



## Effect of Ibuprofen-beta-Cyclodextrin prodrug on Colon Targeted Drug Delivery System

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### Abstract

Targeted drug delivery to colon is highly desired for the treatment of diseases such as colon cancer, IBD, Crohn's disease etc., and for the systemic delivery of proteins and peptide drugs. A colonic drug delivery system is expected to protect the drug during the transit time in the GIT and to allow its release only in the colon. The objectives of the present project are to investigate the colon specificity of polysaccharides in synthesis of prodrugs and in formulations. The polysaccharides as polymer are mainly used to carry the drug moiety to the colon both in prodrug concept and formulation. Two prodrugs (Ibuprofen -  $\beta$ -cyclodextrin and Budesonide -  $\beta$ -cyclodextrin) have been synthesized and investigated. They were found to be colon specific, though, the yield was found to be very poor. From the *IN-VIVO* study they were also found to be very effective. As far as the formulations with polysaccharides are concerned, a novel polymer khaya gum was investigated for its colon specificity and compared with a well established polysaccharide polymer guar gum. It was found that the polysaccharides are very effective for targeting the drug to colon provided they are further coated with enteric polymer. Further, the present investigation also revealed that the effect of solubility of the drugs on the colon specificity of the polysaccharides. The weakly basic drug being very soluble in the acidic pH and the hydrophilic nature of the polysaccharides leads to release the drug in the stomach to greater extent compared to a drug molecule which is poorly soluble in the acidic pH. The investigation revealed that the prodrugs of drug molecules with polysaccharides are better colon specific compared to the formulations prepared with the polysaccharides. This is because the hydrophilicity nature of the polysaccharides releases the drug in the stomach to some extent especially weakly basic drugs. However, they are very effective when coated further with enteric polymer. Prodrugs with polysaccharides, though soluble in the aqueous solutions, there is a need of enzyme system to break the covalent bond formed between the drug molecule and the polysaccharide. Hence, irrespective of the nature of the drugs, prodrug approach is better to target the drugs to colon compared to the formulations with polysaccharides.

**Keywords:** Prodrug, polysaccharide, khaya gum, guar gum, colon specificity.

### Introduction

Prodrug is defined as pharmacologically inert chemical derivatives that can be converted in vivo to the active drug molecules, enzymatically or non enzymatically to exert a therapeutic effect. Ideally the prodrug should be converted to the original drug as soon as the goal is achieved, followed by the derivatizing group<sup>1</sup>. Colon targeted drug delivery system is to protect the drug from absorption and/ or to the environment of the upper GI tract and enable selective release of drugs in the proximal colon. It is naturally of value for the tropical treatment of diseases of colon such as colon's disease, colorectal cancer and amoebiasis<sup>2</sup>. Targeted drug delivery to the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs<sup>3,4</sup>. The colon specific drug delivery system (CDDS) should be capable of protecting the drug *en route* to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon<sup>5</sup>. The

colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity and intensity of digestive enzymes (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus protecting peptide drugs from hydrolysis and enzymatic degradation in duodenum and jejunum and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability<sup>6</sup>. And finally, since the colon has a long residence time which is up to 5 days thus is highly responsive to absorption enhancers<sup>7</sup>. Cyclodextrins are cyclic oligo saccharides consisted of 6-8 glucose units through -1, 4-glycosidic bonds and have been utilized for improvement of certain properties of drugs, such as solubility, stability, bioavailability, etc., by formation of inclusion complexes. CyDs are barely known to be hydrolyzed and only slightly absorbed in passage through the stomach and small intestine. Most bacteroids isolated from the human colon are capable of degrading CyDs, as evidenced by their ability to grow on CyDs using them as sole carbon source and by the stimulation of cyclodextrinase activity by exposure to CyDs. This biodegradable property makes CyDs useful as a colontargeting carrier; thus, CyD prodrugs may serve as a source of site specific delivery of drugs to the colon. A particular challenge in the pharmaceutical field is the development of site specific dosage forms that are able to control time of delivery, for the release of active ingredients in the lower part of the small intestine or colon. The large intestine, though difficult to reach by peroral delivery, is still deemed to be the ideal site for the delivery of agents to cure the local diseases of the colon. A number of other serious diseases of the colon like colorectal cancer might also be capable of being treated more effectively, if drugs were targeted to the colon. Colonic drug delivery is also useful for systemic absorption of drugs, especially peptides and proteins, because of less hostile environment prevailing in the colon compared to stomach and small intestine. Due to the distal location of the colon in the gastrointestinal tract, a colon specific drug delivery should prevent drug release in the stomach and small intestine, and produce an abrupt onset of drug release upon entry into the colon<sup>9,10</sup>. Budesonide is a synthetic glucocorticosteroid with mainly anti-inflammatory activity. Although it is rapidly and almost completely absorbed from the gastrointestinal tract, its bioavailability is low (about 10%) due to extensive first-pass metabolism in the liver. Furthermore, the metabolites produce less than 1% of the glucocorticoid activity when compared to the unchanged budesonide<sup>11,12</sup>.

## Materials and Method

**Materials:** Budesonide was obtained as a gift sample from Astra Zeneca (Bangalore). Khaya gum, Eudragit S-100 obtained from Inaba University, Nigeria and Degussa Pvt Ltd, Germany respectively. Other chemicals like Acetic acid, Pot.dihydrogen phosphate, Hydrochloric acid are obtained from Sd Fine Chemicals, Mumbai. Sodium Hydroxide purchased from Merck India Limited, Mumbai.

### Method:

The preparation includes the following 3 steps

#### **i. Preparation of Fast disintegrating core tablets of budesonide by direct compression technique**

The composition of core tablets of budesonide is given in Table.1. The fast disintegrating core tablets of budesonide (average weight 250 mg) for compression coating were prepared by direct compression technique. Sodium starch glycolate and spray dried lactose were included in the formulation to obtain budesonide tablets with fast disintegrating characteristics (disintegration time < 30seconds). Budesonide, sodium starch glycolate, spray dried lactose, magnesium stearate and talc were weighed and thoroughly mixed. The mixture was compressed into tablet at an applied force of 4000 Kg using 8 mm round, flat-faced, plain punches in single station tablet punching machine (M/s Cadmach, Ahmedabad).

#### **ii. Compression coating of fast disintegrating core tablets of budesonide with granules containing khayagum (formulation K1, formulation K2 and formulation K3)**

The composition of compression coat formulations is given in Table 5.03. The compression coated formulations were prepared using khaya gum. Granules of the above material were prepared by wet granulation technique using 10% starch paste as binder. The prepared granules were dried at 50°C for one hour and passed through sieve number 16, placed over sieve number 44 to separate granules and fines. About 15% of fines were added to the granules. The above granules were lubricated using talc and magnesium stearate in the ratio 2:1. Compression coating was carried out using 13 mm round, flat, plain punches. About one third of the granules were placed in 13 mm die cavity, the fast disintegrating core tablets of budesonide (8 mm) was carefully positioned in the centre of the die cavity and filled with remainder of granules.

#### **iii. Enteric coating of the compression coated tablets of formulation K3 with eudragit S -100 (formulation KBC)**

The compression coated tablets of formulation K3 were further coated using an enteric coating polymer such as eudragit S-100, following dip coating technique. Coating was applied to the tablet core by dipping into the coating liquid (eudragit S-100 dissolved in acetone). The wet tablets were dried in a conventional manner in coating pan. Alternative dipping and drying steps were repeated four times to obtain the desired coating.

## Evaluation

### Evaluation of In-process parameters of the tablets

#### A. Hardness, friability and weight variation tests

Hardness and friability of tablets were measured using Monsanto hardness tester and Roche friabilator respectively. The weight variation test of the tablets was done as per the guidelines of IP.

#### B. Drug content estimation

Ten tablets from each formulation of compression coated (formulation K1, formulation K2, formulation K3) and the core tablets were powdered separately and the powder equivalent to one tablet (250 mg, i.e., equal to core tablet weight) was transferred into a 100 ml volumetric flask. Initially, 25 ml of methanol was added and allowed to stand for 6 h with intermittent shaking to ensure the complete solubility of the drug. After suitable dilutions of 1 ml of above solution, filtered and drug content was estimated using Jasco V 530 UV Visible spectrophotometer at 244.3 nm against a mixture of methanol and phosphate buffer (1:3) as blank. The drug content was estimated by using calibration curve.

#### C. Swelling studies

One tablet each from all the compression coated formulations and formulation KBC, was randomly selected, weighed individually ( $W_1$ ) and placed separately in petri dishes containing 10 ml of phosphate buffer pH 7.4. After 2, 5, 8, 12 and 24 h, the tablets were carefully removed from petri dishes and excess water was removed using filter paper. The swollen tablets were reweighed ( $W_2$ ) and swelling index of each tablet was calculated using the equation 5.1 and expressed in terms of percentage<sup>75</sup>. The experiment was repeated three times. The present research works discuss the development of a UV estimation method for febuxostat. Simple, fast, accurate and cost efficient and reproducible. Spectrophotometric method has been developed for the estimation of febuxostat in bulk and tablet formulations. The wave length ( $\lambda_{max}$ ) selected for the febuxostat at was 315 nm. The linearity for this drug at the selected wavelength is lies between 0.2 to 1 $\mu$ g/ml. Beer's law obeyed in this concentration range with correlation coefficient of 0.9999. The limit of detection and limit of quantification was found to be 1.0585 & 3.2077  $\mu$ g/ml respectively. The validity of the described procedure was assessed. The proposed method was successfully applied to the determination of febuxostat in pharmaceutical formulations without any interference from common excipients.

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$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} \times 100 \quad (5.1)$$

#### D. Dissolution studies

The ability of the khaya gum compression coated tablets to remain intact in the physiological pH environment of stomach and small intestine was assessed by studying the release profile at different pH. The drug release studies were carried out using USP dissolution test apparatus (XXIII), paddle type. Study was conducted in 900 ml of dissolution medium maintained at  $37 \pm 0.5$  °C with a paddle rotation speed of 100 rpm. The pH of the medium was varied over the course of the experiment: 0.1 N hydrochloric acid (pH 1.2) was used for the first 2 h, phosphate buffer (pH 7.4) was used for the next 3 h and of phosphate buffer pH 6.8, till the complete release of drug took place. Samples of 5 ml volume were withdrawn at predetermined time intervals and were replaced with fresh dissolution medium to maintain sink conditions. Samples withdrawn were later filtered and assayed spectrophotometrically at 244.3 nm using corresponding buffers as blank. The amount of budesonide released at each time interval was calculated. The percentage drug release was then plotted against time and the release profiles were studied.

**Table No 1 Composition of budesonide core tablets**

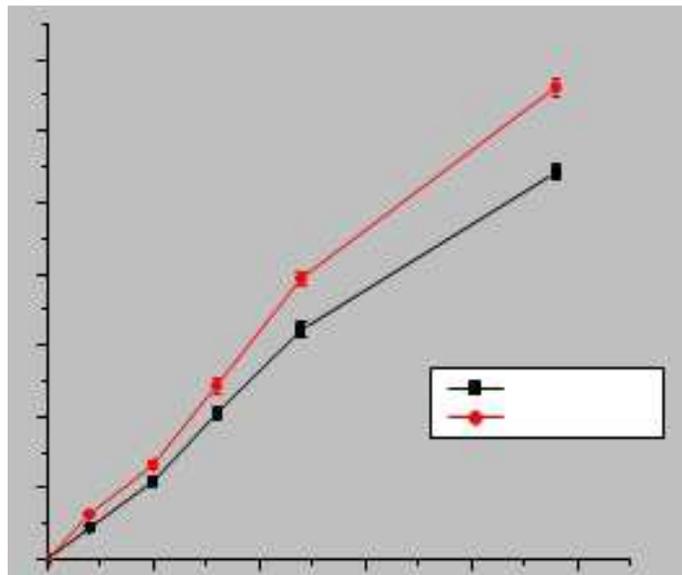
Ingredients	Quantity (mg)
Budesonide	9
Avicel PH 102	80
Spray dried lactose Sodium starch glycolate	80
Talc	75
Magnesium stearate	3.5
	2.5
<b>Average weight</b>	<b>250</b>

**Table No 2 In-process parameters of the budesonide tablets**

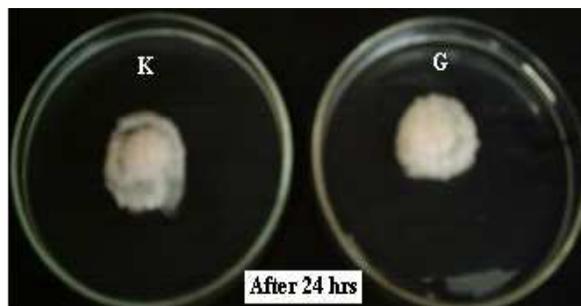
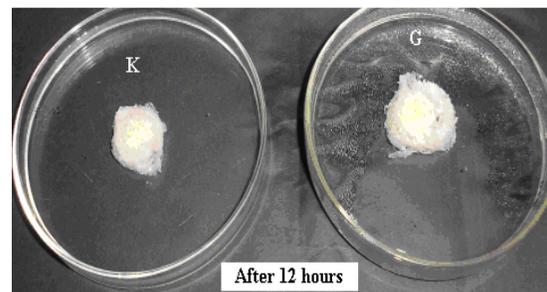
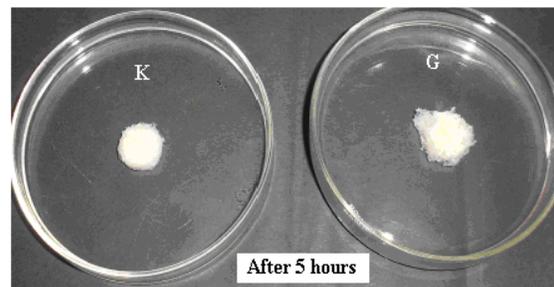
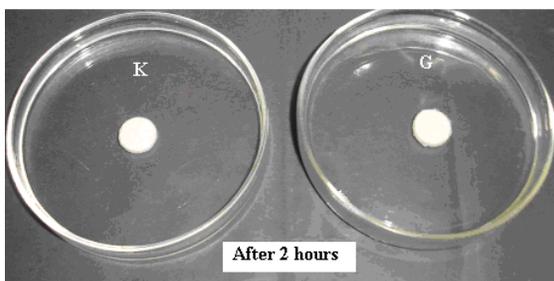
Formulation	Hardness <sup>a</sup> Kg/cm <sup>2</sup>	Percentage Weight Variation *	Percentage Friability* <sup>a</sup>	Percentage Drug content*
<b>Core tablet</b>	3.16 ± 0.859	2.680 ± 0.56	2.76 ± 0.43	100.98 ± 1.04
<b>K1</b>	6.95 ± 0.921	2.56 ± 0.68	2.63 ± 0.69	100.63 ± 1.08
<b>K2</b>	7.25 ± 0.684	2.47 ± 0.45	2.84 ± 0.92	99.41 ± 1.04
<b>K3</b>	8.15 ± 0.850	2.348 ± 0.67	2.74 ± 0.75	100.88 ± 1.03
<b>KBC</b>	8.55 ± 0.980	2.381 ± 0.45	0.820 ± 0.03	-

**Table No.3 Percentage swelling index of compression coated and enteric coated tablets of budesonide**

Formulation	% Swelling index*				
	2 h	5 h	8 h	12 h	24 h
<b>K1</b>	17.23 ± 0.78	39.21 ± 1.28	65.65 ± 1.52	72.36 ± 1.85	155.25 ± 1.97
<b>K2</b>	20.36 ± 1.23	44.58 ± 1.25	70.12 ± 1.65	85.25 ± 1.35	185.56 ± 1.86
<b>K3</b>	22.04 ± 1.78	54.63 ± 3.71	102.12 ± 3.67	160.65 ± 5.13	270.84 ± 5.45
<b>KBC</b>	18.52 ± 1.57	54.00 ± 2.89	99.61 ± 5.34	159.71 ± 4.58	267.59 ± 6.17



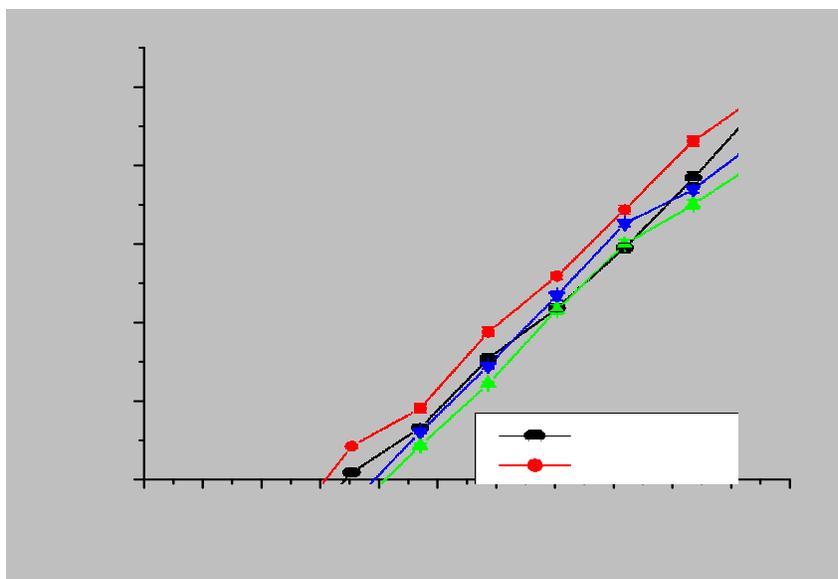
Comparative swelling index graph



Swelling of budesonide compression coated tablets

Time (h)	Percentage Drug Release*			
	Fomulation KB	Formulation GB	Fomulation KBC	Formulation GBC
0.0	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00
0.5	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00
1.0	03.60±0.13	05.78±0.43	00.00±0.00	00.00±0.00
2.0	06.40±0.35	09.65±0.38	00.00±0.00	00.00±0.00
4.0	10.20±0.22	14.24±0.52	02.32±0.07	02.34±0.07
5.0	12.20±0.65	16.40±0.54	05.33±0.09	06.89±0.85
6.0	20.00±0.54	25.54±0.43	11.73±0.14	13.46±0.78
8.0	29.30±0.44	33.47±0.92	25.55±0.56	28.51±0.35
10.0	44.00±0.85	49.62±0.88	38.66±0.47	42.39±0.56
12	54.55±0.78	61.39±0.71	54.22±0.89	57.21±0.91
14	67.33±0.93	75.34±0.96	68.00±0.91	72.44±0.68
16	82.00±1.25	89.77±0.98	76.44±1.01	79.67±0.79
18	97.77±1.02	99.77±1.13	85.88±1.25	90.47±0.91
20	-	-	96.44±1.17	98.11±0.86

\*Each value is an average of triplicates



Comparative *in vitro* drug release profile from khaya gum and guar gum formulations in absence of rat small intestinal and cecal contents

Comparative *in vitro* drug release profile data from khaya gum and guar gum formulations in presence of rat small intestinal and cecal contents

Time (h)	Percentage Drug Release*			
	Fomulation KB	Formulation GB	Fomulation KBC	Formulation GBC
0.0	00.00±0.00	00.00±0.00	00.00±0.00	00.00±0.00
0.5	00.00±0.00	00.80±0.15	00.00±0.00	00.00±0.00
1.0	02.80±0.26	03.40±0.55	00.00±0.00	00.00±0.00
2.0	4.08±0.59	07.80±0.83	00.00±0.00	00.00±0.00
4.0	12.43±0.94	15.60±0.97	02.08±0.57	02.45±0.00
5.0	22.34±0.77	26.40±0.89	08.71±0.34	09.96±0.25
6.0	36.44±0.57	41.33±1.35	17.23±0.82	19.45±0.89
8.0	54.73±0.83	59.00±0.25	32.32±0.75	35.33±0.58
10.0	78.66±0.54	83.11±0.99	52.78±0.92	57.11±0.73
12	97.70±0.99	98.22±0.87	66.87±0.98	71.11±1.35
14	-	-	78.67±0.90	82.77±1.56
16	-	-	93.12±0.97	94.56±0.89

## Results and Discussion

### In-process parameters

In the present study oral colon targeted formulations for budesonide were developed with guar gum as carrier and compared with novel polymer khaya gum. It was earlier reported that guar gum could be used as a carrier for colon specific drug delivery in the form of either a matrix tablet or as a compression coat over a drug core tablet, hence used for comparison of khaya gum in establishing colon specific release. In the earlier chapter colon specificity of khaya gum was investigated at three different concentrations and the effect of highest concentration (40% w/w) of khaya gum was compared with guar gum at same concentration level. It was found that there is no significant difference between the hardness of the compression coated tablets containing khaya gum or guar gum, and the enteric coated tablets (Table 2).

The results of the friability of compression coated tablets prepared with guar gum are within the permissible limits of IP. The results of weight variation studies showed that all the batches of tablets complied with the weight variation limits as per Indian Pharmacopoeia i.e., the percentage weight variation of the individual tablets remained within 7.5% limit for tablets weighing 250 mg and 5% for 450 mg tablets, and not more than 2 tablets in a batch of 20 deviated from  $\pm 5\%$  weight variation. A significant difference in percentage swelling index was seen between different formulations of khaya gum and guar gum (Table 3).

### Conclusion

The present study was aimed at developing colon targeted drug delivery system of budesonide. As far as the in-process parameters are concerned, no significant differences have been observed between the khaya gum and guar gum based formulations. However, the swelling index was found to be higher for guar gum and indicated that guar gum is more hydrophilic than the khaya gum. This result also reflected in the release profile. Though not significantly, the formulations containing guar gum released the drug faster than the khaya gum based formulations.

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