

Development of novel budesonide pellets based on CODES™ technology: In vitro/in vivo evaluation in induced colitis in rats

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ABSTRACT

Background and the purpose of the study: Budesonide is the drug of choice for treatment of active inflammatory bowel disease (IBD). The aim of this study was to develop budesonide pellets based on a novel colon drug delivery system (CODES).

Methods: Pellet cores containing lactulose or mannitol were prepared by extrusion/spheronization and coated with an acid soluble polymer (Eudragit E100), hydroxypropylmethyl cellulose (HPMC) and an enteric coat (Eudragit FS 30D) sequentially. In vitro drug release of coated pellets was studied using USP dissolution apparatus type II in buffers of pH 1.2 (2 hrs), pH of 7.4 (4 hrs) and pH of 6.8 containing 8% rat cecal contents (RCC) (18 hrs). The efficacy of the optimized formulation (containing 50% lactulose coated with Eudragit E (30% w/w) and Eudragit FS 30D (12% w/w)) was evaluated against 2, 4, 6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in rats.

Results: The results of the kind of bacteria in vitro dissolution tests indicated absence of drug release in pHs of 1.2 and 7.4 and controlled release in buffer of pH 6.8 containing RCC. It was found that release rate was controlled by the type and amount of polysaccharide and the thickness of the acid soluble layer. The prepared formulation showed promising results in alleviating the conditions of experimental model of colitis.

Conclusion: The results of this study suggest that pellets based on CODES technology could be useful for colonic delivery of budesonide.

Keywords: Colon targeted delivery, Budesonide, CODES, Extrusion/Spheronization, TNBS-induced colitis.

INTRODUCTION

Several diseases such as IBD can be treated more effectively by local delivery of anti-inflammatory drugs such as 5-aminosalicylic acid and corticosteroids to the colon (1). Recently, for the delivery of such drugs to intestinal diseased sites, much attention has been paid to oral colon drug delivery (CDD) systems (2). Newly developed corticosteroids with high topical activity and low systemic side effects are drugs of choice for treatment of IBD (3). Budesonide is a novel synthetic corticosteroid with a high ratio of topical to systemic anti-inflammatory activity and low systemic effects (4). It has gained a primary role in the treatment of mild to moderate IBD including ulcerative colitis (UC) and Crohn's disease and now is a drug of the first choice in the treatment of active IBD (5). However

rapid pre-systemic elimination of budesonide in hepatocytes and epithelial cells of the small intestine wall prevents good bioavailability of this drug in colonic mucosa (6). Thus there remains a significant need for an oral CDD system for budesonide in a way that maximizes the local concentration in inflamed colon mucosa, improves the effectiveness of the drug in the treatment of IBD while avoiding typical systemic side effects of glucocorticoids. CODES™ is a new single unit based technology that for release works the principle of pH, time and the kind of bacteria (7). This system consists of a three layered coated tablet containing a core drug and one or more biodegradable polysaccharides. The inner coating is an acid-soluble polymer (e.g., Eudragit E), the middle layer is a barrier coat and the outer layer is an enteric coating. Upon arrival in

the colon, the polysaccharide inside the core of the tablet dissolves and diffuses out through the inner coating of Eudragit E. The colonic local bacteria then degrade the polysaccharide into organic acids. This lowers the microenvironment pH surrounding the formulation, and leads to dissolution of acid-soluble coating and subsequent drug release (5). This system reduces the variability associated with time, enzyme or pH-dependent CDD systems (8). The aim of this study was to formulate budesonide pellets based on CODES™ technology. To the best of information this technique has been used only for single unit dosage forms and there is no report on its use on the pellet dosage forms. To assess the influence of dosage form on the capacity of CODES technology for colon targeting, budesonide CODES tablet was also prepared according to the formulation of the most promising CODES pellets and the dissolution profile of two dosage forms were compared. The *in vivo* efficacy of promising formulation was examined using the TNBS-induced colitis rat model.

MATERIAL AND METHODS

Materials

Budesonide was a kind gift from Astra Zeneca (UK). Eudragit E and Eudragit FS 30D (Rohm Pharma, Germany), lactulose (Tolid Daru, Iran), microcrystalline cellulose as Avicel PH101 (FMC, Ireland) lactose monohydrate 200 (Meggle, Germany); Hydroxypropylmethyl cellulose 6 cps (Shin-Etsu Chemical Co, Japan), talc and triethyl citrate (TEC) (Kirsch Pharma, Germany), mannitol (HEBEI HUAXU, China), 2,4,6-trinitrobenzenesulfonic acid and prednisolone (Sigma Chemical Co., USA) were used in this study. All other materials used were of analytical reagent grade and purchased from Merck Co. (Darmstadt, Germany).

Preparation of CODES budesonide pellets

Preparation of core pellets

Budesonide core pellets were prepared by the extrusion-spheronization method in a laboratory scale extruder (Model 20, Caleva, UK), fitted with a spheronizer (model 250, Caleva, UK). The details of the composition of the prepared formulations are given in table 1. Pellets of the size of 840-1000 μm were used in subsequent coating.

Preparation of coated pellets

Three layers of polymeric coatings at different operating conditions (Table 2) were applied to drug loaded pellets in the following order using a top spray fluidized bed coater (VECTOR Corporation, Marion, Iowa): Eudragit E layer (12% Eudragit E 100, 2.4% TEC, and 1.2% talc in mixture of ethyl alcohol/water, 60:40) at 20%, 25%, 30% and 35% (w/w), HPMC layer (5.71% HPMC, 1.71% TEC,

and 2.65% talc in water) at 6% (w/w) and Eudragit FS 30D layer (15% Eudragit FS 30D and 7.5% talc in water) at 12% (w/w) weight gain.

Preparation of CODES budesonide tablets

Bi-convex tablet cores (200 mg) containing 3 mg budesonide were prepared using a single punch tablet machine (ERWEKA, Germany) which contained budesonide (1.5%), lactose (18.5%), lactulose (50%), microcrystalline cellulose (30%) and magnesium stearate (0.5%) added extragranularly. The three layers of polymeric coating were applied to core tablets with the same formulations and in the same order explained earlier using a conventional pan-coating process in a pan coater (ERWEKA, Germany). The coating weight gain for Eudragit E100, HPMC and Eudragit FS 30D were 8%, 2%, and 5% w/w, respectively.

In vitro release experiments

Budesonide release study

Dissolution tests were performed on pellets containing 3 mg of budesonide using paddle method (USP apparatus II). The rotating speed was 50 rpm at 37 ± 0.5 °C. Dissolution test of uncoated pellets was performed in phosphate buffer saline (PBS) of pH 6.8 (250 ml) for 3 hrs. The release of Eudragit E coated pellets was evaluated in PBS of pH of 6.8 (250 ml) for 24 hrs. The influence of the type and concentration of polysaccharide (mannitol or lactulose) was evaluated in PBS of pH of 7.4 (250 ml) for 4 hrs and in PBS of pH of 6.8 (100 ml) in the presence or absence of 8% RCC for 18 hrs under continuous supply of CO_2 , to simulate the colon environment. Preparation of RCC containing media was carried out according to a reported method (9). To determine the dissolution profile of the most promising CODES pellet formulation and budesonide CODES tablet in simulated gastrointestinal (GI) fluids, a dissolution test was performed using three consecutive media as mentioned above and 0.1 N HCl (250 ml) for the first 2 hrs. In all drug release studies 0.5 percent (w/v) of sodium lauryl sulphate was used in each dissolution medium to maintain sink conditions. Dissolution samples of a certain volume were withdrawn at 2, 4, 6, 8, 10, 12, 14, 16, 18 and 24 hrs and replaced with fresh solution. The amount of released budesonide was determined using an HPLC method described below.

Lactulose / Mannitol release study

Lactulose and mannitol release studies were performed in 250 ml PBS of pH 6.8 for 12 hrs under the same conditions described above. Lactulose concentration was determined by a reported method (10) and mannitol concentration was determined by the USP method (11).

HPLC analysis

The quantitative determination of budesonide in

Table 1. Different budesonide pellet core formulations prepared by extrusion spheronization method.

Batch Code	Budesonide (%)	Avicel PH101 (%)	Lactose (%)	Mannitol (%)	Lactulose (%)	Granulating liquid (Water) (g)	yield (%)	Mean pellet size (µm)	Drug Released (%) after 2h ±SD (pH 6.8)
F1	1.5	98.5	-	-	-	58.2	92.1	998.98	10±0.89
F2	1.5	30	68.5	-	-	46.5	98.1	922.20	32±2.70
F3	1.5	30	58.5	-	10	42	80.2	920.14	38.8±2.13
F4	1.5	30	48.5	-	20	37.3	83.9	911.38	58.2±3.35
F5	1.5	30	38.5	-	30	34.5	86.8	897.56	69.3±2.50
F6	1.5	30	33.5	-	35	32	87	924.9	82.4±1.62
F7	1.5	30	28.5	-	40	30.5	88.4	903.5	85.9±3.91
F8	1.5	30	18.5	-	50	28.4	89.5	926.9	91.5±4.13
F10	1.5	30	48.5	20	-	42	80.4	900.5	40±0.8
F11	1.5	30	28.5	40	-	40.5	78.8	896.2	61.5±3.8
F12	1.5	30	8.5	60	-	37	70.5	879.8	83±5.1
F13	1.5	18.5	-	80	-	35.4	59.8	656.4	-

Table 2. Operating conditions for the coating experiments.

Operating condition	Acid resistance coating with Eudragit E	Barrier coating with HPMC	Enteric coating with Eudragit FS 30D
Before coating preheating to (°C)	-	-	33 °
Coating nozzle diameter (mm)	1	1	1.2
Spraying rate (g/min)	2	0.4	2
Inlet air temperature (°C)	30-32	70-72	35-42
Outlet air temperature (°C)	25-27	56-58	25-28
Curing in fluid bed on trays	30 min at 35 °C	-	-
	-	48 hrs at room temperature	24 hrs at 40 °C

assay and dissolution studies was performed by HPLC method equipped with UV detector using dexamethasone as an internal standard (12). The analysis was carried out by using a Shimpack C8 column (150 mm × 4.6 mm, 5 mm particle size) at a wavelength of 244 nm. The mobile phase consisted of acetonitrile, monobasic potassium phosphate (0.025 M) (55:45, pH of 3.2). The flow rate was 1.0 ml/min and injection volume of 20 µl. Quantitation was achieved by measurement of the peak area ratios of the drug to the internal standard. The retention time of the budesonide chromatographic peak was found at 5 min.

Scanning electron microscope (SEM) studies

The morphology of optimized formulations of uncoated and coated pellets was characterized using SEM. The Samples were gold coated using a sputter coater and then analyzed using SEM (Philips, XL30, Philips, Eindhoven, Netherlands).

In vivo study

Induction of colitis and treatment

Colitis was induced according to the method of

Morris et al. (13) by some modification. Male Wistar rats (180-220 g) were randomly assigned to groups of six. Following a 24 hrs fasting, rats were anesthetized and TNBS (20 mg) dissolved in 0.5 ml of ethanol (40% v/v) was instilled into the colon up to 8 cm intra-rectally using a polyethylene tube (2 mm in diameter). After 24 hrs, budesonide CODES pellets (300 µg/kg/day, oral) were administered via a NG tube (No. 8) fixed on a feeding tube No. 18 (group C) for 7 days. Different control and treatment groups were used: A: normal control group received only 0.5 ml normal saline, B: colitis control group received TNBS and treated with normal saline, D: FS 30D coated pellets (without Eudragit E layer) (300 µg/kg/day), E: free polysaccharide coated pellets (300 µg/kg/day), F: budesonide solution (300 µg/kg/day), G: uncoated pellets (300 µg/kg/day), H: placebo pellets, I: mesalazine enema (400 mg/kg/day), J: budesonide enema (20 mcg/kg/day) and K: prednisolone (5mg/kg/day, orally). All animal experiments were performed in compliance with the guidelines of ethics committee of Isfahan University of Medical Science.

Table 3. Scoring system for histopathological assessment of induced colitis (16).

Scoring parameter	Score definition
Inflammation severity	0: None
	1: Mild
	2: Moderate
	3: Severe
Inflammation extent	0: None
	1: Mucosa
	2: Mucosa and submucosa
	3: Transmural
Crypt damage	0: None
	1: Basal 1/3 damaged
	2: Basal 2/3 damaged
	3: Crypts lost, surface epithelium present
	4: Crypts lost, surface epithelium lost

Assessment of colitis

Rats were euthanized 24 hrs after the treatment for 7 days. Using the distal portion of the colon (8 cm), weight ratios of colon wet weight versus rat body (mg/g) and ulcer surface area were measured (14) and macroscopic damage score was calculated according to the criteria reported previously (15). The modified scoring system is: 0, normal appearance; 1, erythema and inflammation without ulcer; 2, Inflammation and ulcer; 3, ulcer with necrosis. After macroscopic evaluation, full thickness biopsy specimens were fixed in 10% buffered formalin solution, embedded in paraffin, stained with haematoxylin and eosin (H & E) and subjected to the histopathological studies. Microscopic evaluation was performed by a pathologist unaware of the study design. The histological scoring was carried out as previously described (16) with a slight modification according to the criteria shown in table 3.

Statistical analyses

The data of drug released at the end of each dissolution test were analyzed using one-way analysis of variance (ANOVA). The in vivo data were expressed as mean±SEM. Differences between mean values of colon weight/body weight ratio and ulcer surface area were analyzed using ANOVA followed by a Dunnett's post hoc. Comparison between macroscopic and microscopic damage scores were performed using Mann-Whitney U-test and $p < 0.05$ was considered significant in all cases.

RESULTS AND DISCUSSION

In vitro results

Budesonide core pellets were prepared successfully by extrusion-spheronization method using lactulose or mannitol as main excipients. These saccharides pass into the colon unchanged, hydrolyzed rapidly and degraded by colonic enterobacteria to organic acids

(17, 18).

It is the first time that lactulose is used as an excipient for pellet preparation. The surfaces of the pellets of two types of formulations were smooth and spherical. However, lactulose containing pellets compared to those containing mannitol were smoother (Figs.1A, B). Figures 2a and 2b show budesonide release from lactulose and mannitol containing pellet cores respectively. While lactulose improved budesonide release rate even at concentration of 35%, mannitol was ineffective in concentrations below 60% w/w. Based on these results the core formulations containing 35, 40 and 50% lactulose and 60% mannitol were selected as optimum for the coating processes.

The effect of Eudragit E layer thickness on budesonide release is presented in figure 3a. Pellets which were coated to weight increase of 30% (w/w) showed 29.3% of drug release at the end of dissolution time after a lag time of 8 hrs which was enough to retard the drug release under the conditions of simulated intestinal fluid (19). However, the overall budesonide release was very low to ensure drug targeting.

Figures 3b and 3c show the effect of Eudragit E coating level on the polysaccharide release. Expectedly, the higher the coating levels, the slower the polysaccharide release. However, retardation of lactulose release was achieved with thicker Eudragit E layer in comparison to mannitol perhaps due to higher water solubility of lactulose. A comparison of figures 3a, 3b and 3c, shows that mannitol and lactulose were released at a much higher rate than budesonide which could guarantee sufficient acidification of microenvironments around pellets (10).

The influence of the type of polysaccharide on drug release is shown in figure 4a. The release of budesonide from lactulose containing pellets in the presence of RCC were faster than those without RCC (82.5% versus 29.3%, $p < 0.05$) which show that the release under the physiological condition of colon is under influence of microbial degradation of lactulose (20). In contrast, addition of RCC to dissolution medium, had no effect on the release of budesonide from mannitol containing pellets (39.2% versus 33.8%) ($p > 0.05$). These results may be explained either by very low concentration of enzymes responsible for hydrolysis of mannitol or the low rate of hydrolysis of mannitol. Based on these findings, it seems that only easily fermentable polysaccharides such as lactulose with high fermentation rate (21) and water solubility (≈ 75 g/100 ml) were suitable for this formulation design. Figure 4b shows the effect of lactulose concentration on the drug release. As the lactulose concentration increased in the pellet cores, drug release increased (43.4%, 54.7% and 82.5%, respectively) which were higher than those without RCC (29%, $p < 0.05$). Another parameter which was affected by the concentration of lactulose was the lag

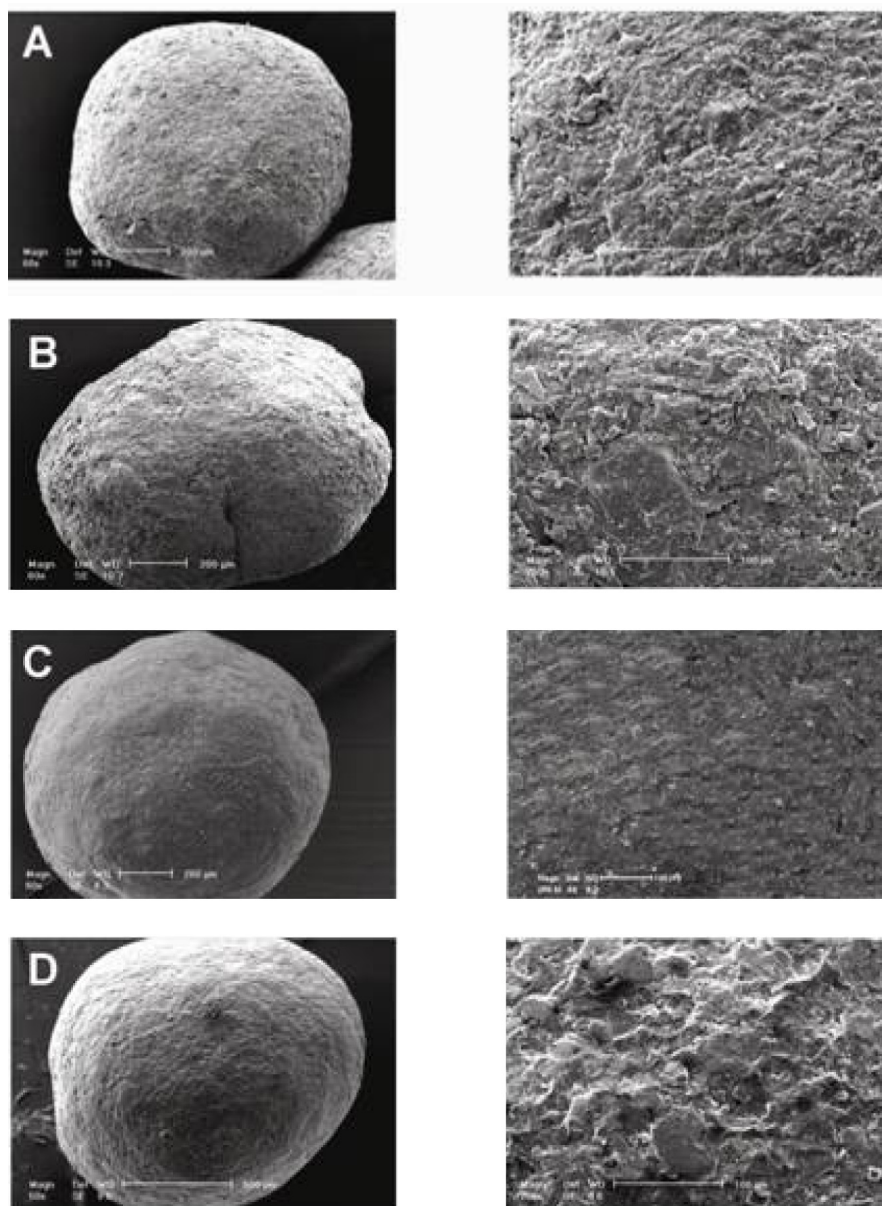


Figure 1. SEM micrographs of budesonide pellets containing A) lactulose, B) mannitol, C) Eudragit E coating and D) Eudragit FS 30D coating with $\times 50$ and $\times 60$ magnification.

time of drug release which decreased as the amount of lactulose increased. The lag time of 50% lactulose containing pellets in the presence of RCC was 6 hrs and in its absence was 8 hrs.

The drug release characteristics of budesonide CODES tablet and optimized pellet formulation containing 50% lactulose coated with 30% Eudragit E and 12% Eudragit FS 30D are shown in figure 4c. In the absence of RCC, the drug release from tablet formulation was slower than that of pellets ($p < 0.05$) with longer lag time which might be due to lower surface area of tablets. However, in the presence of RCC, the drug release from tablets was higher than pellets ($p < 0.05$). The tablets showed no

release up to the end of 8th hour, released 80% of the drug in the next 6 hrs and released was almost complete after 24 hrs. In contrast, pellets after a lag time of 6 hrs released their contents gradually during 18 hrs.

In vivo study

Figure 5A shows a normal colon with no macroscopic damage. In contrast the colon in colitis control group was severely damaged, showing the mucosal congestion, haemorrhage, deep ulcers and budesonide (Fig.5B). Oral administration of budesonide-CODES pellets significantly healed the damaged colon (Fig. 5C) and was more effective

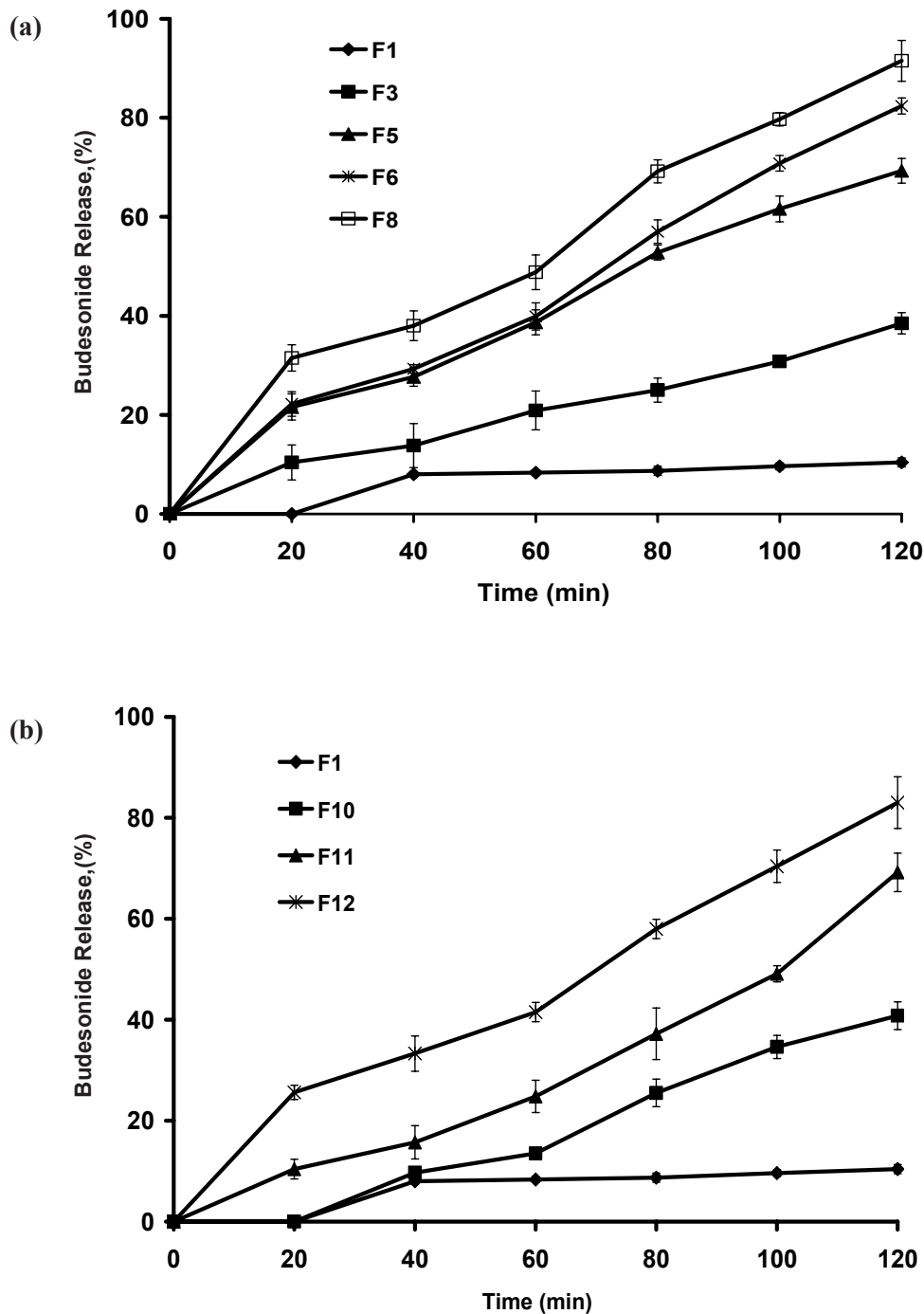


Figure 2. Effect of a) lactulose and b) mannitol amount on budesonide release from core pellets in PBS (pH 6.8 containing 0.5% SLS).

than other treatment groups ($p < 0.05$) except the groups treated with oral prednisolone (Fig. 5K) and budesonide enema (Fig. 5J). After oral administration of budesonide CODES pellets, colon/body weight ratio decreased significantly ($p < 0.05$) compared to colitis group. Further, a better therapeutic effect was observed after administration of budesonide

CODES pellets compared to budesonide solution (22), budesonide uncoated pellets, FS 30D coated pellets and lactulose free coated pellets ($p < 0.05$). This significant decrease in colon/body weight ratio was comparable to the group treated with mesalazine enema and budesonide enema ($p > 0.05$). The percent of ulcerative area was also decreased in the group

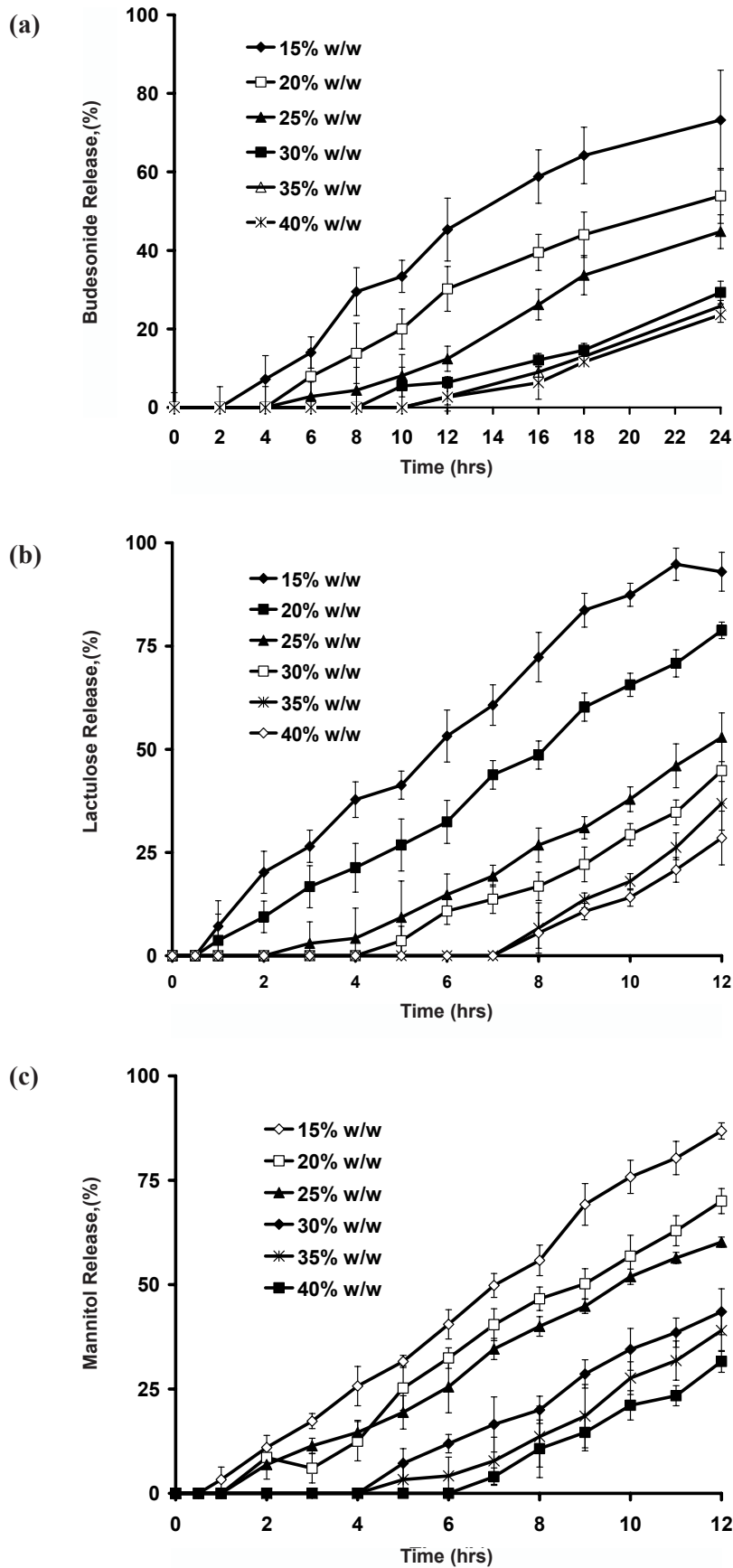


Figure 3. Effect of Eudragit E layer thickness on a) budesonide b) lactulose c) mannitol release from coated pellets.

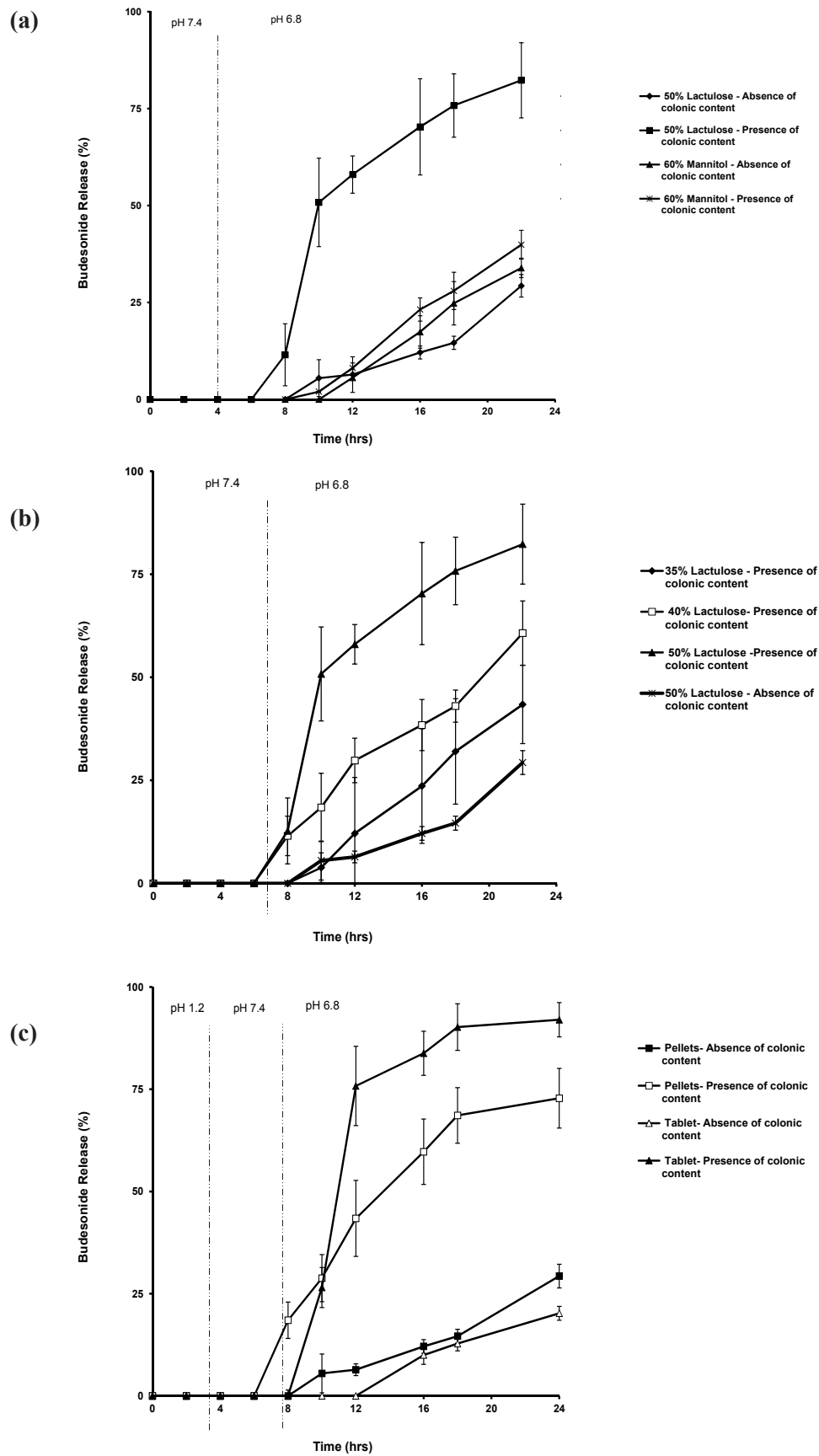


Figure 4. Effect of a) polysaccharide type b) polysaccharide amount c) Dosage form on budesonide release

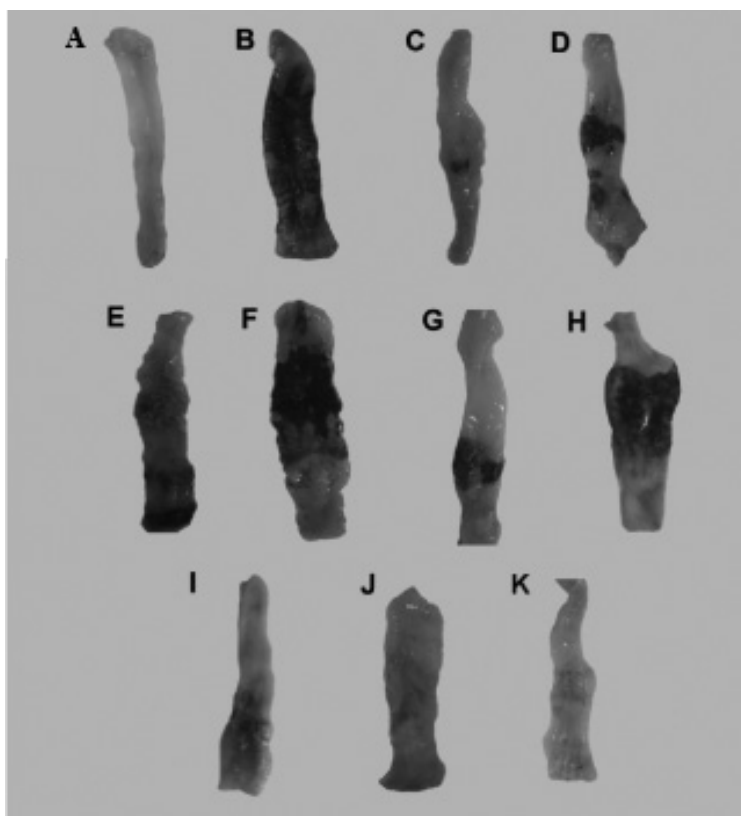


Figure 5. Representative macroscopic appearance of rat colonic mucosa. A= Normal control, B= colitis control, C= Budesonide CODES pellets (300 $\mu\text{g}/\text{kg}/\text{day}$) improved TNBS-induced colitis and decreased the ulcer surface, D= FS 30D coated pellets, (300 $\mu\text{g}/\text{kg}/\text{day}$), E= Lactulose free coated pellets (300 $\mu\text{g}/\text{kg}/\text{day}$), F= Budesonide solution (300 $\mu\text{g}/\text{kg}/\text{day}$), G=Budesonide uncoated pellet (300 $\mu\text{g}/\text{kg}/\text{day}$), H= Placebo pellets, I= Mesalazine enema (400 mg / kg/day, rectally), J=Budesonide enema (20 mcg/kg/day, rectally) and K= Prednisolone (5 mg / kg / day, oral) groups.

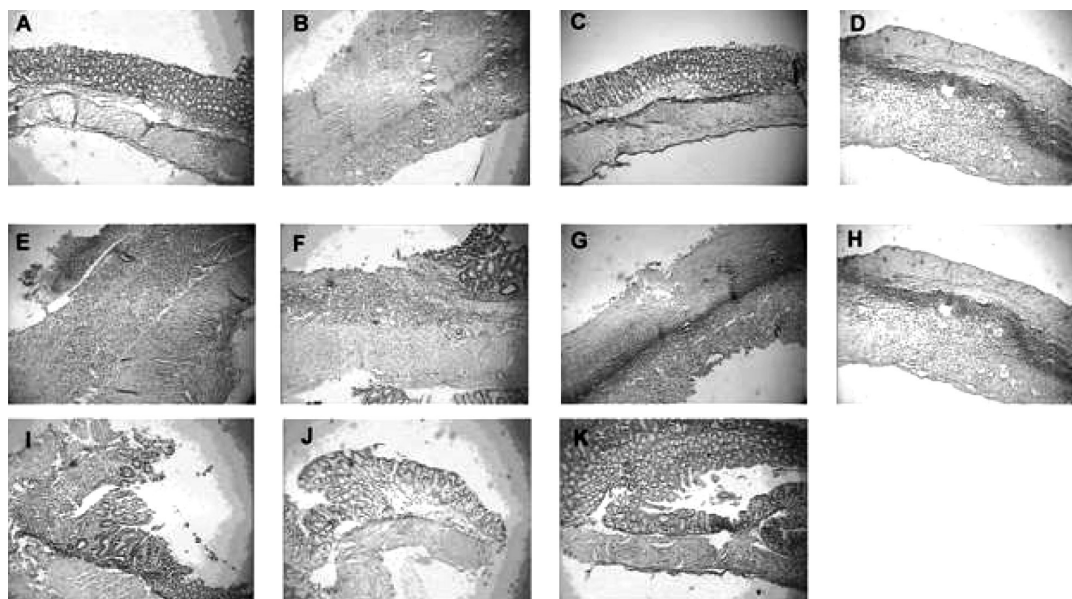


Figure 6. Representative histological appearance of rat colonic mucosa. A= Normal control, B= Colitis control, C= Budesonide CODES pellets (300 $\mu\text{g}/\text{kg}/\text{day}$): The degree of inflammatory cell infiltrate was markedly reduced and there was a near absence of hemorrhage in the mucosa. However crypt structure had not returned to control levels, D=FS 30D coated pellets (300 $\mu\text{g}/\text{kg}/\text{day}$), E= Lactulose free coated pellets (300 $\mu\text{g}/\text{kg}/\text{day}$), F= Budesonide solution (300 $\mu\text{g}/\text{kg}/\text{day}$), G= Budesonide uncoated pellets (300 $\mu\text{g}/\text{kg}/\text{day}$), H= Placebo pellets, I= Mesalazine enema (400 mg/kg/day, rectally), J=Budesonide enema (20 mcg/kg/day, rectally) and K= Prednisolone (5 mg / kg / day, oral). Hematoxylin and eosin stain and original magnification 10 \times .

Table 4. Data of clinical score and macroscopic evaluation of colitis in control and treatment groups after 7 days treatment.

Groups	A	B	C	D	E	F	G	H	I	J	K
Body weight difference (g)	28.3±1.6	-34±5.0	13.8±3.5*	-2.3±2	-13.2±2.8	3.5±2.7	6±2.8	-20±3.2	-5±5.1	17.8±1.7	-9±6.9
Colon /Body ratio (mg/g)	2.5±0.7	12.9±0.7	5.9±1*	7.3±0.7	10.9±0.8	9.1±0.2	8.3±0.2	11.7±0.9	5.5±0.3	4.7±0.4	3.6±0.6
Ulcerative area(%)	0.0±0.0	69.7±5.3	16.2±5*	40.8±9	54.5±6.4	50.2±4.1	51.8±3.7	71.8±3.9	40±7.8	24±6.5	13.3±4.9
Macroscopic score	0.0±0.0	3.0±0.0	2.2±0.2*	2.3±0.4	2.5±0.3	2.7±0.2	2.5±0.3	2.8±0.4	2.7±0.2	2.1±0.4	2.0±0.08

A= Normal control, B= Colitis control, C= Budesonide CODES pellets (300 µg/kg/day), D=FS 30D coated pellets (300 µg/kg/day), E= Lactulose free coated pellets (300 µg/kg/day), F= Budesonide solution (300 µg/kg/day), G= Budesonide uncoated pellets (300 µg/kg/day), H= Placebo pellets I= Mesalazine enema (400 mg / kg/day, rectally) J= Budesonide enema (20 mcg/kg/day, rectally) and K= Prednisolon (5 mg / kg / day, oral). The results were expressed as arithmetic mean ± SEM, (n=6)

*p<0.05 denote significant difference vs negative control group.

Table 5. Data of histopathologic evaluation of colitis in control and treatment groups after 7 days treatment.

Groups	IS	IE	CD	TMS
A	0±0	0+0	0±0	0±0
B	2.83±0.15	2.83±0.15	3.28±0.47	8.14±1.32
C	2.33±0.38	1.83±0.36	1.28±0.64	5.28±1.08*
D	2.41±0.74	2.36±0.39	2.98±0.86	6.94±0.66
E	2.75±0.45	2.59±0.47	3.34±0.52	7.45± 0.74
F	2.33±0.30	2.16±0.36	3.70±0.28	7.57±0.89
G	2.50±0.20	2.16±0.27	2.83±0.76	7.0±0.97
H	2.66±0.20	2.66±0.36	3.0±0.8	7.57±0.71
I	2.83±0.15	2.66±0.19	2.28±0.99	6.14±1.15
J	3.0±0.90	2.50±0.20	2.57±1.1	6.85±0.46
K	2.16±0.36	1.66±0.19	1.85±1.30	4.71±1.14

A= Normal control, B=Colitis control, C= Budesonide CODES pellets (300 µg/kg/day), D=FS 30D coated pellets (300 µg/kg/day), E= Lactulose free coated pellets (300 µg/kg/day), F= Budesonide solution (300 µg/kg/day) G=Budesonide uncoated pellets (300 µg/kg/day), H= Placebo pellets, I= Mesalazine enema (400 mg / kg/day, rectally) J= Budesonide enema (20 mcg/kg/day, rectally) and K= Prednisolone (5 mg / kg / day, oral). IS= Inflammation Severity, IE= Inflammation Extent, CD= Crypt Damage, TMS= Total Microscopic Score. The results were expressed as arithmetic mean ± SEM, (n=6)

*p<0.05 denote significant difference vs colitis control groups

treated with budesonide CODES pellets and groups of prednisolone, mesalazine enema and budesonide enema ($p<0.05$). Table 4 summarizes the data of macroscopic evaluation of colon damage of control and treatment groups.

Figure 6A shows the histology of normal colon. As it is shown in figure 6B other than inflammatory cellular infiltration, the colitis induced colon showed extensive necrotic destruction of epithelium, hemorrhage, edema, crypt damage and ulceration at mucosal and sub-mucosal layers. Examination of the histopathology slides (Fig. 6 A-K) revealed a dramatic decrease in the mucosal injury after

treatment with CODES pellets (Fig. 6C). The degree of inflammatory cell infiltrate was markedly reduced and almost no hemorrhage was observed in the mucosa. Table 5 shows the means of histological parameters in colon tissue for each group. All groups treated with prednisolone, mesalazine enema, budesonide enema and budesonide CODES pellets, showed histological improvement compared to colitis control group and could attenuate the total histological score of colitis ($p<0.05$).

From the results of this study it seems that CODES budesonide pellets could be used to enhance the effectiveness of budesonide in treatment of IBD.

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