

INVESTIGATION AND COMPARISON OF COLON SPECIFICITY OF NOVEL POLYMER KHAYA GUM WITH GUAR GUM

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ABSTRACT

To investigate the colon specificity of novel natural polymer khaya gum and compare with guar gum. Release profile of tablets was carried out in presence and absence of rat cecal contents. The fast disintegrating core tablets of budesonide, were initially prepared by direct compression technique. Later, these tablets were coated with khaya gum or guar gum. After suitable pre compression and post compression evaluation, these tablets were further coated using Eudragit L-100 by dip coating technique. X-ray images were taken to investigate the movement, location and the integrity of the tablets in different parts of gastro intestinal tract in rabbits. The release profiles revealed that khaya gum or guar gum, when used as compression coating, protected the drug from being released in the upper parts of the gastro intestinal tract to some extent but the enteric coated formulations completely protected the drug from being released in the upper parts of the gastro intestinal tract, and released the drug in the colon by bacterial degradation of gums. It was found that both the polysaccharide polymers exhibited different release profiles in presence and absence of rat cecal contents. However, further enteric coat helped in targeting the drug to colon very effectively. Better dissolution models revealed the colon specificity of polysaccharides and alone can not be used either for targeting the drug to the colon or for sustaining or controlling the release of drug.

Keywords: Colon-specific, Budesonide, Khaya gum, Guar gum, compression coated tablets.

INTRODUCTION

Oral controlled release formulations for small intestine and colon have received considerable attention in the past 20-25 years for variety of reasons including pharmaceutical superiority and clinical benefits derived from the drug release pattern that are not achieved with traditional immediate or sustained release formulation (Nykanen *et al.*, 2001). Colonic drug delivery has gained increased importance, not only for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, Ulcerative colitis, Irritable bowel syndrome, but also for the potential it holds for the systemic delivery of proteins and therapeutic peptides. 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 (Asqhar and Chandran, 2006).

Colon is a site where both local and systemic delivery can take place. Local means of drug delivery could allow topical treatment of Inflammatory Bowel Diseases like Crohn's disease or Ulcerative colitis. The treatment might be more effective if the drug substance were targeted directly to the site of action in 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 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 (Al Saidan *et al.*, 2005). The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about 6 m of the small intestine (Ashford and Fell 1994). 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. Such a system can be formulated utilizing some specific conditions existing in the colon, in comparison to other parts of the GIT.

Khaya gum is a polysaccharide obtained from the incised trunk of tree *Khaya grandulifolia*, Family Meliaceae, a typical West African mahogany tree. Odeku *et al* (2005) reported that khaya gum is capable of protecting the drug from being released in the acidic environment prevailing in the stomach and small intestine. They are degraded by the colonic bacterial enzymes, thereby releasing the drug in the colon where there is local action and improved absorption (Odeku and John, 2005). Guar gum is a natural polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, Family Leguminosae. Guar gum

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hydrates and swells in cold water forming viscous colloidal dispersion or solution. This gelling retards the drug release from the tablet and susceptibility to microbial degradation in large intestine. Drug release studies mimicking mouth to colon transit have shown that the guar gum protects the drug from being released completely in the physiological environment of the stomach and small intestine.

Budesonide is an anti-inflammatory synthetic potent corticosteroid. Once absorbed, distribution of budesonide is extensive and protein binding is roughly 90%. Budesonide undergoes approximately 85% first pass metabolism. Plasma half life is approximately 2 h and when absorbed systemically, it shows severe adverse effects (Maria *et al.*, 2005). To overcome these drawbacks, the present study was undertaken to investigate the colon targeted drug delivery system of budesonide. The drug delivery system was prepared using natural novel polymer khaya gum and results compared with already established guar gum in the form of compression coating. The release profiles of these tablets were further compared in presence and in absence of rat cecal contents, with tablets which are enteric coated using Eudragit L-100.

MATERIALS AND METHODS

Materials

Budesonide (micronized) was obtained as a gift sample from Zydus Cadila Pharmaceuticals, Ahmedabad. Khaya gum was obtained from University of Ibadan, Nigeria. Guar gum was purchased from Merck limited, Mumbai. Eudagit L-100 was purchased from Degussa, Mumbai. All other chemicals used were of analytical grade.

Methods

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 the budesonide tablets with fast disintegrating characteristics (disintegrating 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 using a single station tablet punching machine (M/s Cadmach, Ahmedabad). The fast disintegrating core tablets were tested for hardness, disintegration, friability etc.

Table 1: Composition of Budesonide core tablets

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

mg = milligram

Compression coating of fast disintegrating core tablets of Budesonide with granules containing Khaya gum/guar gum (Formulation K/G)

The composition of compression coat formulation is given in table 2. 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. The total weight of the coat formulations used in Formulation K is 200 mg and in Formulation KC is 400 mg. It was then compressed around the core tablets at an applied force of 5000 Kg on a single station tableting machine (M/s Cadmach, Ahmedabad). The compression coated tablets were subjected to hardness, disintegration, friability, weight variation, drug content and drug release characteristics. Similar procedure was followed for the preparation of fast disintegrating tablets with Guar gum polymer as well (Formulation G).

Table 2: Composition of coating formulation using Khaya gum or Guar gum

Ingredients	Core tablet (mg)
Khaya gum or Guar gum	200
Tri calcium phosphate	8
Starch past (10% w/v)	30
Talc	8
Magnesium stearate	4

mg = milligram

Enteric coating of the compression coated tablets with Eudragit L-100 (Formulation KC & GC)

The compression coated tablets of micronized budesonide prepared using khaya gum and guar gum separately, were further coated using an enteric coating polymer such as Eudragit L-100, using dip coating technique.

Evaluation of physico-chemical properties of tablets

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 (1996).

Drug content estimation

One tablet of each formulation 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 Jasco V 530 UV Visible spectrophotometer at 244.3 nm and methanol was taken as blank. The drug content was estimated by using calibration curve.

Swelling studies

One tablet from each formulation was randomly selected, weighed individually (W_1) and placed separately in petri dishes containing 10 ml of phosphate buffer pH 7.4. After 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 1 and expressed in percentage (Yeole *et al.*, 2006).

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} \times 100 \quad (1)$$

Dissolution studies

The ability of the khaya gum and guar 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 various 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 $37 \pm 0.5^\circ\text{C}$ 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 3 h and 0.05 M phosphate buffer (pH 7.2) was used for the next 3 h. 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

methanol as blank. The amount of micronized budesonide released at each time interval was calculated from the absorbance of the samples. Dissolution studies were performed in triplets and mean values were reported. The percentage drug release was then graphed against time and the release profiles were studied.

In order to assess the susceptibility of khaya gum 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.

In order to mimic intestinal environment, especially enzymes glycosidase specially acting on khaya gum and guar gum in the caecum, male albino rats weighing between 150-200 gm maintained on normal diet were incubated with teflon tubing and 4% dispersion of khaya/guar gum in water were administered for 7 days. All the rats were killed by spinal traction, 30 minutes before the commencement of drug release studies. The abdomens were opened, cecal bags were isolated, ligated at both ends and cut loose and immediately transferred into phosphate buffer pH 6.8 previously bubbled with nitrogen gas. As the caecum is naturally anaerobic, all these operations were carried out under nitrogen gas.

In vitro drug release studies in the presence of rat cecal contents were carried out using USP dissolution test apparatus (XXIII), basket type. The dissolution medium used for the compression coated tablets were 900 ml of 0.1M hydrochloric acid pH 1.2 for first 2 h, 900 ml of Sorensen's buffer pH 7.4 for 3 h and finally 500 ml of phosphate buffer pH 6.8 having rat cecal contents till the complete release of drug took place. The basket was rotated at 100 rpm and the medium was maintained at a constant temperature of $37 \pm 0.5^\circ\text{C}$. Samples of 5 ml volume were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 244.3 nm. Dissolution studies were performed in triplets and mean values were reported. The percentage drug release was then graphed against time and the release profiles were studied.

In vivo targeting efficiency

In vivo targeting efficiency study was carried out to check the efficiency of the formulation to target to colon after obtaining ethical clearance. In this study, healthy rabbits were fasted overnight. The enteric coated tablets (4 mm) of micronized budesonide containing radio opaque material such as barium sulphate (15%) were given to the fasting rabbits with a glass of water. After the administration of the formulation, X-ray images were taken under the supervision of a radiologist, to follow the movement, location and the integrity of the tablets in different parts of GIT (Purushotham *et al.*, 2003).

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for budesonide using khaya gum and guar gum as carrier. 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 here for comparison for khaya gum in establishing colon specific release.

Physico chemical characteristics of tablets

The comparatively low hardness of the core tablets indicates that the main forces holding the particles together are probably weak bonds due to interlocking of the irregularities on the surface of particles. It was found that there is no significant difference between the hardness of the core tablets containing khaya gum or guar gum, and the enteric coated tablets.

The results of the friability of core tablets & compression coated tablets are within the permissible limits. The core tablets had higher percentage friability due to lower hardness. The low friability of the compression coated tablets may be attributed to inter particulate bridges that are formed due to the gums used, which holds the drug

and excipient particles between them very strongly, whereas the enteric coated tablets had lowest friability due to the polymer coating. 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 5% limit 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 using khaya gum and guar gum. Formulations containing guar gum (Formulation G) showed higher percentage swelling index than the formulations containing khaya gum (Formulation K). The matrix tablets were found to contain 99.1-101.5% of the labeled amount of budesonide indicating uniformity of drug content.

In order to investigate the extent to which these polymers succeed in targeting the drug to the colon, four formulations have been formulated and *in vitro* drug release studies have been conducted in the pH range, which normally accounted in the GI tract (fig. 1). Further to mimic the colon environment, the colonic microflora was also taken into consideration for the *in vitro* release study, as polysaccharide polymers release the drug faster in the presence of colonic microflora as they release

Table 3: Percentage swelling index of compression coated and enteric coated tablets of micronized budesonide.

Formulation	% Swelling index*				
	2 h	5 h	8 h	12 h	24 h
K	22.04	54.63	102.12	160.65	270.84
G	31.52	66.00	121.61	196.71	330.59

* = one reading only, h = hours

Table 4: Comparison of different orders of *in vitro* release of compression coated and enteric coated tablets of micronized budesonide in the absence of rat cecal content.

Formulation	Zero – order R^2	First – order R^2	Higuchi's model R^2
K	0.975	0.865	0.831
G	0.992	0.702	0.916
KC	0.948	0.920	0.685
GC	0.954	0.909	0.701

Table 5: Comparison of different orders of *in vitro* release of compression coated and enteric coated tablets of micronized budesonide in the presence of rat cecal content.

Formulation	Zero-order R^2	First-order R^2	Higuchi's model R^2
K	0.908	0.942	0.725
G	0.981	0.750	0.880
KC	0.902	0.887	0.714
GC	0.908	0.878	0.722

glycosidases (fig. 2). Dissolution studies (fig. 1) revealed that khaya gum compression coated tablets (Formulation K) showed 12.20 % of drug release in 5 h, whereas, guar gum compression coated tablets (Formulation G) showed 30.40% drug release in 5 h. This indicates that, khaya gum when used have better capacity to protect the drug from being released in the upper parts of the GIT than guar gum compression coated tablets. This may be due to guar gum being more hydrophilic compared to khaya gum as the swelling index is better for guar gum (table 3), released the drug relatively at a faster rate than khaya gum. It was also observed that throughout release study; khaya gum compression coated tablets (Formulation K) released the drug at slower pace compared to guar gum compression coated tablets (Formulation G).

In comparison, the formulations coated further by pH dependent polymer such as Eudragit L-100, i.e., Formulation KC and GC, showed less than 1% release till 4 h and hence proved to have more efficiency in protecting the drug release in the upper part of the GIT. The release profile is shown in Figure 1. At the end of 16 h the Formulation K and G released 97.77% and 80.00% of the drug respectively. Whereas, Formulation KC released only 68% and GC released 72.44% drug during the same period. The Formulation KC and GC released 96.44% and 97.11% at the end of 22 h. This indicates that Formulation KC and GC succeeds in not only targeting the drug to colon but also in prolonging the release in comparison to Formulation K and G. The present investigation has revealed that, in spite of use of these natural polymers, the hydrophilic nature of these polymers make them vulnerable to release the drug to some extent in the upper digestive tract. Hence, they have less efficiency in site specific drug delivery. As a result, the use of these polymers alone may not successfully target the drug to the colon. Hence there is a need of further coating of the tablet with pH dependent enteric polymer.

When the drug release of formulations K, G, KC and GC

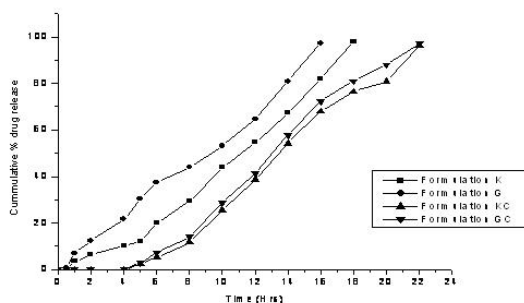


Fig. 1: *In vitro* drug release profile of various formulations in absence of rat cecal contents. Y- Error bar was found to be between 2-11 %.

was carried out in the presence of rat cecal content (fig. 2) there was a significant increase in the drug release as compared to that of the release studies performed in the absence of rat cecal content. The rat cecal content in the release study was considered to mimic the human colonic environment as it contains micro flora which releases many glycosidases and degrade the polysaccharide polymers.

The drug release from Formulations KC and GC was negligible in the first few h (5 h). However, the release may be complete once the drug reaches the colon. Hence, a delayed action was observed. It was seen that Formulation K and G released 97.70% and 94.22% of the drug respectively in 12 h. Whereas, formulation KC and GC released 83.33% and 79.11% of the drug respectively in 12 h. The formulations KC and GC showed maximum release of the drug in 14 h i.e., 96.88% and 97.77% respectively. However, the release data revealed that approximately 80% of the drug release took place in the colon in 7 h from all formulations, if, the release of the drug excluded from Formulation K & G during the initial h (upper G.I. tract). This indicates that the drug release from formulations is mainly due to the presence of enzymes released by micro-organisms of rat cecal contents (degradation).

From the above two dissolution data (in the presence and in the absence of rat cecal content) significant changes in the release behavior was observed. Though the release data of dissolution study in the absence of rat cecal content, indicated sustained action of the drug, the better dissolution model (dissolution model mimicking human intestine) revealed that no sustained action was observed. The release studies in presence of rat cecal content also revealed that, non enteric coated tablets also released about 70% of drug in the colon in 5 h (excluding the release of drug in the stomach region) which coincides with the drug release from enteric coated tablets which too released same amount in 5 h. This indicated that the selection of better dissolution model helps in

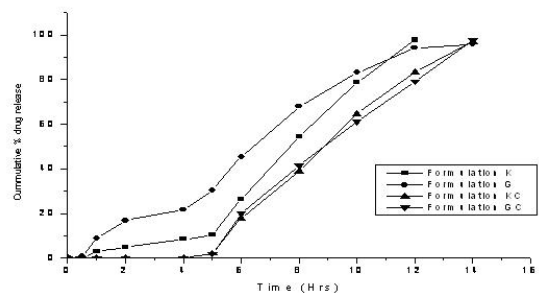


Fig. 2: *In vitro* drug release profile of various formulations in presence of rat cecal contents. Y- Error bar was found to be between 2-10 %.



(a) Image showing presence of tablet in the stomach at first hour.



(b) Image showing presence of swollen tablet in the colon at seventh hour.

Fig. 3: X-ray image showing the location of tablet in different parts of GIT, in rabbit.

understanding the release pattern. From this data it can be concluded that polysaccharides can be used for targeting the drug to the colon rather than sustaining or controlled release of drug. Further, if, they are coated with enteric polymer, efficiently can be targeted to the colon by avoiding the release in the upper intestinal part and the release of the drug is basically dependent upon the colon microflora degradation rather than any other factors. When the degradation is based on colon microflora sustained action or controlled release can not be expected as the degradation process is based on the concentration of microflora and its ability to release the necessary enzyme system. To strengthen the *in vitro* release study finding, *in vivo* efficiency study was carried out (fig. 3). It can be concluded from the X-ray images that the enteric coated tablets have remained intact in the upper part of the intestinal tract and swollen tablet picture in the colon indicates that the formulation releases the drug in the colon and hence the colon specificity. Hence combination of enteric polymer coated formulations containing polysaccharides as compression coated, can be ideal for targeting the drug to colon. The premature release of drug from only enteric coated formulations by variation in intestinal pH due to certain pathological condition can be avoided from formulation containing polysaccharides as compression coat.

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log cumulative percentage of drug remaining Vs time), Higuchi's (1963) (cumulative percentage of drug released Vs square root of time), and zero order (cumulative amount of drug released Vs time) pattern. It was found that the formulation followed zero order kinetics when the release studies were conducted in absence of rat cecal contents. However, when better

dissolution model (in presence of rat cecal content) was used the drug release pattern did not follow any of the mathematical models. This indicated that these polymers can be used for targeting the drug to the colon rather than sustaining or controlling the release, as the release of drug is dependent upon the fermentation of the polymers by the enzymes secreted by the microflora.

CONCLUSION

The present study was aimed at developing colon targeted drug delivery system of micronized budesonide. Khaya gum when used as compression coating, exhibited more capacity to protect the drug from being released in the upper parts of the GIT than guar gum. Formulations KC and GC, showed 0% release up to 4 h and hence proved to have more efficiency in protecting the drug release in the upper part of the GIT, indicated that the formulations succeeds in targeting the drug to colon better than Formulation K and G and hence can be considered better for site specificity. Selection of better dissolution model helped in understanding the release pattern. From the data it can be concluded that polysaccharides alone can not be used either for targeting the drug to the colon or for sustaining or controlled release of drug.

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