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Exploration and Formulation of Oral Selective Polysaccharide Based, Budesonide-β-Cyclodextrin for Colon Specific Drug Delivery System

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A B S T R A C T

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. 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. Prodrug, Budesonide-β-cyclodextrin have been synthesized and investigated. This was 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

A R T I C L E I N F O

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1. Introduction

Since from last decade a novel oral colon-specific drug delivery system (CDDS) has been developing as one of the site-specific drug delivery systems. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration[1,2]. CDDS is convenient for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation *etc.*, CDDS, also selectively deliver drug to the colon, but not to the upper GI tract[3-7]. Colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon. CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis[8,9].

Glucocorticoids (GCs) and aminosalicylates (e.g., 5-ASA) constitute the mainstays of treatment for inflammatory bowel diseases (IBD) which includes ulcerative colitis (UC) and Crohn's Disease (CD). Biological medicinal products such as antibodies to TNFa are becoming more established but these remain expensive and less widely available. Corticosteroids are especially useful for inducing remission in acute cases of IBD. Their chronic use is however limited by serious systemic side effects[10]. This range from cosmetic problems such as Cushingoid features, to growth failure in children, hypertension, osteoporosis, diabetes mellitus and glaucoma as well as more rare CNS dysfunctions including depression and psychosis. There have been intensive efforts made to develop GC therapies for IBD treatment that minimize side effects[11, 12].

The prodrug approach can be an effective way to target the colon as reflected in the clinical success of azo prodrugs such as osalazine. This is specifically activated by the activities associated with the colonic microflora to which it is exposed following transit through the intestinal tract[13]. Prodrug approaches have also been investigated for targeting budesonide, including compounds employing as vectors glycosidases associated with the colonic microflora. We have recently introduced a novel design for colon targeting that exploits azoreductases to trigger drug release. Reduction of the prodrug leads to liberation of an anilide ester that is poised to undergo ring closure, releasing the drug. The design was developed for targeting prednisolone to the colon by attachment of the promoiety to the steroid 21-OH group that depresses intestinal absorption[14]. 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 cyclodextranase activity by exposure to CyDs. This biodegradable property makes CyDs useful as a colon targeting carrier; thus, CyD prodrugs may serve as a source of site specific delivery of drugs to the colon[15]. 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.

2. Materials and Methods

Materials: Budesonide was obtained as a gift sample from Astra Zeneca (Banglore). 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[16]:

The preparation includes the following 3 steps

i. **Preparation of Fast disintegrating core tablets of budesonide:** 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 < 30 seconds). 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**: 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:** 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 S100 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[17]. 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 dilations 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 in terms of percentage. 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 febuxost at in bulk and tablet formulations[18]. The wave length (λ max) selected for the febuxost at was 315 nm. The linearity for this drug at the selected wavelength is lies between 0.2 to 1µg/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 µg/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. 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 febuxost at in bulk and tablet formulations. The wave length (λ max) selected for the febuxost at was 315 nm. The linearity for this drug at the selected wavelength is lies between 0.2 to 1µg/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 µg/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.

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

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[19]. 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 ± 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 (pH1.2) 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[20]. 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 1: Composition of budesonide core tablets

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

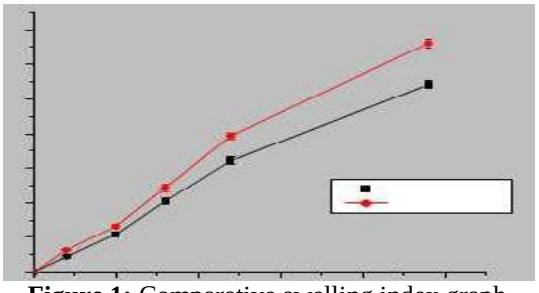

Figure 1: Comparative swelling index graph

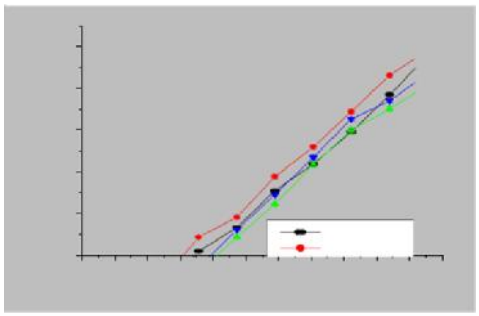

Figure 2: Comparative in vitro drug release profile from khaya gum and guar gum formulations in absence of rat small intestinal and cecal contents

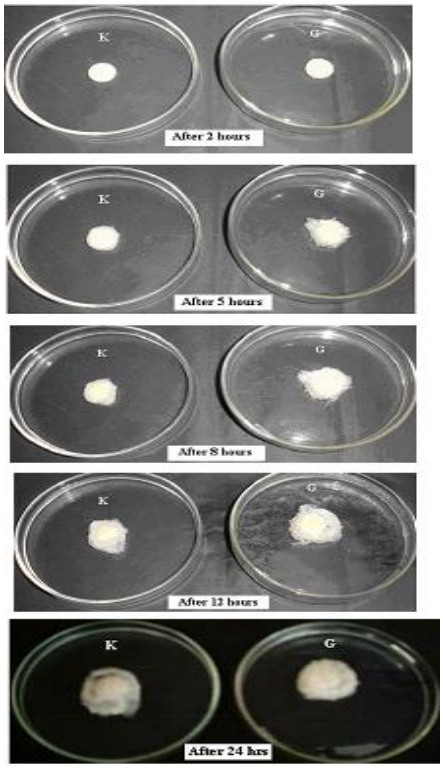

Figure 3: Swelling of budesonide compression coated tablets

3. Results and Discussions

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 ± 5% weight variation. A significant difference in percentage swelling index was seen between different formulations of khaya gum and guar gum (Table 3).

4. 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.

Table 2: In-process parameters of the budesonide tablets

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

Table 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
K1	17.23 ± 0.78	39.21 ± 1.28	65.65 ± 1.52	72.36± 1.85	155.25± 1.97
K2	20.36 ± 1.23	44.58 ± 1.25	70.12 ± 1.65	85.25± 1.35	185.56± 1.86
K3	22.04 ± 1.78	54.63 ±3.71	102.12± 3.67	160.65± 5.13	270.84± 5.45
KBC	18.52 ± 1.57	54.00 ±2.89	99.61 ± 5.34	159.71± 4.58	267.59± 6.17

Table 4: Cumulative percentage drug release

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

Table 5: Percentage Drug Release

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

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