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Investigation of Colon Specificity of Novel Polymer Khaya Gum

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Abstract

The fast disintegrating core tablets of budesonide, were prepared by direct compression technique. These tablets were coated with khaya gum (Polysaccharide polymer). These tablets were further coated using eudragit S-100 by dip coating technique. The tablets were evaluated for hardness, friability, weight variation, swelling index, drug content, in vitro release studies and in vivo studies in rabbits. In vitro drug release studies were carried out in presence and absence of rat cecal contents and revealed that khaya gum, when used as compression coating, protected the drug from being released in the upper parts of the gastro intestinal tract (GIT) to some extent but the enteric coated formulations completely protected the drug from being released in the upper parts of the GIT, and released the drug only in the colon by bacterial degradation of gums. It was found that the polysaccharide polymer khaya gum did not completely protect the drug release in the upper digestive tract and exhibited different release profiles in presence and absence of rat cecal contents. Hence, khaya gum alone can not be used either for targeting the drug to the colon or for sustaining or controlling the release of drugs.

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[1]. 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[2]. Colon is a site where both local and systemic delivery can take place. Local drug delivery could allow topical treatment of Inflammatory Bowel Diseases like Crohn's disease or Ulcerative colitis. A number of other serious diseases of the colon like colorectal cancer might also be capable of being treated more effectively if drugs are 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[3]. The most critical challenge in such drug delivery approach is to preserve the formulation during its passage through the stomach and about 6 meters of the small intestine[4]. 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.

Khaya gum is a polysaccharide obtained from the incised trunk of tree *Khaya grandulifolia*, Family Meliaceae, a typical West African mahogany tree[5]. Odeku O.A. et al., evaluated the effects of khaya gum on the mechanical and release properties of paracetamol tablets in comparison with two standard binding agents, poly vinyl pyrrolidone and gelatin. It has been found that the crushing strength, friability ratio, disintegration time, dissolution time, t_{50}, t_{90} and t_{1hr} all increased with increase in binder concentration. Crushing strength and friability ratio were found to be PVP > gelatin > khaya gum and dissolution was found to be gelatin > khaya gum > PVP[6]. It was also 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

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in the colon where there is local action and improved absorption[5].

Budesonide is an antiinflammatory 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 hr and when absorbed systemically shows severe adverse effects[7]. To overcome these drawbacks, the present study was undertaken to investigate the colon targeted drug delivery system of budesonide. The release profiles of these tablets were further compared in presence and in absence of rat cecal contents.

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. Eudragit S -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.

Compression coating of fast disintegrating core tablets of Budesonide with granules containing Khaya gum (Formulation K1, Formulation K2 and Formulation K3):

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 all the formulations was 200 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 total weight of the compression coated tablet was about 450 mg. The compression coated tablets were subjected to hardness, friability, weight variation, drug content and drug release characteristics.

Enteric coating of the compression coated tablets of Formulation K3 with Eudragit S -100 (Formulation KC):

The compression coated tablets Formulation K3 were further coated using an enteric coating polymer such as eudragit S-100, using dip coating technique. Coating was applied to the tablet cores by dipping them 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 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[8].

DRUG CONTENT ESTIMATION:

Ten tablets from each formulations of compression coated (Formulation K1, Formulation K2, Formulation K3) and the core tablets were powdered and the powder equivalent to one tablet (250 mg) was transferred into a 100 ml volumetric flask. Initially, 50 ml of methanol was added and allowed to stand for 6 hr 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 with methanol as blank. The drug content was estimated by using calibration curve.

SWELLING STUDIES:

One tablet each from all the compression coated formulations and formulation KC, 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 hr, 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[9]. The test was repeated three times and results are tabulated in **Table 4**.

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

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 carrying out release profile at various 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 ± 0.5° C temperature 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 hr and 0.05 M phosphate buffer pH 7.4 was used for the next 3 hr and 500 ml of phosphate buffer pH 6.8, till the complete release of drug took place. Samples of 5 ml 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 micronized budesonide released at each time interval was calculated from the absorbance of the samples. The cumulative percentage drug release was then plotted against time and the release profiles were studied.

In order to assess the susceptibility of khaya 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. This study was carried out after obtaining the Institutional Animal Ethics Committee clearance from K.S. Hegde Medical Academy, Mangalore. In order to mimic intestinal environment, especially enzymes glycosidase specially acting on khaya gum in the cecum, male albino rats weighing between 150 – 200 gm maintained on normal diet were incubated with teflon tubing and 4 % w/v dispersion of khaya in water were administered for 7 days. All the rats were sacrificed by spinal traction, 30 minutes before the commencement of drug release studies. The abdomens were opened, small intestinal and cecal bags were isolated, ligated at both ends and cut loose and immediately transferred into Sorensen's buffer pH 7.4 and phosphate buffer pH 6.8 previously bubbled with nitrogen gas, respectively.

In vitro drug release studies in the presence of rat small intestine and 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 hr, 900 ml of Sorensen's buffer pH 7.4 for 3 hr with 2% of rat small intestine contents and finally 500 ml of phosphate buffer pH 6.8 having rat cecal contents (4% w/v) till the complete release of drug. The basket was rotated at 100 rpm and the medium was maintained at a constant temperature of 37 ± 0.5°C and nitrogen gas was bubbled throughout the dissolution study. Samples of 5 ml volume were withdrawn at predetermined time intervals and analyzed spectrophotometrically at 244.3 nm. The cumulative percentage drug release was then plotted 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% w/w) 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[10].

Curve fitting analysis

The drug release data were fitted to models representing Higuchi's (cumulative percentage of drug released Vs square root of time), Korsmeyer's equation (log cumulative percentage of drug released Vs time), zero order (cumulative amount of drug released Vs time) and first order (log percentage of drug remaining Vs log time) kinetics to know the release mechanisms. The data were processed for regression analysis using MS- EXCEL statistical function[11].

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for budesonide using khaya gum as carrier. It was reported earlier that Khaya 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[3].

Physicochemical properties:

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 a significant difference exists between the hardness of the tablets containing khaya gum and core tablets. However, no significant differences in the hardness was observed between compression coated and enteric coated tablets (**Table 3**). Further within the compression coated Formulations (Formulation K1, formulation K2 and Formulation K3) marginal variation in hardness was observed. As the proportion of khaya gum increased the hardness of the tablets increased marginally. The higher hardness values of the compression coated tablets may be due to the use of khaya gum in raw form. The results of the friability of core tablets and compression coated tablets were within the permissible limits. The core tablets had higher percentage friability due to lower hardness (**Table 3**). The low friability of the compression coated tablets may be attributed to inter particulate bridges that are formed due to the gum 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 (**Table 3**) showed that the tablets of all the formulations of compression coated 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 250 mg tablets and 5 % for 450 mg tablets.

Swelling index and drug content estimation:

Significant difference in percentage swelling index was seen between different formulations (**Table 4**), though, the difference between formulation K3 and formulation KC was not significant. Swelling index was carried out in phosphate buffer pH 7.4 as polysaccharides are used for targeting the drugs to colon area and the complete swelling can be expected in the region. It was observed that as the proportion of khaya gum increased the percentage swelling index increased due to hydrophilic nature of the polymer. As the amount of polymer increased amount of water absorption was also increased. As a result percentage swelling index was also increased. Further, the GI transit time varies between 24-48 hr in individuals; the study was carried out for 24 hr. Also, from the experimental experience it was observed that maximum swelling was observed at 24 hr. However, in biological system tablets may disintegrate due to the movement and the presence of microflora causing fermentation of the polymers may lead to drug release faster. Further the enteric coated tablets are expected to swell above pH 6 as the polymer eudragit S -100 dissolves above pH 6. Hence after the proximal small intestine (pH 6.6), in the distal small intestine (pH 7.5) eudragit S -100 may dissolve and the tablets may start swelling, and thereafter the drug may release from the formulation. There was no significant difference in drug content among the different formulations. It was evident from the results (**Table 3**) that polymer has least effect on drug content. Further in the study methanol was used as blank during the spectrophotometric estimation as the drug was completely soluble in the solvent.

***IN VITRO* RELEASE PROFILE:**

In order to investigate the extent to which khaya gum succeeded in targeting the drug to the colon, three formulations have been formulated and *in vitro* drug release studies have been conducted in the pH range, which normally accounted in the GI tract (**Figure 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 glycosidases (**Figure 2**). Dissolution studies (**Figure 1**) revealed that khaya gum compression coated tablets showed approximately 15% (maximum at lower proportion) of drug release in 2 hr. This indicated that, khaya gum when used alone can protect the drug from being released in the upper parts of the GIT to some extent. This marginal release may be due to the hydrophilic nature of the polymer khaya gum as the polysaccharides are known to be hydrophilic in nature. Further within the formulations slow release of drug was observed from the formulation which contains higher proportion of polymer (Formulation K3).

In comparison, the formulations coated further by pH dependent polymer such as Eudragit S-100, i.e., formulation KC showed less than 1% release till 5 hr and hence proved to have more efficient 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 hr the formulation K3 released 95% of drug, whereas, formulation KC released only 68% drug during the same period and 96.44% at the end of 22 hr. It was also observed that formulation K3 and Formulation KC followed similar release pattern except for first 5 hr. This may be attributed to the presence of enteric coat on the formulation KC as the difference between them is eudragit S-100 coating. This indicates that formulation KC succeed in not only targeting the drug to colon but also in delaying the release in comparison to compression coated tablets. The present investigation has revealed that, the hydrophilic nature of the polymer makes it vulnerable to release the drug to some extent in the upper digestive tract and has less efficiency in delivering the drug to colon. As a result, the use of this polymer 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. Eudragit S-100 was chosen for coating the formulation to prevent the release of the drug in the upper part of the digestive tract as observed with formulations K1, formulation K2 and formulation K3. Though, the dip coating process lacked the speed, versatility, and reliability of spray-coating techniques and no commercial pharmaceutical application, for the present study method was followed only to make the tablet to remain intact in the upper digestive tract, so that it can reach to the colon. In the present study its significance is not related to the release rate and the aim is entirely on investigation of colon specificity of polysaccharide polymers.

When the drug release of compression coated formulations (formulation K1, formulation K2 and formulation K3) and KC was carried out in the presence of rat small intestine and cecal contents (**Figure 2**) there was a significant increase in the drug release as compared to that of the release studies performed in the absence of rat small intestine and cecal content. The rat small intestine and cecal content in the release study was considered to mimic the human colonic environment as it contains microflora which releases many glycosidases and degrade the polysaccharide polymers. The drug release from formulation KC was negligible in the first few hr (5 hr). However, the release may be complete once the drug reaches the colon. Hence, a delayed action was observed. It was seen that formulation K3 released 20% of the drug in 5 hr (**Figure 2**) when compared with the release profile in absence of rat intestinal matter (20% drug release in 8 hr). Whereas, formulation KC released approximately 100% of the drug in 7 hr compared to 17 hr in absence of animal intestinal contents (**Figure 1 and 2**) provided the exclusion of initial 5 hr. The formulation KC showed maximum release of the drug in 14 hr i.e., 96.88%. However, the release data revealed that approximately 85 to 95% of the drug release took place in the colon in the range of 6 to 10 hr from all formulations, if, the release of the drug excluded from the initial hours (2 hr). Hence presence of rat small intestine and cecal matter released the drug from formulations much faster. This indicates that the drug release from formulations is mainly due to the presence of enzymes released by micro-organisms of rat intestinal contents (degradation). Small intestinal contents 2% w/v and cecal matter 4% w/v was used in the study, for the simple reason that the microbial load in the small intestine is assumed to be around 10^5-10^7 CFU/ml, where as in the colon is $10^{11} - 10^{12}$ CFU /ml .

From the above two dissolution data (in the presence and in the absence of rat small intestine and cecal content) significant changes in the release behavior was observed. Though the release data of dissolution study in the absence of rat intestinal and cecal contents indicated

prolonged release of the drug, the better dissolution model (dissolution model mimicking human intestine) revealed that no prolonged release was observed. From the data it can be concluded that polysaccharides alone neither can be used effectively for targeting the drug to the colon nor for sustaining or controlling the release of drug. However, if they are coated with enteric polymer, effectively can be targeted to the colon by avoiding the release in the upper intestinal tract as 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 enzymatic system. 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 both enteric polymer as coating and polysaccharides as compression coat**.** To strengthen the *in vitro* release study finding, *in vivo* efficiency study was carried out (Figure 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.

Drug release kinetics:

To know the mechanism of drug release from the formulations, the data were treated according to first-order (log cumulative percentage of drug remaining Vs time), Higuchi's (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 formulations followed zero order kinetics to some extent as they did not follow any other mathematical model, except for formulation KC (**Table 5 and Table 6**) which did not follow any of the mathematical models significantly. This indicated that khaya gum 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. Hence natural polymer like khaya gum is ideal for site specificity especially in combination with some enteric synthetic polymer to target the drugs to colon.

CONCLUSION

The present study was aimed at developing colon targeted drug delivery system of micronized budesonide with polysaccharide. Khaya gum, a novel polysaccharide polymer when used as compression coating, exhibited protection of the release of the drug from formulation to some extent in the upper parts of the GIT. Formulation KC, showed 0% release up to 5 hr 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 formulations containing only khaya gum, 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 efficiently or for sustaining or controlled release of drug.

ACKNOWLEDGEMENT

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Table No 1: Composition of Budesonide core tablets.

Ingredients	**Quantity (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**

Table No 2: Composition of coating formulation using Khaya gum

Ingredients	**Quantity (mg)**		
	Formulation		
	K1	**K2**	**K3**
Khaya gum	90	135	180
Starch paste (10%w/v)	q.s.	q.s.	q.s.
Talc	4	4	4
Magnesium stearate	2	2	2
Dibasic Calcium Phosphate	90	45	0
Average weight	200	200	200

Table No 3: Physicochemical properties and drug content of the tablets.

Formulation	**Hardness [a] Kg/cm^2**	**Percentage Weight Variation [a]**	**Percentage Friability [a]**	**Percentage Drug content[a]**
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
KC	8.55±0.980	2.381 ± 0.45	0.820 ± 0.03	*******

[a] *All values are expressed as mean ± SD, n=3*

Table No 4: Percentage swelling index of compression coated and enteric coated tablets of budesonide

Formulation	% Swelling index[n]				
	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
KC	18.52 ± 1.57	54.00± 2.89	99.61 ± 5.34	159.71 ± 4.58	267.59 ± 6.17

All values are expressed as mean ± SD, n=3

Table No 5: Comparison of Release Kinetics in absence of rat cecal content.

Formulation	Zero – order R^2	First – order R^2	Higuchi's model R^2
K1	0. 9761	0.8392	0.8666
K2	0.9748	0.8699	0.9088
K3	0.9742	0.7063	0.8399
KC	0.9480	0.7719	0.7916

Table No 6: Comparison of Release Kinetics in presence of rat small intestine and cecal contents.

Formul -ation	Zero-order R^2	First-order R^2	Higuchi's model R^2
K1	0.9671	0.8285	0.9088
K2	0.9833	0.8536	0.8969
K3	0.9703	0.7432	0.8301
KC	0.9017	0.7472	0.7141

Figure 1: *In vitro* drug release profile in absence of rat small intestinal and cecal contents

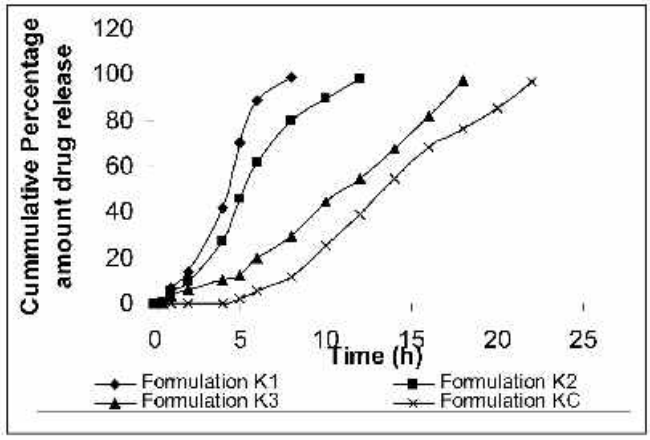


Figure 2: *In vitro* drug release profile in Presence of rat small intestinal and cecal contents

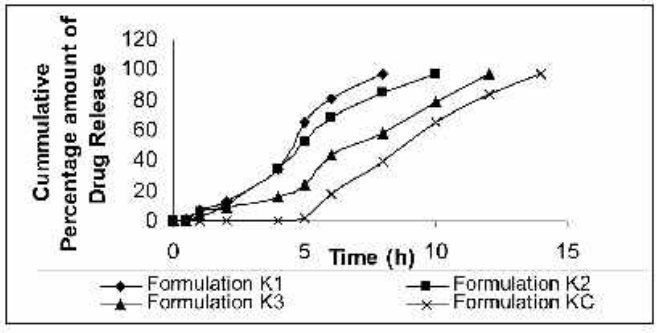
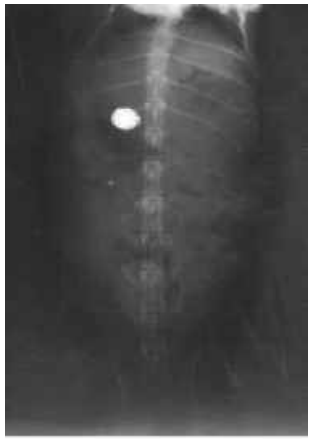
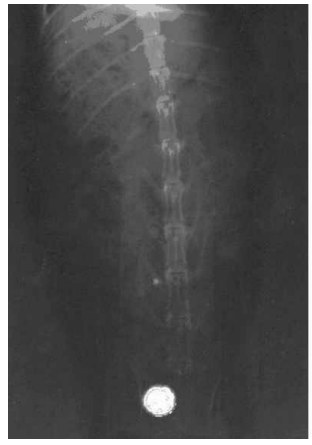


Figure 3: X-ray image showing the location of tablet in different parts of GIT, in rabbit.



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



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

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