ganson coater of 1 kg capacity was used to apply a coating of Eudragit® L30D aqueous dispersion to the compressed matrix tablets. Using a stainless steel container, the necessary amount of distilled water was mixed with commercially available Eudragit® L30D to create suspensions of the acrylic polymer coatings at a concentration of 10%w/w. The filtered water was whirled into a vortex using a mechanical stirrer. To prevent clumping and keep the vortex going, a slow, continuous stream of Eudragit® L30D dispersion was poured into its core. After adding the coating ingredient, the stirrer speed was slowed to prevent a vortex from forming. This vortex was then homogenized in water for 10 minutes while 6% w/w Triethyl citrate (a plasticizer) and 30%w/w talc (an anti-caking agent) were added. Mixing was continued for 45 min. Finally the slurry was passed through 0.5 mm filter.

Tablets were added to the Ganson coater and pre-warming process parameters were adjusted as per preset conditions. For film coating the inlet temperature was adjusted to 40°C±10 while the bed temperature was adjusted to 25°C±5. The coating dispersion was sprayed at the rate of 1.5 – 2 ml/min at 1.5 bar air pressure. The coating was done using the coating dispersion to achieve a target weight gain of 15-20 % w/w. Coated tablets were dried for 20 min using below mentioned parameters. After completion of drying process, cooled and then unload in aluminum bags and kept in air-tight bottles.

Determination of Assay of Tablet7

A random sample of ten tablets was selected, crushed, and weighed. Before being filtered using Whatman filter paper, the drug was sonicated for 15 minutes in phosphate buffer at a pH of 6.8. Using a Systronics UV Spectrophotometer 2102 set to a wavelength of 246 nm, filtered, appropriately diluted solutions were analyzed. Concentration of Budesonide was determined by measuring its absorbance.

Drug Content in Tablets8

An individual tablet was dissolved in 100 ml of phosphate buffer, pH 6.8, and sonicated for 15 minutes to assess the drug concentration of the matrix tablet. The concentration of Budesonide in a phosphate buffer in pH 6.8 buffer was measured using Systronics UV-VIS spectrophotometer 2102 to 246 nm after filtering through Whatman filter paper (0.45µm).

Determination of Swelling Index9

Each batch had one tablet sampled and weighed before being transferred to 10 ml buffer solution in a petri dish. Every two Hr, a tablet was taken out of its plate, filtered to eliminate excess buffer, and weighed again. This was done for 12 Hr. Following formula was used to determine the swelling index.

$$\boldsymbol{Swelling\ Index} = \frac{(\boldsymbol{W_t} - \boldsymbol{W_0})}{\boldsymbol{W_0}} \times \mathbf{100}$$

Where Wt = Weight of tablet at time t and Wo = Weight of tablet before placing in the petri plate.

Determination of Mucoadhesive Strength10

The wash-off method of in-vitro adhesion testing was used to analyze the mucoadhesive characteristics of the final formulations. The intestinal mucosa from sheep was cut into little pieces

and put on glass slides with the right kind of backing. Intestinal mucosa was knotted and draped over the apparatus's tissue holder; the tissue membrane was then covered with a lid, revealing only the aperture. A magnetic stirrer was attached to the accessory's base, and the whole thing was placed in pH 6.8 buffer at 37°C in a beaker. The probe was taped to the instrument's shaft, and the tablet was taped to the probe. The probe's aperture was aligned with the tissue membrane surface by lowering the instrument arm. After exerting 50 gm of power for five seconds, the probe was removed. The force required to separate the tablet from the membrane was measured. The obtained values were multiplied by 0.0098 to get the result in newton unit.

$$Mucoadhesive\ Force\ (N)\ =\ mucoadhesive\ strength\ (gm)\ x\ 0.0098$$

Equation 2: Formula for calculation of Mucoadhesive strength

Following formula was used:

$$\%\ \boldsymbol{Mucoadhesion} = \frac{(\boldsymbol{Ws} - \boldsymbol{Wp})}{\boldsymbol{Ws}} \times \mathbf{100}$$

Equation 3: Formula for calculation of Percent Mucoadhesion

Where, Ws = Weight of added sample & Wp = Weight of detached particles

In-vitro Drug Release Studies11

The coated Budesonide tablets' release was measured by rotating them at 50 RPM in a basket at 37±0.5°C in a USP XXIII tablet dissolution test apparatus-II (Electrolab). The release research was conducted in 250 ml HCl buffer pH 1.2 for 2 Hr, followed by 250 ml PBS pH 6.8 for 3 Hr, and finally 250 ml PBS pH 7.4 till the conclusion of the study. At each time point up to 12 Hr, one ml of the dissolution medium was removed and replenished. The removed portion was filtered over a 0.45 µm membrane, the collected media was then subjected to spectrophotometric analysis at 246 nm.

Evaluation of In-vitro Kinetics of Prototype Core Matrix Tablets

Budesonide dual matrix tablet dissolution was analyzed using well-known drug release kinetic methods like Zero-order, First-order, Higuchi, Peppas and erosion equation models. The kinetics of drug dissolution from core matrix tablets was explained by zero-order or first-orders kinetics. Higuchi and Peppas models were used to explain the drug release mechanism of core matrix tablets by erosion. The dissolution times of 30%, 50%, and 80% of Budesonide in dual matrix tablets were investigated.

Statistical Approaches for Optimization of Core Matrix Tablets

Budesonide core matrix tablet dissolution profiles were investigated as a function of selected parameters, including Eudragit® L100, PolyoxTM WSR303, and Carbopol® 971 concentrations, with the 30 minute drug release (D30) and 90% drug release (T90%) as the important responses. D30 drug release was used as a measure of when formulation release actually began and as a control for dose dumping during the onset of drug release. As a countermeasure to guarantee the complete and significant release of the Budesonide from the matrix core tablets, T90% was chosen.

Results from design of experiments studies show that the time to 90% drug release and the percentage of Budesonide released after 30 minutes were very sensitive to the formulation factors chosen.

Stability studies of tablets

In order to assess the physicochemical stability with regards to assay and dissolution profiles over the course of the three-month period, stability tests were undertaken on the optimized formulation at accelerated stability conditions (40°C±2°C and 75% RH±5%).

In-vivo Roentgenographic study of Budesonide tablets

The study utilized normal white New Zealand, 2 to 2.5 kg rabbit. To locate the dual matrix tablet in the GIT, a radio-opaque substance called barium sulphate was added to one tablet from the optimized batch B5. The rabbit participated in a 12 Hr fast prior to the trial and was given access to purified water throughout. Test formulation was given orally via feeding tube. The X-ray images of the dual matrix tablet in the GIT were recorded at 1, 3, 5, 7, 9, 11, and 15 Hr to check on its form, integrity, and location.12

RESULT AND DISCUSSION

It was observed that there was no change in physical characteristics of drug and excipients blend, indicating that the excipients selected for the formulation were compatible with Budesonide. From the drug excipients compatibility study by IR, there was no characteristic change or interaction between the Budesonide and the excipients. The prominent peaks of Budesonide are also visible in the FTIR spectra of physical mixtures that contain other excipients in the final formula. As a result, it was determined that the polymers chosen for the formulation were compatible with Budesonide. The spectrum of Budesonide, physical mixture of formulations with and without Budesonide, is shown in Figure 1.

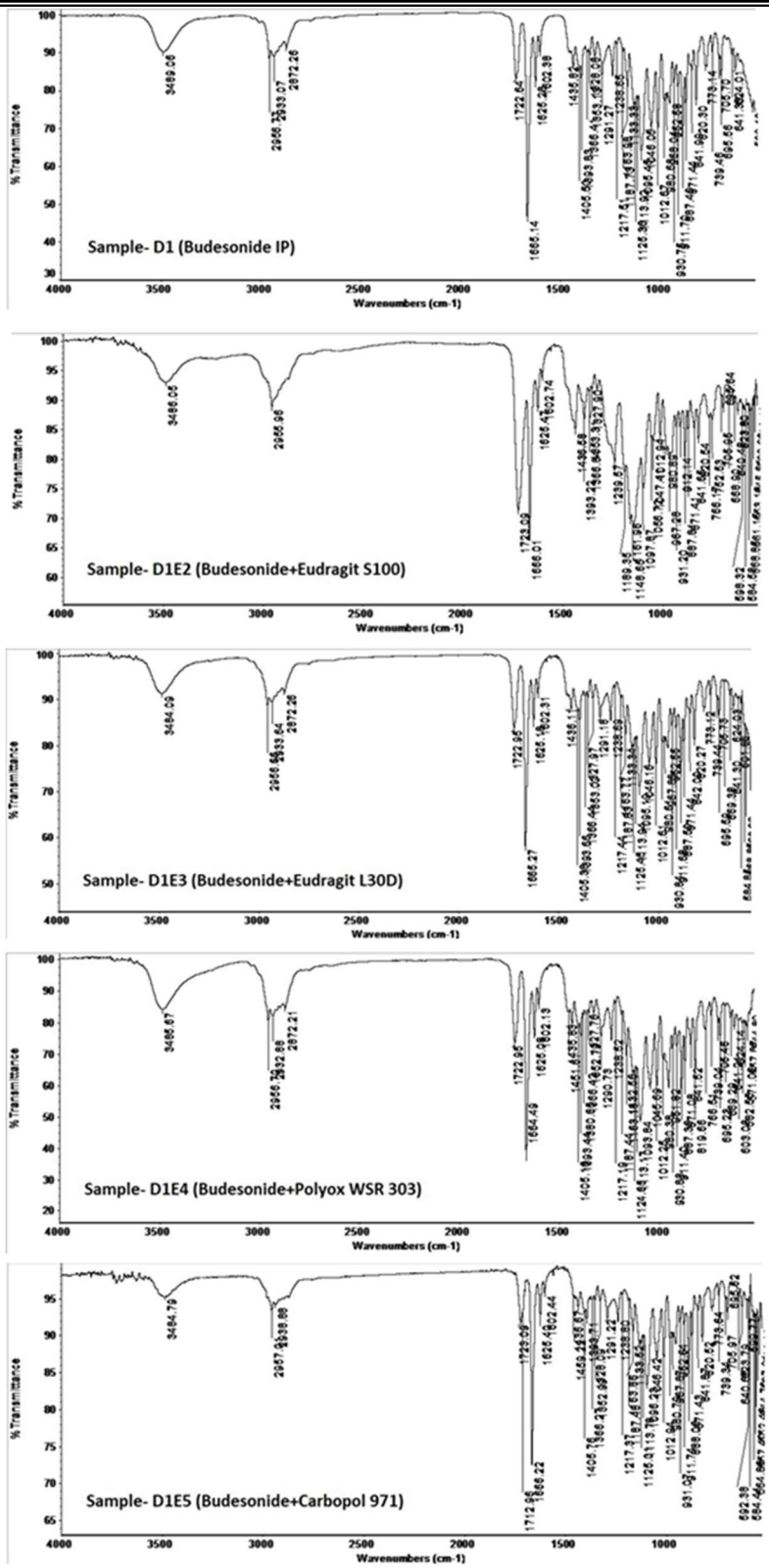

Figure 1: IR spectra of Budesonide and the blend og polymers

All of the formulations had a loose bulk density between 0.43 and 0.49 gm/cm3 and a tapped bulk density between 0.56 and 0.64 gm/cm3. The results obtained were reasonable, with little distinction between the loose and tapped bulk densities. The outcomes of this research may have further effects on properties like compressibility and tablet dissolution. Table 4 displays the important micromeritic features of the powder blend. Use of Carr's compressibility index yielded the displayed percentage of powder mix compressibility. All of the formulations have Hausner's ratios and % compressibilities that fall between 1.27-1.37 and 12.33-17.12 respectively. The compressibility and flow properties of all the formulations were satisfactory. All of the formulations had angle of repose values between 24.51° and 32.42°, suggesting good flow qualities; the lower compressibility index values corroborated this.

Table 4: Pre-compression parameters of blend of Budesonide

Batches	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (Deg.)
B1	0.46±0.01	0.63±0.01	17.12±0.21	1.37±0.05	24.51±0.02
B2	0.45±0.01	0.58±0.01	13.12±0.05	1.29±0.02	25.39±0.03
B3	0.48±0.00	0.62±0.01	14.90±0.13	1.29±0.02	24.73±0.02
B4	0.46±0.01	0.59±0.02	13.43±0.21	1.28±0.05	26.15±0.02
B5	0.49±0.01	0.64±0.02	15.31±0.03	1.31±0.05	27.38±0.06
B6	0.44±0.01	0.56±0.01	12.33±0.16	1.27±0.02	24.61±0.03
B7	0.46±0.01	0.60±0.02	14.61±0.15	1.30±0.04	32.42±0.02
B8	0.43±0.01	0.56±0.02	13.39±0.20	1.30±0.04	26.67±0.02

(All values represent mean ± Standard Deviations, n=3)

The percent weight gain of tablets after coating was found to be in the range between 114.59 to 119.48%. Lowest gain was of 14.59% was found in batch B2 and highest gain of 19.48% was found in batch B4.

Thickness, hardness, weight variation, drug content, and friability were among the characteristics tested for tablets from formulations B1 to B8. All batches' tablets were found to be the same concave circular shape and white yellowish tint upon physical inspection. Coated tablets ranged in thickness from 4.37 mm to 4.64 mm, whereas uncoated tablets were between 4.60 mm and 4.80 mm thick. Tablets weighing 330 mg must fall within the Pharmacopeia-required tolerance for percentage of weight deviation (±5%). All tablet formulations were considered to be acceptable due to the fact that their average percent deviation is below the threshold for failure. All tablet formulations had a hardness of between 5.35 and 6.07 kg/cm2. Variation in tablet friability across formulations was between 0.22% and 0.43%.

Table 5: Evaluation and characterization of optimization batches

Batch	Thickness (mm)		Hardness (kg/cm^2) (n=6)		Weight Variation (mg, n=20)	Friability (%)	Weight Variation of coated tablets (mg) (n=20)
	Uncoated Tablets	Coated Tablets	Uncoated Tablets	Coated Tablets			

B1	4.60 ± 0.029	4.75 ± 0.029	5.85±0.05	5.85±0.05	336.33±3.21	0.43±0.032	390.33±3.43
B2	4.58 ± 0.069	4.71 ± 0.069	5.92±0.12	5.53±0.12	336.01±4.58	0.39±0.026	385.03±4.78
B3	4.64 ± 0.043	4.80 ± 0.043	5.35±0.10	5.35±0.10	332.66±4.21	0.33±0.043	389.67±4.71
B4	4.37 ± 0.024	4.60 ± 0.024	6.05±0.12	5.71±0.12	333.66±3.16	0.31±0.012	398.66±4.89
B5	4.56 ± 0.025	4.76 ± 0.025	5.58±0.07	5.78±0.07	331.66±4.72	0.33±0.035	393.66±4.32
B6	4.61 ± 0.044	4.77 ± 0.044	5.36±0.09	5.36±0.09	330.04±3.05	0.22±0.028	392.04±4.25
B7	4.55 ± 0.015	4.73 ± 0.015	5.97±0.08	5.97±0.08	334.07±3.00	0.25±0.030	387.07±3.09
B8	4.52 ± 0.037	4.68 ± 0.037	6.07±0.07	6.05±0.07	335.33±4.03	0.32±0.028	391.33±5.13

(All the values represent mean ± Standard Deviation)

The percentage purity of formulation blend was found to be in the range of 92.71 to 101.01 and of tablet is 90.39 to 98.86 and is shown in table 6.

Table 6: Drug content / Assay

Batch	Assay (%Purity)	
	% Purity of Blend	% Purity of Tablets
B1	97.60±0.27	98.30±0.15
B2	94.00±0.10	93.99±0.33
B3	94.00±0.66	95.32±0.31
B4	95.37±0.13	94.81±0.10
B5	101.01±0.18	98.86±0.12
B6	98.69±0.29	97.46±0.45
B7	93.99±0.12	93.61±0.22
B8	92.71±0.39	90.39±0.50

(N = 3, Values are expressed in Mean ± SD)

Modified physical balance was used to study in-vitro swelling index and mucoadhesive strength. Result of mucoadhesion parameters are given in table 7. The mucoadhesion and swelling characteristics are affected by the type of polymer used and by the ratio of different polymer used in different formulation. The mucoadhesiveness was established at highest in case of formulation B5 i.e. 98%. The quantities of PolyoxTM WSR and Carbopol® in formulation B5 showed good mucoadhesivity and were considered here as optimum. PolyoxTM, a hydrophilic polymer formed slow dissolving bioadhesive matrix in combination Carbopol.13 These formulations showed maximum mucoadhesivity.14 Polyox has synergistically increased mucoadhesion when used with Carbopol®.

Table 7: Evaluation of Swelling Index and Mucoadhesive Strength

Batch	Swelling Index (%)	Mucoadhesion (%)	Mucoadhesive Strength (gm)	Mucoadhesive Force (N)
B1	175±2.34	97±1.23	19.32±0.25	0.189±0.002
B2	115±3.24	95±2.11	14.91±0.42	0.146±0.004
B3	145±2.34	97±2.66	20.52±0.53	0.201±0.005

B4	147±4.76	94±3.12	13.15±0.62	0.129±0.006
B5	177±2.33	98±2.33	21.22±0.47	0.208±0.005
B6	165±2.14	96±1.78	16.23±0.36	0.159±0.003
B7	147±2.90	96±3.44	18.52±0.69	0.181±0.007
B8	167±3.76	92±2.39	11.77±0.48	0.115±0.005

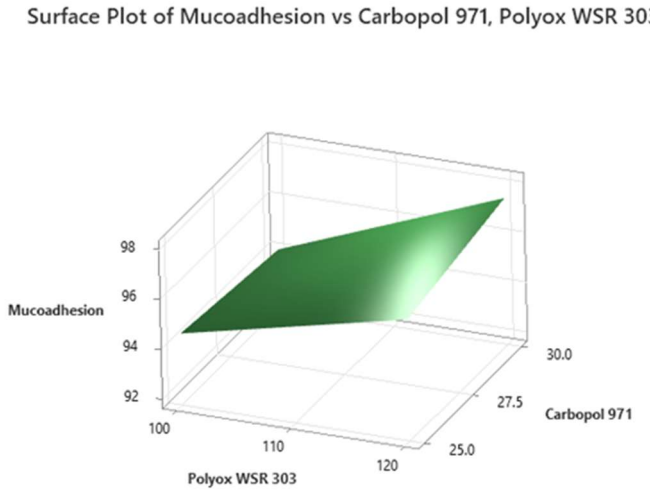

Figure 2: Surface plot of influence of polymers on Mucoadhesion

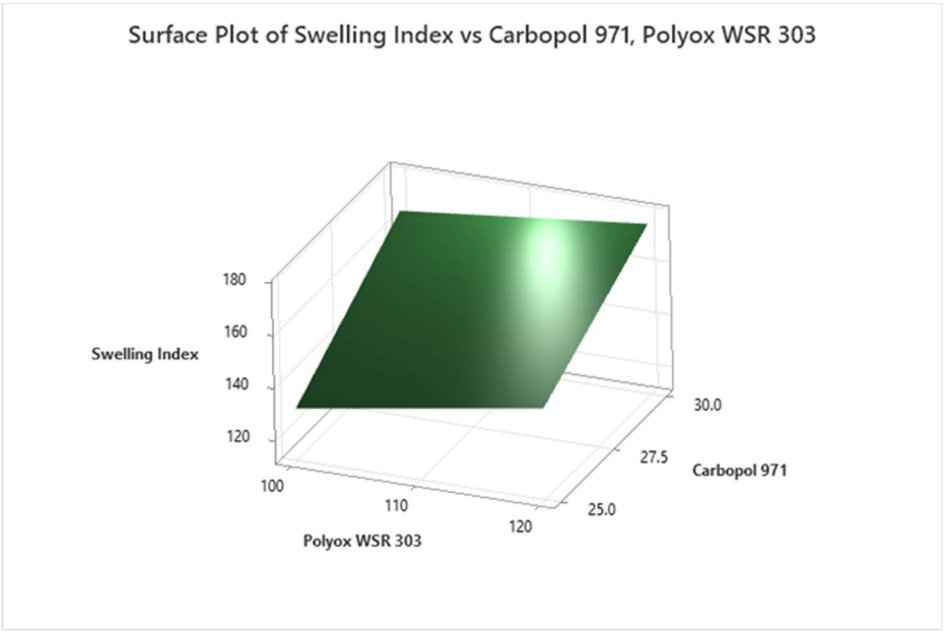

Figure 3: Surface plot of influence of polymers on Swelling index

Table 8: % Release from coated matrix in 0.1 N HCl and 6.8 pH Phosphate buffer

Batch	In 0.1 N HCl for 2 Hr	In pH 6.8 for 3 Hr
B1	1.17±0.02	9.17±0.01
B2	1.61±0.01	8.51±0.02

B3	1.04±0.03	7.26±0.01
B4	0.91±0.02	3.82±0.01
B5	0.80±0.02	5.74±0.01
B6	0.87±0.02	6.12±0.02
B7	1.23±0.02	8.10±0.02
B8	1.29±0.02	7.11±0.01

(All values represent mean ± Standard Deviations, n=3)

Table 9: In-Vitro Dissolution Data of Uncoated Formulations in pH 7.4 for 3 h and pH 6.8 till end of study

Time (h)	Percentage Cumulative Drug Release (%)							
	B1	**B2**	**B3**	**B4**	**B5**	**B6**	**B7**	**B8**
0.5	2.43±0.02	2.29±0.02	1.23±0.02	1.03±0.02	1.07±0.02	3.25±0.02	1.6±0.02	1.83±0.01
1	4.01±0.01	3.56±0.01	2.91±0.01	3.44±0.01	3.21±0.01	6.13±0.01	5.43±0.01	3.49±0.02
1.5	5.67±0.02	6.78±0.02	4.97±0.02	5.67±0.02	7.63±0.02	8.74±0.02	8.804±0.02	10.09±0.03
2	8.43±0.03	9.09±0.03	7.45±0.03	7.99±0.03	11.13±0.02	12.06±0.02	12.74±0.03	16.76±0.02
3.5	10.23±0.02	15.32±0.02	15.15±0.02	12.23±0.02	25.97±0.02	19.52±0.03	36.82±0.02	39.76±0.01
5	19.07±0.01	21.21±0.01	29.76±0.01	20.65±0.01	38.18±0.01	32.82±0.01	45.24±0.02	52.21±0.02
7	42.77±0.01	42.13±0.01	45.98±0.01	56.27±0.01	51.24±0.02	41.83±0.02	62.19±0.01	64.31±0.02
12	77.21±0.01	79.9±0.01	83.09±0.01	69.12±0.01	88.22±0.02	78.83±0.01	74.43±0.03	71.65±0.02

(All values represent mean ± Standard Deviations, n=3, p ≤0.005)

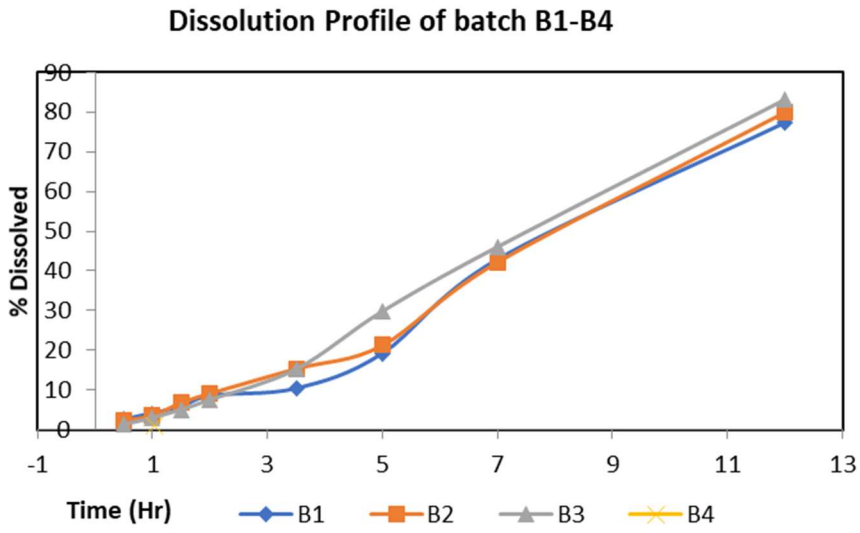

Figure 4: Dissolution profile of batches B1-B4

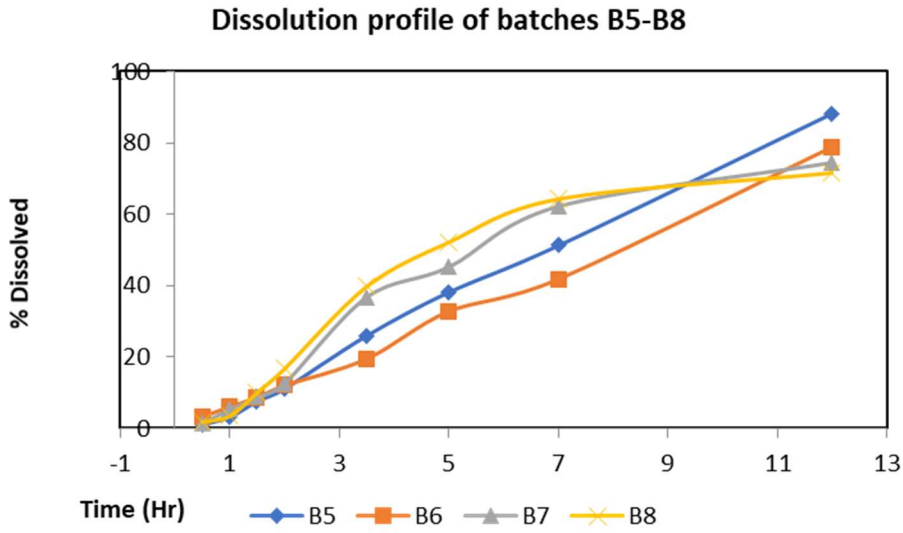

Figure 5: Dissolution profile of batches B5-B8

The influence of formulation variables on the chosen responses was analyzed using statistical tools such as Response Surface Methodology to arrive at optimum concentration levels of Eudragit® L100, PolyoxTM WSR303 and Carbopol® 971 using Minitab® 18 software for the statistical analysis and to perform the interpretation of effect of the formulation variables. The in-Vitro dissolution data of uncoated formulations in pH 7.4 for 3 h and pH 6.8 till end of study is shown in Table 8 while the otpimization of drug delivery is shown in Table 9.

Table 10: Optimization of drug release

Batch	DE (%)	T_{30} (min)	T_{50} (min)	T_{80} (min)
B1	77.21±0.01	194	327	527
B2	79.9±0.01	198	333	535
B3	83.09±0.01	213	359	579

B4	69.12±0.01	189	318	511
B5	88.22±0.02	228	383	614
B6	78.83±0.01	195	326	521
B7	74.43±0.03	209	345	551
B8	71.65±0.02	206	340	540

The Roentgenographic study showed that the tablet remained intact in the stomach and small intestine. The X-ray photographs were taken at 2 Hr and 4 Hr of post-administration showed intact of tablet thereafter slowly intactness was reduced and appeared in colon as in swollen state at 12 Hr interval. The complete disappearance of the tablet was seen at 15 Hr intervals that indicate degradation of the tablet. In-vivo roentgenographic study photographs are shown in Figure 6. So, the results of in-vitro and roentgenographic studies revealed that formulation containing matrix of Eudragit® L100, PolyoxTM WSR303 and Carbopol® 971 and coated with Eudragit® L30D was found to be a promising carrier for Budesonide to colon.

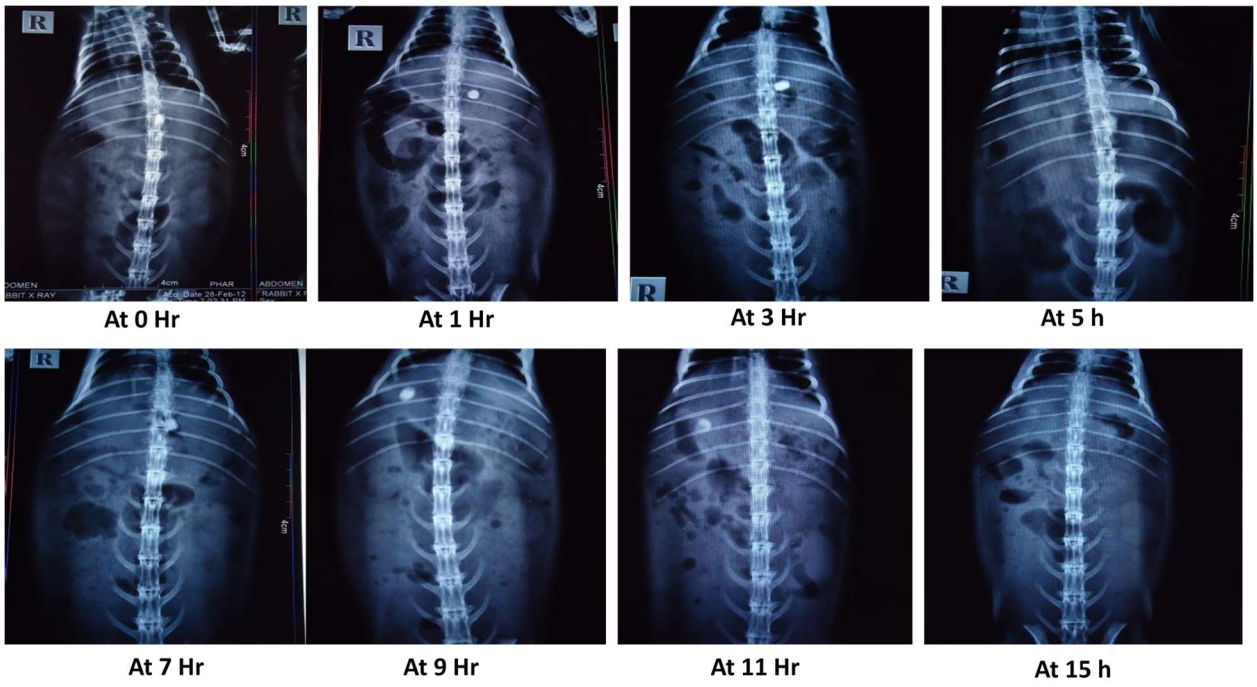

Figure 6: Observations for Roentgenographic study of Budesonide tablets

Table 10: Composition of optimized formulation

Ingredients	mg/Tablet	% w/w
Core		
Budesonide	9.0	2.73
Eudragit® L100	100.0	30.30
Microcrystalline Cellulose (Avicel® PH101)	70.0	21.21
Polyox™ WSR 303	120.0	36.36
Carbopol® 971	25.0	7.58
Magnesium Stearate	6.0	1.82
Core Tablet Weight	**330.0**	**100.0**
Film Coat$		
Eudragit® RL 30D	60.00	18

Purified water	q.s.	q.s
Total Weight of Film Coated Tablet	**390.00**	**100.00**

CONCLUSION

The prepared tablets met the compendia limits in terms of physiochemical parameters and dissolution studies. The tablet prepared from Eudragit® L100 (100 mg), Polyox™ WSR303 (120 mg), Carbopol®9 71 (30 mg) and Avicel® PH101 were best suitable in colon targeted drug delivery system to provide optimum Budesonide release and protect it from SGF and SIF. As a result, colon delivery of Budesonide appeared to be a promising alternative to its traditional oral formulation.

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