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Der Pharmacia Lettre, 2013, 5 (3):1-12
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Formulation and evaluation of oral colon targeted tablet of budesonide

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ABSTRACT

Colon targeted tablets of budesonide were prepared using pectin, guar gum as enzyme dependent polymers along with HPMC, HEC as time dependent polymers followed by pH dependent polymers like Eudragit S100 and Cellulose acetate phthalate. Fast dissolving core tablet of budesonide was prepared by using CCS as a superdisintegrant by direct compression method which showed rapid release within 2 min. The compression coating was done over the core tablets by using pectin, guar gum, HPMC and HEC in different ratios by direct compression method. The enteric coating was done on the compression coated tablets by using ES100 and CAP in different ratios by dip coating method. The FTIR of drug-polymer and polymer-polymer was studied and revealed the compatibility of drug-polymer and polymer-polymer. The tablets were studied for post compression parameters like thickness, hardness, friability, weight variation, and drug content were in acceptable range of pharmacopeial specification. In vitro swelling and in vitro drug release studies were carried out at different pH (1.2, 6.8 and 7.4). The compression coated formulation C1 (pectin: guar gum 1:2), C2 (HPMC: HEC 1:2) and C3 (HPMC, HEC: pectin, guar gum 2:1) showed good swelling (493.42%, 411.08% and 393.61%) up to 18, 20 and 21 h respectively. pH dependent polymers ES100: CAP in the ratio 2:1 as an enteric coating material applied over compression-coated tablet was capable of protecting the drug from being released in physiological environment of stomach and small intestine. This study proved that Budesonide compression-coated tablet, enteric coated with ES100: CAP in the ratio 2:1 may be beneficial in the treatment of irritable bowel syndrome and nocturnal asthma.

Keywords: Budesonide colon targeted tablets, enzyme dependent polymers, time dependent polymers, ES100, CAP.

INTRODUCTION

Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea, and colon cancer. In addition, the colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs [1]. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease [2]. Specific targeting of drugs to the colon is recognized to have several therapeutic advantages. Drugs, which are destroyed by the stomach acid and / or metabolized by pancreatic enzymes, are slightly affected in the colon, and sustained colonic release of drugs can be useful in the treatment of nocturnal asthma, angina pectoris and arthritis. Treatment of colonic diseases such as ulcerative colitis, colorectal cancer and Crohn's disease is more effective with direct delivery of vermicides and colonic diagnostic agents require smaller doses [3]. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability [4]. Different approaches are used for colon targeted drug delivery, among the primary approaches include pH sensitive polymer coated drug delivery to the colon, delayed (time controlled release system) release drug delivery to colon, microbially triggered drug delivery to colon and newly developed approaches are pressure controlled drug-delivery systems, novel colon targeted delivery system, osmotic controlled drug delivery system[1]. Many researchers developed and reported different colon specific drug

delivery system for metronidazole [5], tinidazole [6], ornidazole [7], prednisolone[8], naproxen [9] and also of mesalazine [10] by using various polymers such as pectine, guar gum, chitosan, Eudragit L100, Eudragit S100 etc [4].

Enteric-coated systems are the most commonly used for colonic drug delivery, but the pH difference between the small intestine and colon is not being very pronounced leading to poor site specificity. The drawback of the time-dependent release system is its inability to sense any variation in the upper gastrointestinal tract transit time; besides, any variation in gastric emptying time may lead to drug release in the small intestine before arrival to the colon. There is a steep gradient of enzyme activity along the gastrointestinal tract; these enzymes are derived from gut microflora. In humans, the stomach and small intestine contain roughly 103–104 colony forming units (CFU)/mL [11,12]. However, the concentration of microflora rises dramatically passing from the terminal ileum to the ascending colon where the numbers reach 1,011–1,012 CFU/mL. These bacteria survive and thrive by fermenting a wide range of substrates (e.g., oligosaccharides, polysaccharides, mucopolysaccharides) left undigested in the small intestine [13]. Hence, enzymatically controlled delivery system is considered convenient approach for site-specific drug delivery to the colon where no drug release can occur unless the system arrives to the colon [14-16].

Budesonide, a second generation glucocorticoid exhibits high affinity to the corticosteroid receptors with a high ratio of topical to systemic anti-inflammatry activity by decreasing the production of cytokines and interleukins [17]. Budesonide have half life of 2-4 h with an oral bioavailibility of 10%. Budesonide is used in the treatment of irritable bowel syndrome and nocturnal asthma [18]. BUD is approximately twice as active as beclomethasone dipropionate, and it is over 1,000 times more active than either prednisolone or hydrocortisone in inducing intracutaneous vasoconstriction (as a marker of anti-inflammatory activity). BUD is commercially available in the market in the form of enteric-coated preparations mainly for the treatment of small intestine active Crohn's disease. However, these products, similar to other available site specific dosage forms, are not sufficiently selective to treat colonic inflammatory bowel disease. It was found that less than 5% of the drug was available beyond the ileum and cecum, and therefore, colonic delivery still needs to be optimized by a more reliable colon-specific system. Previous workers have developed BUD microparticles and compression coated tablets for colon delivery [19]. However, being relatively complex systems, their large-scale manufacturing requires a lot of technological advancement and skills. So, an attempt was made to formulate compression-coated tablets enteric coated with pH dependent polymers, which could be formulated easily, using the usual tableting techniques.

The aim of the present study was to formulate colon targeted tablets of budesonide using pectin, guar gum as enzyme dependent polymers along with HPMC, HEC as time dependent polymers followed by pH dependent polymers like Eudragit S100 and Cellulose acetate phthalate. The compression coating was done over the core tablets by using pectin, guar gum, HPMC and HEC in different ratios by direct compression method. The enteric coating was done on the compression coated tablets by using ES100 and CAP in different ratios by dip coating method.

MATERIALS AND METHODS

The drug budesonide batch no. BDS-01-08 was obtained as gift sample and used as supplied by Ajanta Pharma, Mumbai. All other polymers and chemicals obtained were used as supplied by the standard manufacturers.

Preparation of core tablets of Budesonide:
Direct compression method was employed to prepare fast dissolving core tablet of budesonide using croscarmellose sodium as a super disintegrant. All the ingredients including drug and excipients were weighed accurately according to the batch formula. (Table 1) The drug and all the ingredients except lubricants were taken on a butter paper with the help of stainless steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min in mortar and pestle. After uniform mixing of ingredients, lubricants was added and again mixed for 2 min. The prepared blend of formulation was compressed into fast dissolving tablet weighing 50 mg using 6.3 mm flat punchs in a rotary tablet press (Rimek, mini-press 10 station rotary machine, Karnavati engineering).

Preparation of compression coated tablets:
Fast dissolving tablets of Budesonide were compression-coated with HPMC, HEC as time-dependent, and Pectin, Guar gum as enzyme-dependent polymers by direct compression method. The core tablets were compression-coated with 300 mg of compression coating materials as shown in Table 2 by using 9.6 mm concave punches. About 50% of the coat formulation was placed in the die cavity and core tablet was placed over the coating material then remainder of the coat formulation was placed over the core tablet. Then, it was compressed into the compression coated tablet.

Enteric coating of prepared compression coated tablets [20]:
Compression coated tablets of Budesonide were further coated with enteric coating polymers by dip coating method. Required quantity of ES 100 and CAP as shown in Table 3 was dissolved in acetone using a magnetic stirrer. After complete solubilization of polymer, castor oil (10% w/w of dry polymer) was added as plasticizer. Talc (0.1% w/v) was added as antiadherant and the solution was stirred for 15 min. Pre-weighted compression coated tablets were dipped for 3-5 times into the solution until 10% weight gain.

Table 1: Formulation of single fast dissolving core tablet of Budesonide

Ingredients	Quantity (mg/tablet)
Budesonide	9
Microcrystalline cellulose	34.8
croscarmellose sodium	5.0
Talc	0.7
Magnesium sterate	0.5
Total	**50**

Table 2: Formulation of compression coat

Ingredients (mg/tablet)	Formulation Code		
	C1	C2	C3
Pectin	30	-	20
Guar gum	60	-	40
HPMC	-	30	10
HEC	-	60	20
MCC	210	210	210
Total weight	**300**	**300**	**300**

Table 3: Composition of enteric coating material

Ingredients(mg)	Formulation Code								
	Enteric coating on C1			Enteric coating on C2			Enteric coating on C3		
	E1	E2	E3	E4	E5	E6	E7	E8	E9
ES 100	500	250	750	500	250	750	500	250	750
CAP	500	750	250	500	750	250	500	750	250
Castor oil	100	100	100	100	100	100	100	100	100
Talc	50	50	50	50	50	50	50	50	50
Acetone	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml	Up to 10 ml

Polymer drug interaction by FTIR study:
The drug polymer and polymer-polymer interaction was studied by FTIR spectrometer with KBr pellets.

Evaluation of tablets for post compression parameter (Hardness, Thickness and weight variation):
Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge. The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Drug content uniformity [21]:
One core tablet of budesonide was powdered and the powder was transferred into a 100 ml volumetric flask. Initially, 50 ml of methanol was added and allowed to stand for 6 h with intermittent shaking to ensure the complete solubility of the drug. The volume was then made up to 100 ml using methanol. One ml of the above solution was suitably diluted, filtered and the drug content was estimated using UV Visible spectrophotometer at 247.5 nm and methanol was taken as blank. The drug content was estimated by using calibration curve.

***In vitro* disintegration study:**
The *in-vitro* disintegration study of the core tablets were determined using disintegration test apparatus as per I.P specifications. Place one tablet in each of the six tubes of the basket. Add the disc to each tube and run the apparatus using 900 ml of PBS pH 7.4 as the immersion liquid. The assembly should be raised and lowered between 30 cycles

per min in distilled water maintained at 37ºC. The time in seconds for complete disintegration of the tablets with no palable mass remaining in the apparatus was measured and recorded.

***In vitro* Swelling study [21]:**
Swelling index of the tablet was evaluated in different medium (HCl buffer pH 1.2, PBS pH 6.8 and 7.4). The initial weight of the tablet was determined (W1)and then tablet was placed 10 ml HCl buffer pH 1.2 for 2 h then 10 ml of PBS pH 6.8 for 3 h and finally 10 ml of PBS pH 7.4 up to 24 h in a petridish. The tablet was removed at different time intervals (1, 2, 3, 4, 5… 24 h) blotted with filter paper and reweighed (W2). The swelling index is calculated by the formula:

Swelling index = 100 (W2 - W1)/ W1

Where; W1 = initial weight of the tablet.
W2 = final weight of the tablet.

***In vitro* Drug Release Studies [19, 21]:**
Budesonide release from the coated tablets was assessed by dissolution testing using the USP XXIII tablet dissolution test apparatus-II (rotating basket) at a rotation speed of 50 rpm maintained at 37.0±0.5°C (Electro-TDT-06). The release study was performed in 250 ml HCl buffer pH 1.2 for 2 h, followed by 250 ml PBS pH 6.8 for another 3 h, and finally 250 ml PBS pH 7.4 till the end of the 24 h to simulate the pHs pertaining to the stomach, proximal and middle small intestine (duodenum and jejunum), and distal small intestine (ileum), respectively. 1 ml of dissolution medium was withdrawn at 1 h interval up to 24h and replaced with an equal volume of media. The collected media was filtered through 0.45 µm membrane and analyzed spectrophotometrically at 247.5 nm.

***In vitro* drug release studies in presence of rat caecal content [5, 19, 21]:**
In order to assess the susceptibility of pectin and guar gum, being acted upon by colonic bacteria, drug release studies were carried out in presence of rat cecal content because of the similarity with human intestinal flora. Six rats weighing (150–250 g) and maintained on a normal diet were used. To induce enzymes acting specifically on pectin and guar gum in the caecum, 1 ml of 2% w/v pectin and guar gum (2:1) aqueous dispersion was directly administered to the rats daily for 5 days. 30 min before the studies, the rats were killed by spinal traction. The abdomens were opened, the caecai were isolated, ligated at both ends, dissected and immediately transferred into PBS pH 7.4 previously bubbled with CO2. The caecal bags were opened; their contents were individually weighed, pooled and then suspended in PBS to give a final caecal dilution of 4% w/v. As the caecum is naturally anaerobic, all these operations were carried out under CO2. The drug release studies were carried out in USP dissolution rate test apparatus (apparatus II, 50 rpm, 370C) with slight modification. The swollen formulations after completing the dissolution study in HCl buffer pH 1.2 (2 h) and PBS pH 6.8 (3 h) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal content medium. The drug release studies were carried out up to 24 h and 1 ml samples were withdrawn at specified time intervals and replaced with 1 ml of fresh phosphate buffer. Samples were analyzed spectrophotometrically at 247.5 nm.

Short term stability studies [22]:
Short term stability study was performed at a temperature of 40 ± 20C over a period of 3 months (90 days) on the promising budesonide colon targeted tablets. Sufficient numbers of tablets (10) were individually wrapped using aluminium foil and packed in amber colour screw cap bottle and kept in stability chamber for 3 months. Samples were taken at each month interval for evaluation of drug content and in vitro drug release study.

Data Analysis: Regressional analysis was performed by using microsoft office excel on the *in-vitro* release data to best fit into various kinetic models like zero order, first order, Higuchi, Korsemeyer-Peppas, Hixson-Crowell model according to the regression coefficient 'r^2' values.

RESULTS AND DISCUSSION

Fast dissolving core tablets of budesonide were prepared using CCS as a superdisintegrant and MCC as a diluent by direct compression method which dissolves within 3±0.058 min. The post compression parameters are depicted in Table 4. All the prepared tablets complies the IP standards. The thickness of the core tablet was 2.11±0.08 mm and hardness of the core tablet was 2.54±0.08 kg/cm^2 kept constant as to study the *in vitro* release profile. The average percent deviation for weight variation of core tablet of budesonide was less than ±10%, which provides good weight uniformity. The % friability of core tablet was in the range of 0.293±0.046, so less than 1% ensuring that tablets were mechanically stable. The drug content of core tablet was 99.01±0.86 suggested uniform mixing of drug.

Table 4: Evaluation parameters of core tablets of budesonide

Thickness (mm)	Hardness (kg/cm^2)	Weight (mg)	Friability (%)	Drug content (%)	Dissolution (min)
2.11±0.08	2.54±0.08	48.26±4.01	0.293±0.046	99.01±0.86	3.01±0.58

(n=3, mean±SD)

The prepared tablets were compression-coated with HPMC, HEC as time-dependent, and Pectin, Guar gum as enzyme-dependent polymers and with combined approach of time-enzyme dependent polymers by direct compression method. The core tablets were compression-coated with 300 mg different coat mixtures. All the compression coated formulations were evaluated for post compression parameters like thickness, hardness, friability, weight variation, *in vitro* swelling study and *in vitro* dissolution study. The post compression parameters are depicted in Table 5. All the prepared tablets complies the IP standards. Thickness of the prepared compression coated tablets was from 4.39 to 4.57 mm. The hardness of the tablets was from 6.47 to 8.30 kg/cm^2 and increased due to the nature of polymers used. The average percent deviation for weight variation of compression coated tablets of each formula was less than ±5%, which provides good weight uniformity. The % friability of compression coated tablet was in the range of 0.51% to 0.73%, so less than 1% ensuring that tablets were mechanically stable. The compression coated tablets were further enteric coated with ES100: CAP by dip coating method in varying concentration. The enteric coated formulations were further evaluated for post compression parameters like thickness, hardness, friability, weight variation, *in vitro* swelling study and in vitro dissolution study. The post compression parameters are depicted in Table 5. All the prepared tablets complies the IP standards. Thickness of the prepared enteric coated tablets was from 5.78 to 5.90 mm. The hardness of the tablets was from 6.74 to 8.86 kg/cm^2 and increased due to the enteric coating. The average percent deviation for weight variation of enteric coated tablets of each formula was less than ±5%, which provides good weight uniformity. The % friability of enteric coated tablet was in the range of 0.50% to 0.53%, so less than 1% ensuring that tablets were mechanically stable.

Table 5: Evaluation parameters of colon targeted tablets of budesonide

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)
C1	4.41±0.02	6.52±0.05	348.66±7.00	0.72±0.01
C2	4.55±0.02	8.25±0.05	348.63±6.42	0.52±0.01
C3	4.50±0.01	7.82±0.01	348.89±7.56	0.62±0.03
E1	5.80±0.02	6.82±0.08	377.66±5.87	0.51±0.01
E2	5.86±0.03	7.12±0.07	370.75±6.69	0.52±0.01
E3	5.87±0.03	8.01±0.05	381.72±8.14	0.51±0.03
E4	5.85±0.03	8.75±0.05	380.00±8.39	0.50±0.01
E5	5.85±0.01	8.72±0.06	383.01±8.31	0.51±0.02
E6	5.86±0.02	8.79±0.07	381.02±7.01	0.50±0.01
E7	5.85±0.01	8.25±0.01	381.72±8.08	0.52±0.01
E8	5.85±0.01	7.75±0.01	379.61±8.74	0.52±0.01
E9	5.85±0.01	8.23±0.01	383.07±8.00	0.51±0.01

FTIR study: The drug-polymer interaction was studied using FTIR spectroscopy for selected combination of drug with different polymers used. The FTIR spectra obtained is illustrated in Fig 1. Budesonide exhibits a broad peak in its IR spectrum at 3450 cm^{-1} corresponding to alcoholic –OH group. Broad hump observed from 2957 cm^{-1} to 2873 cm^{-1} due to C-H stretching for $-CH_2$ and $-CH_3$ groups. Strong absorption broad peaks at 1720 cm^{-1} and 1667 cm^{-1}characteristic peaks of –C=O group corresponding to ketone. A strong absorption peak at 1098 cm^{-1} corresponds to C-O-C of ether. When budesonide is incorporated with the pectin: guar gum, HPMC: HEC alone and in combination of pectin: guar gum with HPMC: HEC their respective peaks are not disturbed in the observed IR concluding that there was no drug-polymer and polymer-polymer interaction. Further more for the confirmation of the drug-polymer and polymer-polymer interaction; when ES100: CAP is incorporated with pectin: guar gum, HPMC: HEC and within combination of pectin: guar gum: HPMC: HEC with drug also showed all the characteristic peaks due to respective polymers revealing the fact that there was no drug-polymer and polymer-polymer interaction. The above observations recommended use of polysaccharides as an enzyme dependent polymers used with combination to other polymers like time-dependent and pH dependent.

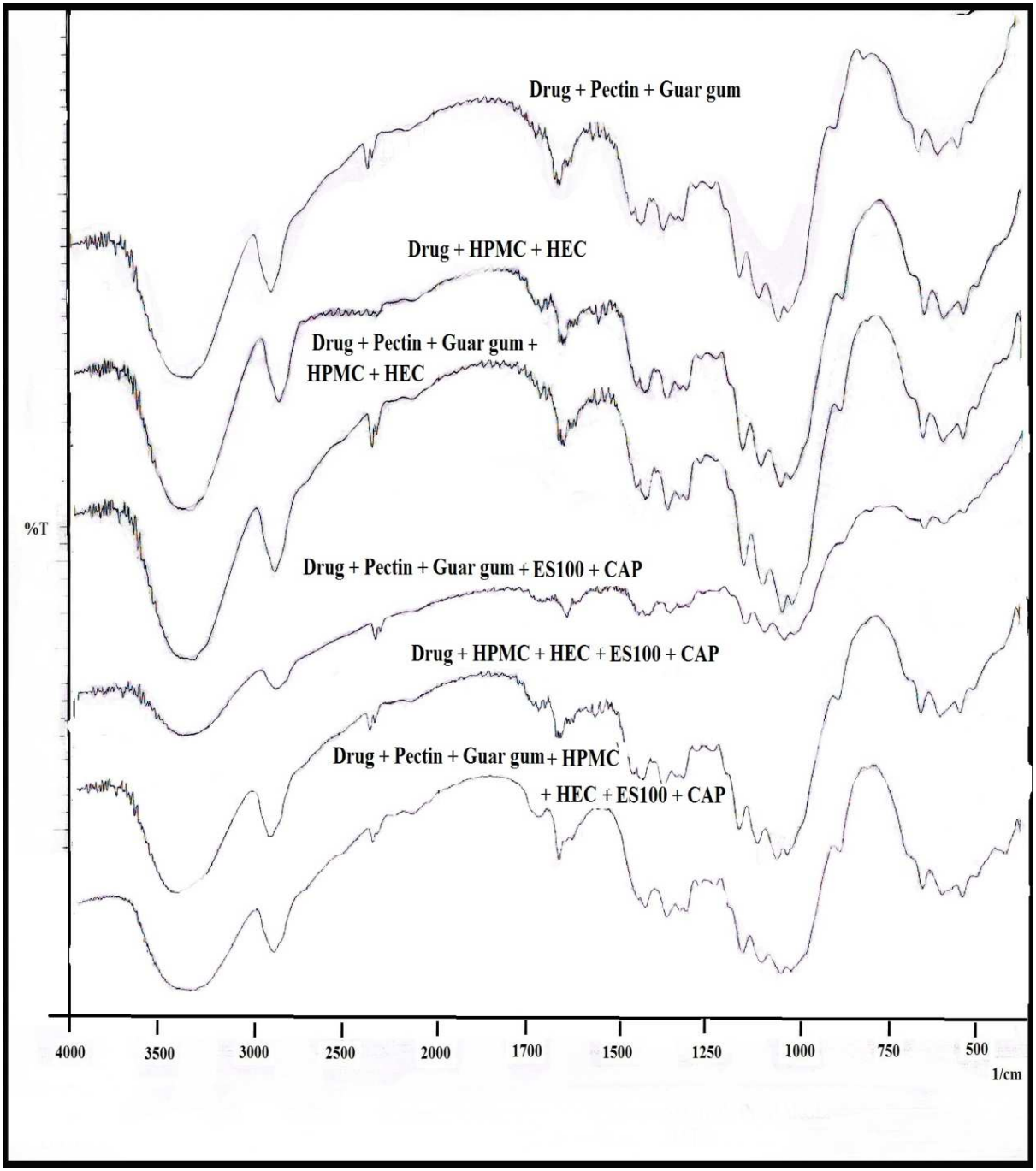

Figure 1: FTIR spectra of selected colon targeted tablets of budesonide

Swelling study: The swelling study of coated tablet was performed in HCl buffer pH 1.2 for first 2 h then from 3 to 5 h in PBS pH 6.8 and then 6 to 24 h in PBS pH 7.4 and the results are presented as percentage weight change with respect to time in Fig 2 to 3. The swelling behavior of colon targeted system is an important property for uniform and prolonged release of drug. The swelling behavior depends upon nature of polymer, concentration of polymer and pH of the medium. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The hydrophilic polymer layer hydrates/swells first and as the hydrated layer progressively dissolves or disperse, the hydration swelling process will continuous towards new expose surfaces thus maintaining the integrity of dosage form [23]. Compression coated tablets of budesonide which contains pectin, guar gum alone (C1) showed 96.21% swelling in HCl buffer pH 1.2 after 2 h; when the medium changed to PBS pH 6.8 for 3 h then swelling was found to be 119.52% at the end of 6^{th} h and finally tablet incubated up to 24 h in PBS pH 7.4 , showed 493.42% of swelling obtained in 18 h due to the less amount of pectin it showed less swelling in HCl buffer pH 1.2 and PBS pH 6.8 and due to the higher amount of guar gum which swells immediately to form highly viscous surface [24] and hence water uptake is more and in controlled manner

giving highest swelling extended up to 18 h. In case of HPMC, HEC containing formulation (C2) showed 373.05% of swelling in HCl buffer pH 1.2 after 2h then 384.07% at the end of 5th h in PBS pH 6.8 and finally in PBS pH 7.4 showed 411.08% of swelling in 20 h after that tablets were not being able to retain its shape; due to the less amount of HPMC and more HEC forming a gel layer and reduces the water uptake in controlled manner. Compression coated tablets contains HPMC, HEC in combination with pectin, guar gum (C3) showed 98.40% in HCl buffer pH 1.2 after 2h; when the medium is changed to PBS pH 6.8 showed 313.21% of swelling after 5 h and finally in PBS pH 7.4 showed 393.61% of swelling in 21 h depends on the pH of solution, nature and amount of polymers in coat. In case of C3 due to low amount of pectin, guar gum and more polarity of HEC, water uptake is more and it swells highest and in controlled manner [25] up to 21 h.

All the enteric coated formulations (E1 to E9) showed no swelling in HCl buffer pH 1.2 after 2 h. Enteric coated formulations contains pectin, guar gum (E1, E2 and E3) showed 93.27%, 139.25% and 128.17% of swelling in PBS pH 6.8 after 5 h and finally in PBS pH 7.4 showed 398.46%, 411.63% and 423.05% of swelling after 23, 21 and 21 h respectively. E1 and E3 showed swelling in a controlled manner but in case of E2 highest swelling was observed in PBS pH 7.4. Enteric coated formulations E4, E5 and E6 contain HPMC, HEC showed 256.31%, 264.23% and 241.53% of swelling in PBS pH 6.8 after 5 h and 409.02%, 387.24% and 415.57% in PBS pH 7.4 after 24, 24 and 21 h. F13 doesn't show swelling for first 3 h due to high amount of ES100 in formulation but at 4th h it starts swelling in controlled manner and swells up to 24 h. E7 to E9 all three formulations doesn't shows swelling at first 3 h due to the ES100 and combination of pectin, guar gum with HPMC, HEC; F16,F17 and F18 showed 55.39%, 128.53% and 69.15% of swelling at the end of 5th h in PBS pH 6.8 and 305.77%, 309.37% and 367.88% in PBS pH 7.4 after 24, 20 and 22 h. E7 showed swelling up to 24 h due to the higher amount of HEC and guar gum which takes more water and swells immediately and forms gel layer on the surface and reduces the water uptake and in controlled manner. E9 showed highest swelling as compared to E8 due to the more amount of HPMC, HEC which swells more. Swelling behavior of all the enteric coated formulations E1 to E9 is affected by pH of the medium. Swelling study indicated that all the formulations swell in a controlled manner.

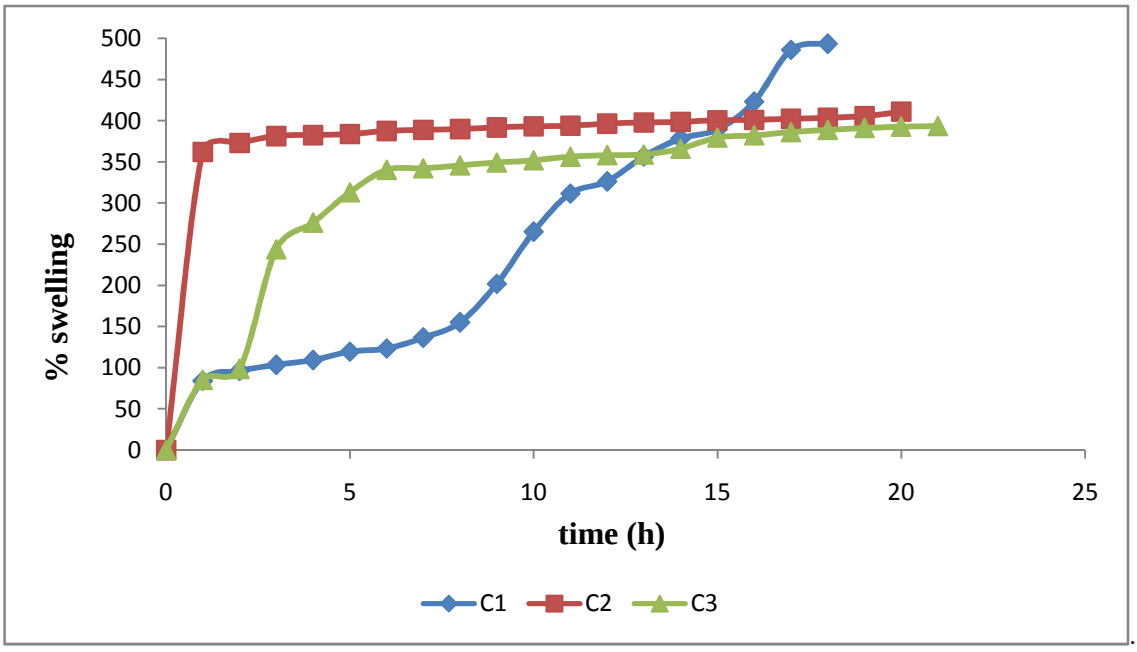

Figure 2: *In vitro* swelling study of compression coated tablets of budesonide containing Pectin: Guar gum (C1); HPMC: HEC (C2) and combination of HPMC: HEC with Pectin: Guar gum (C3)

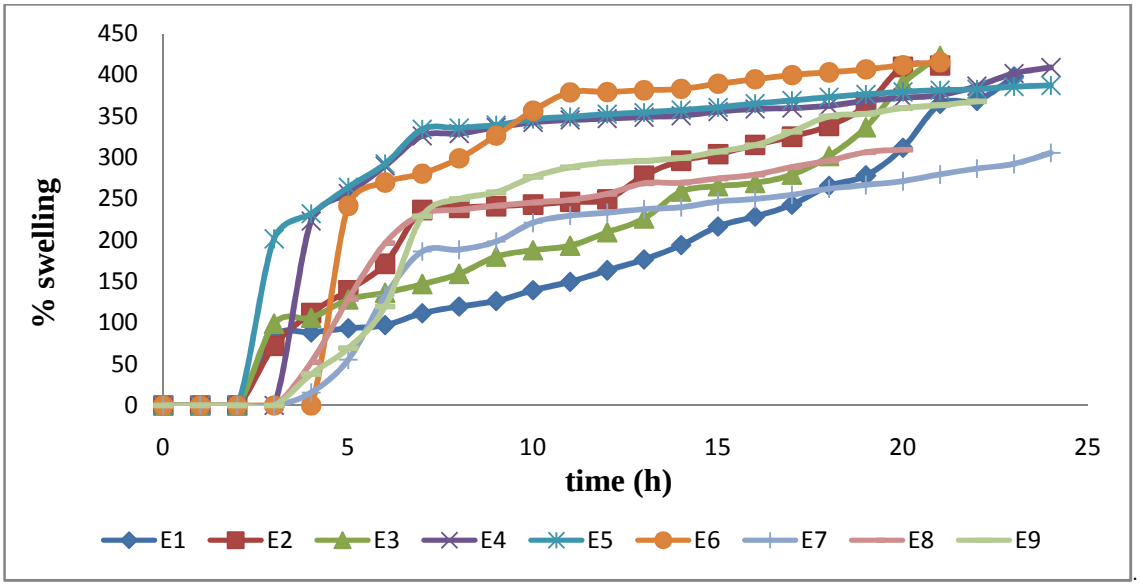

Figure 3: *In vitro* swelling study of enteric coated tablets of budesonide containing Pectin: Guar gum (E1 to E3); HPMC: HEC (E4 to E6) and combination of HPMC: HEC with Pectin: Guar gum (E7 to E9)

***In vitro* release study:** *In vitro* release of budesonide was performed in HCl buffer pH 1.2 for first 2 h, then from 3 to 5 h in PBS pH 6.8 and then from 6 to 24 h in PBS pH 7.4. The *in vitro* release data was illustrated in Fig 4 to 6. The *in vitro* release of budesonide was mainly affected by polymer ratio, nature and amount of polymer, and the dissolution medium. The *in vitro* release of budesonide was also depends on swelling behavior of the polymers used. All the compression coated tablets showed drug release in first 2 h. The compression coated tablets containing pectin: guar gum 1:2 alone in C1 showed bust release of the drug at 11th h followed by >80% release within 24 h. Guar gum rapidly hydrated and swelled to forming a viscous gel layer that slows down with further seeping-in of dissolution fluids toward the core tablets. When water reaches the core tablet, drug release takes place by diffusion which is supported by mechanical erosion of the swollen polymer [19]. The addition of time dependent polymers like HPMC: HEC 1:2 along with pectin: guar gum in formulations C3 prolonged the release of budesonide up to 24 h. The formulation containing HPMC: HEC 1:2 alone in C2 showed a maximum drug release of >90% within 24 h which gives best release. The extent of drug release in the target area of the formulas coated with enzyme dependent, time-dependent and combination of time-enzyme dependent polymers could be arranged in descending order as follows: C3 (90.87%) >C2 (90.03%) >C1 (83.06%).

For the successful delivery of drugs to the colon requires the protection of drug from being released in stomach and small intestine; hence the compression coated tablets were enteric coated to prevent the drug release in upper part of GIT. The release profile of all enteric coated formulations is shown in Fig 5. Formulation E1, E4 and E7 coated with ES100: CAP 1:1 showed 81.94%, 83.06% and 89.75% of drug release in 24 h. In formulation E2, E5 and E8 coated with ES100: CAP 1:2 showed 76.09%, 79.72% and 88.91% of drug release in 24 h; these three formulations shows less drug release as compared to F10, F13 and F16 due to lesser amount of ES100 and higher amount of CAP in coat formulation; ES100 and CAP shows pH dependent solubility [26,27], ES100 having threshold pH 7 and CAP having pH 6. Hence due to high amount of CAP as it is soluble in pH 6.8 buffer and less amount of ES100 is unable to prevent the drug release in pH 6.8 buffer, so all three formulations shows the drug release in first 2 to 3 h. In case of formulation E1, E4 and E7 showed drug release in first 3 to 4 h due to the lesser amount of ES100 in formulation coat. In comparison, formulation coated by pH dependent polymers such as ES100: CAP 2:1 in E3, E6 and E9 showed no drug release in 6 h except E3 showed drug release at 5th h hence proved to have more efficiency in protecting the drug release in the upper part of the GIT. After 24 h testing, the cumulative percentage drug release from E3, E6 and E9 was found to be 83.06%, 82.22% and 89.87% respectively, indicating that the mixed polymer coat substantially retarded the drug release as the ES100 content increased due to the pH dependent solubility of ES100, most of the drug release occurred in PBS pH 7.4. Also due to the decreasing the concentration of pectin: guar gum in coating of F18 showed maximum drug release than E7and E8.

Optimized formulations E3, E6 and E9 were selected to continuing the drug release studies in rat caecal content medium for 19 h after 5 h of testing in simulated gastric and intestinal fluid also the susceptibility of pectin: guar gum coatings to the enzymatic action of colonic bacteria, was assessed by continuing the drug release studies in rat caecal content. *In vitro* release data in Fig 6 shows that the presence of rat caecal contents in the dissolution medium resulted in a significance increase in drug release, when compared to the drug release study in absence of rat caecal

contents. The cumulative percentage drug released after 24 h from E3 and E9 increased from 83.06% and 89.87% in the absence of rat caecal contents to 93.65% and 94.21% in presence of rat caecal matter, respectively, indicating that polysaccharidases metabolizing pectin and guar gum are present in rat caecal contents. As the pectin: guar gum might have been more hydrated and subsequently degraded by the caecal enzymes at a faster rate [5,28,29], explaining the relatively higher drug release from E3 and E9, compared with E6 which doesn't show any significant change in cumulative percentage drug released after 24 h.

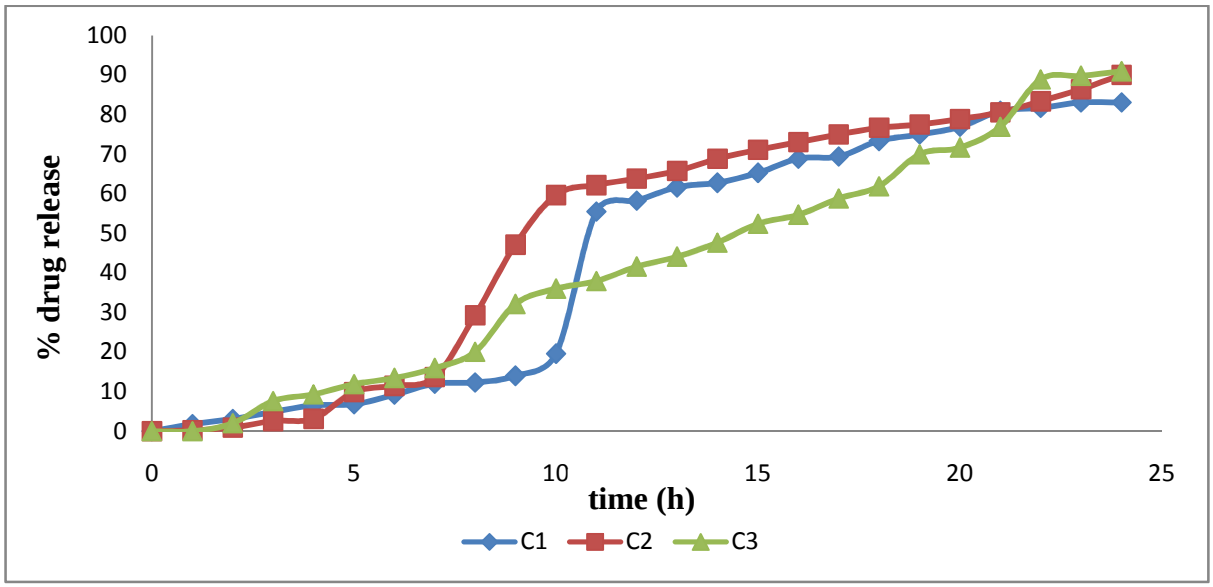

Figure 4: *In vitro* release study of compression coated tablets of budesonide containing Pectin: Guar gum (C1); HPMC: HEC (C2) and combination of HPMC: HEC with Pectin: Guar gum (C3)

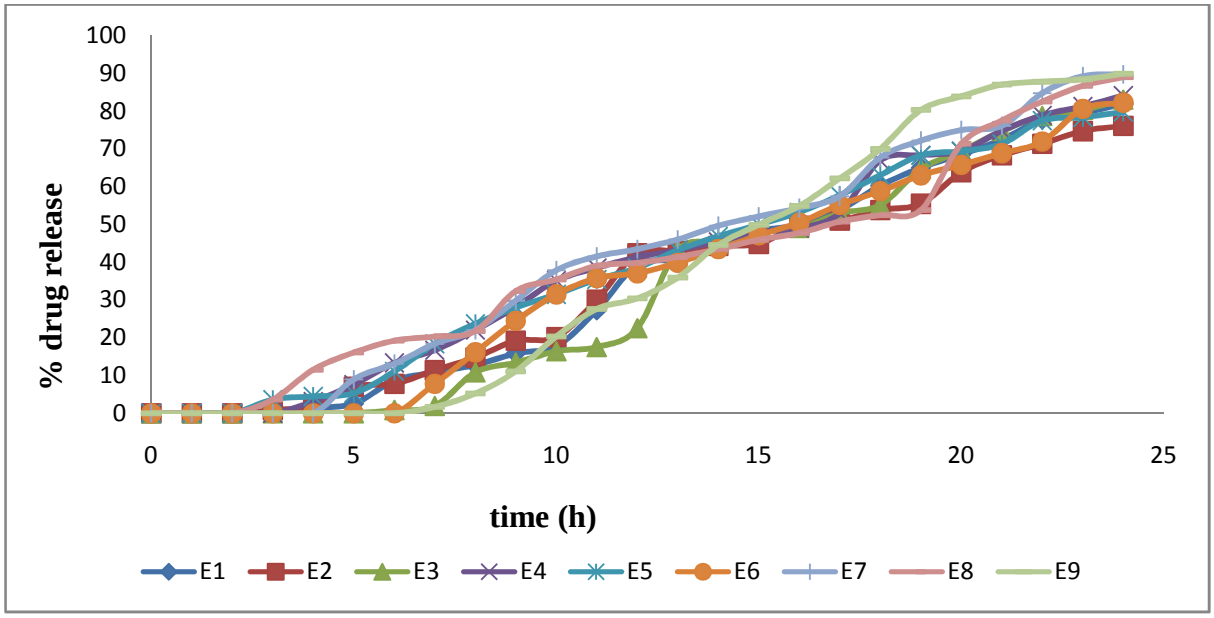

Figure 5: *In vitro* release study of enteric coated tablets of budesonide containing Pectin: Guar gum (E1 to E3); HPMC: HEC (E4 to E6) and combination of HPMC: HEC with Pectin: Guar gum (E7 to E9)

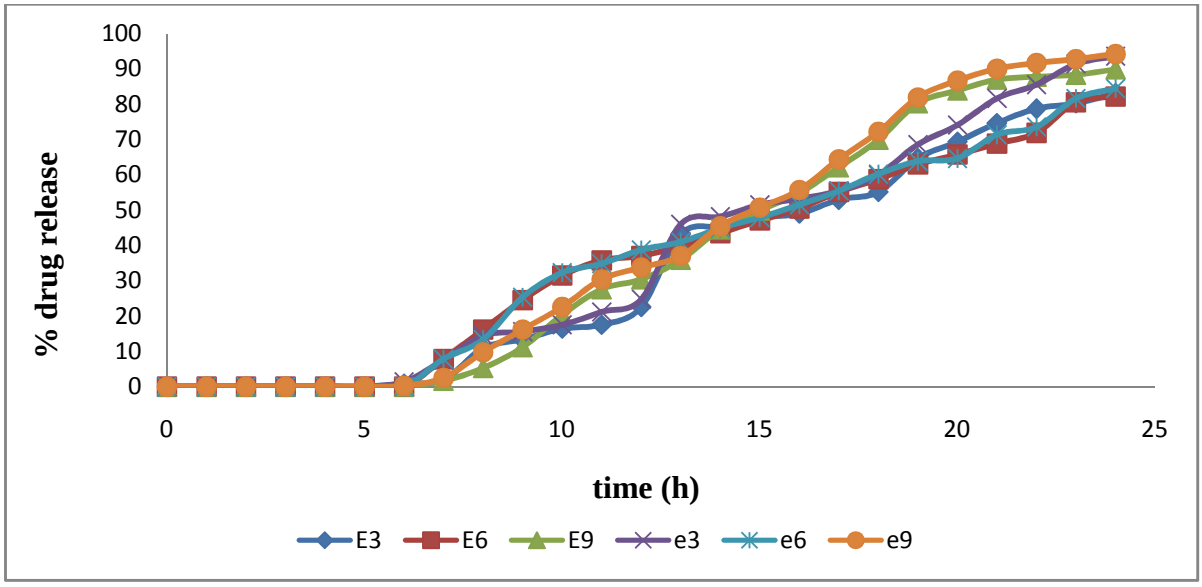

Figure 6: Comparative *in vitro* release study of colon targeted tablet of budesonide in absence (E3, E6 and E9) and presence (e3, e6 and e9) of 4% colonic content

The *in vitro* release data was subjected to zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Peppas in order to establish the drug release mechanism and kinetics of drug release from the matrix tablets. The regressional analysis with correlation coefficient r^2 value for different kinetic models is summarized in Table 6. When the data was subjected to zero order and first order kinetic model, a linear relationship was observed with high r^2 values for zero order model (0.8059 to 0.9922) as compared to first order model (0.8162 to 0.9777) suggested that the formulations were zero order release. Higuchi's model was applied to the *in vitro* release data, linearity was obtained with high r^2 value (0.8628 to 0.9955) suggested that the drug release from tablet followed diffusion mechanism as all the polymers used were gel based matrix type. When the *in vitro* release data was subjected to Hixson Crowell cube root model; good linearity was observed with high r^2 values (0.8669 to 0.9909) suggested that the geometrical shape of tablet diminished proportionally over the time due to polymer erosion. In order to define a perfect model which will represent a better fit for the *in vitro* release data, Korsmeyer-Peppas model was applied which will define exact release mechanism when more than one type of release phenomenon was observed. Good linearity with high r^2 (0.7628 to 0.9711) value was with Korsmeyer-Peppas model. The value of release exponent n calculated as a slope defines the release mechanism. The n values for C1 to C3 and E1-E9 were >0.89, indicating super case II transport, values for n>1 (super case II transport) would be the consequence of a plasticization process in the gel layer arising from reduction of the attractive forces among polymeric chains that increases the mobility of macromolecules.

Table 6: Regressional analysis of the *in vitro* release data according to various release kinetic models

Formulation Code	Zero order	First order	Higuchi	Hixon-Crowell	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	n	r^2
C1	0.8477	0.9530	0.8880	0.9240	1.7286	0.8497
C2	0.8059	0.9470	0.8628	0.9185	1.2346	0.7628
C3	0.9858	0.8713	0.9770	0.9307	1.3320	0.9715
E1	0.9864	0.9651	0.9841	0.9829	1.7156	0.9704
E2	0.9738	0.9654	0.9794	0.9769	1.5746	0.9536
E3	0.9785	0.9554	0.9767	0.9748	2.8320	0.8666
E4	0.9833	0.9424	0.9789	0.9664	1.2603	0.9737
E5	0.9922	0.9777	0.9955	0.9909	1.2785	0.9711
E6	0.9833	0.9500	0.9880	0.9752	1.5205	0.9041
E7	0.9869	0.9089	0.9837	0.9546	1.2862	0.9708
E8	0.9394	0.8162	0.9100	0.8669	1.0905	0.9541
E9	0.9795	0.9527	0.9859	0.9750	2.7330	0.8765
Regressional analysis of the in vitro release data according to various release kinetic models in presence of 4% colonic content.						
e3	0.9831	0.8775	0.9736	0.9411	2.3979	0.8866
e6	0.9801	0.9411	0.9859	0.9707	1.5746	0.8984
e9	0.9866	0.9225	0.9854	0.9636	3.1624	0.8000

The short term stability study was performed as per ICH guidelines using selected colon targeted tablets for a period of 3 months. The tablets were periodically evaluated for drug content and *in vitro* drug release and the results are represented in Table 7. The evaluated parameters did not show any significant change during the time course of storage confirmed that the prepared colon targeted tablets were stable.

Table 7: Short term stability study data of budesonide colon targeted tablet

Duration (Month)	Parameter studied	Formulation Code					
		C1	C2	C3	E3	E6	E9
0	Drug content	99.39	99.08	99.45	99.25	99.11	99.01
	% Drug release	83.06	90.03	90.87	83.06	82.22	89.87
1	Drug content	99.02	99.07	99.40	99.31	99.09	98.89
	% Drug release	82.56	89.71	90.48	83.65	82.29	89.91
2	Drug content	99.02	99.05	99.41	99.29	99.07	98.81
	% Drug release	82.36	89.52	90.33	83.66	82.26	89.86
3	Drug content	99.02	99.06	99.38	99.13	98.97	98.82
	% Drug release	81.56	89.26	90.09	83.14	81.76	89.88

CONCLUSION

Hence, the combined approach of using time dependent along with enzyme dependent polymers like HPMC, HEC and pectin, guar gum followed by enteric coating polymers like ES100 and CAP would be helpful to prepare the colon targeted tablet of budesonide, so as to improve the oral bioavailability of budesonide and the better management of IBS and nocturnal asthma.

Acknowledgements
Authors are thankful to Ajanta Pharma Ltd., Mumbai-Maharashtra for providing a gift sample of Budesonide.

REFERENCES

[1] A. K. Philip, Betty Philip. *Oman Medical Journal*., **2010**, 25, 70-78.
[2] E. O. Akala, et al. *Drug Dev Ind Pharm*., **2003**, 29, 375.
[3] K.V. Vinay, Sivakumar, T. Tamizh. *Int J Pharm Biomed Sc.i*., **2011**, 2, 1, 11-19.
[4] W. Shailendra, P. Poonam. *International Journal of Pharmaceutical Sciences Review and Research*., **2011**, 6, 2, 031.
[5] M. A. Nasra, M.A. Massik, Naggar. *Asian Journal of Pharmaceutical Sciences*.,**2007**, 2, 1, 18 -28.
[6] S. Srikanth, S. Kumar, K. Sundaramoorthy, S. Shanmugam, T. Vetrichelvan. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*., **2011**, 02, 01, 469-481.
[7] P. Pragnesh, R. Anupkumar, V. Kumar, K. Martand. *International Journal of Drug Development & Research*., **2011**, 03.01, 52-61.
[8] S. C. Chetan, S. N. Pushpendra, S. R. Rajendrapal, B. Viralkumar. *Journal of Chemical and Pharmaceutical Research.*, **2010**, 2, 4, 993-998.
[9] K. Purushotham Rao, et al. *Yale journal of biology and medicine.*, **2003**, 76, 149-154.
[10] L. J. Josephine, K. Vijaya, S. Ra, B. Raj, S. Ayesha. *International Journal of PharmTech Research*., **2010**, 02, 01, 535-541.
[11] G. L. Simon, S. L. Gorbach. *Dig. Dis. Sci. 319 Suppl*, **1986**, 147S–162S.
[12] S. L. Gorbach. Intestinal microflora. *Gastroenterology*., **1971**, 606, 1110– 1129.
[13] A. Rubinstein. *Drug Dispos.*,**1990**, 116, 465–475.
[14] V. R. Sinha, R. Kumria. *Int. J. Pharm.* **2001**, 224, 19–38.
[15] V. R. Sinha, and R. Kumria. *Eur. J. Pharm. Sci.*,**2003**, 18, 3–18.
[16] L. S. Liu, M. L. Fishman, J. Kost, K. B. Hicks. *Biomaterials.*, **2003**, 24,3333–33 43.
[17] H.P Range, M.M. Dale's Pharmacology, Elsevier publication,**2007**, 1, 428.
[18] G.M. Mallikarjuna, S.A. Ramakrishna, S.M. Shantakumar, S.S. Somashekar, R. Putta. *Journal of Applied Pharmaceutical Science.* **2011**, 01, 07, 158-161.
[19] A.Y. Soad , H.E. Ahmed, S. Ibrahim, H.S. Ahmed*American Association of Pharmaceutical Scientists PharmSciTech*. **2009**, 10, 01, 147-157.
[20] S. Nitesh, P. Mayur, S. Tejal, A. Avani. *J Pharm Educ Res*. **2011**, 2, 1, 42-49.
[21] P. Prabhakara et al. *Pak J Pharm Sci*. **2010**, 23, 3, 259-265.
[22] United State Pharmacopoeia. XXIV/NF ed. Rockville: United State Pharmacopoeial Convection; **2000**.
[23] M. A. Saleem, M. Dhaval, P. Jaydeep , Y. Murali, Naheed. . *IJPSR*. **2012**, 3, 08, 2786-2794.
[24] K.Gupta , I. Singhvi ,V Kale , J. Avari, N. Agrawal. *Int. J. Drug Dev. & Res*.**2011**, 3 ,2, 162-170.
[25] Donald L. Wise. Handbook of Pharmaceutical Controlled Release Technology. CRC Press. **2000**, 5.

[26] Nikam et al. Eudragit A Versatile Polymer: A Review. Newsletter *Pharmacologyonline*.**201**1, 1, 152-164.
[27] M. Rahman, S. Islam, S. Sharmin, J. Chowdhury, R. Jalil. *Dhaka Univ. J. Pharm. Sci.***2010**, 9,1, 39-46.
[28] A. Marianne, F. John, A. David , S. Harbans,W. Philip. *J of Contr Release*. **1993**, 26 , 3, 213–220.
[29] S. Shyale, K. Chowdhary, Y. Krishnaiah. *Drug Development Research*. **2005**, 65, 2, 76-83.