www.ijrps.pharmascope.org

ISSN: 0975-7538
Research Article

Investigation of effect of drug solubility on colon specificity of polysaccharide polymers khaya gum and guar gum

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ABSTRACT

The fast disintegrating core tablets of budesonide and domperidone, were prepared separately by direct compression technique. Later, these tablets were compression coated with khaya gum/guar gum, polysaccharide polymers. 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. *In vitro* drug release studies were carried out in presence and absence of rat cecal contents and revealed that khaya gum/guar gum, when used as compression coating, though protected the poorly soluble drug budesonide from being released in the upper parts of the gastrointestinal tract to some extent, but could not prevent the release of a weakly basic drug domperidone significantly. Further, the enteric coated formulations completely protected the drugs irrespective their solubility from being released in the upper parts of the gastrointestinal tract, and released the drug in the colon by bacterial degradation of gums. Though, the cumulative amount of drug release from the formulations of two different drugs remained same, the release difference in the different parts of gastrointestinal tract was observed from compression coated formulations due to their difference in solubility in the upper parts of gastrointestinal tract. It was also found that different release profiles in presence and absence of rat cecal contents. Different solubility nature of the drugs did produce significant effect on the MDT values of compression coated tablets and enteric coated tablets. Further, effect of dissolution environment on MDT values was observed only with formulations containing budesonide as drug but not with domperidone, indicated that the effect of solubility of drugs plays a significant role in determining the efficiency of colon specificity of polysaccharide polymers in targeting the drugs to colon.

Keywords: Khaya gum; guar gum; colon specificity; solubility; domperidone; budesonide.

INRODUCTION

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 P *et al,* 2001). 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. Colonic drug delivery has gained increased importance, not only for the delivery of 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. The treatment might be more effective if the drug substances were targeted directly to the site of action in the colon (Asqhar LF *et al,* 2006). 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 (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. 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 (Ashford M and Fell JT, 1994).

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Received on: 20-06-2010
Revised on: 29-06-2010
Accepted on: 02-07-2010

Khaya gum is a polysaccharide obtained from the incised trunk of tree *Khaya grandulifolia*, Family Meliaceae, a typical West African mahogany tree. Odeku OA and John TF (1995) reported that khaya gum is capable of protecting the drug from being released in the acidic environment prevailing in the stomach and small intestine. Prabhu P *et al* (2010) reported that the formulation of poorly soluble drug like budesonide along with khaya gum as compression coat did not protect the drug being released in the stomach completely due to its hydrophilic nature. However, further coating the compression coated tablets with synthetic enteric polymer, delivered the drug to colon very effectively. Usually polysaccharides are degraded by the colonic bacterial enzymes, thereby releasing the drug in the colon where there is local action and improved absorption. Guar gum is a natural polysaccharide derived from the seeds of *Cyamopsis tetragenolobus*, Family Leguminoseae. Guar gum hydrates and swells in cold water forming viscous colloidal dispersion or solution (Wade A and Weller PJ, 1994). 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 antiinflammatory synthetic potent corticosteroid. It is a poorly soluble drug in the gastrointestinal tract (GIT) region. Domperidone is a weakly basic drug and highly soluble in the acidic environment. To investigate the effectiveness of the colon specificity of the khaya gum/guar gum with the drugs which have difference in the solubility, the present study was carried out with the above said two drugs. The drug delivery system was prepared using natural novel polysaccharide polymer khaya gum and the results were compared with well established guar gum. 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 S-100.

MATERIALS AND METHODS

Materials

Budesonide (micronized) was obtained as a gift sample from Zydus Cadila Health Care Ltd Ahmedabad. Domperidone was procured from KAPL, Bangalore. Khaya gum was obtained from University of Ibadan, Nigeria. Eudagit S -100 was purchased from Degussa, Mumbai. All other chemicals used were of analytical grade.

Methods

Preparation of fast disintegrating core tablets of budesonide/ domperidone by direct compression technique

The composition of core tablets of budesonide/domperidone is given in Table-I. The fast disintegrating core tablets (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 tablets with fast disintegrating characteristics (disintegrating time < 30 seconds). Budesonide/domperiodne, 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 core tablets

Ingredients	Quantity	
	(mg)	(mg)
Budesonide	9	-
Domperidone	-	20
Avicel PH 102	80	75
Spray dried lactose	80	75
Sodium starch glycolate	75	75
Talc	3.5	3
Magnesium stearate	2.5	2
Average weight	250	250

Compression coating of fast disintegrating core tablets with granules containing khaya gum/guar gum (Formulation KB / KD or GB/GD)

The composition of compression coat formulation is given in Table-2. The compression coated formulations were prepared using khaya gum/guar gum. Granules of the above materials were prepared by wet granulation technique using 10% w/w starch paste as binder. The prepared granules were dried at 50 ° for one hour and passed through sieve number 16, placed over sieve number 44 to separate granules and fines. About 15% w/w 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 formulation 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 with eudragit S -100 (Formulation KBC/ KDC or GBC/GDC)

The compression coated tablets prepared 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. 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.

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

Ingredients	Quantity (mg)
Khaya gum / Guar gum	180
Starch paste (10%w/v)	q.s
Talc	4
Magnesium stearate	2
Average weight	200

Evaluation of physico-chemical properties of tablets

Hardness and friability tests of the 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

Ten tablets from each formulation including for the core tablet were powdered and the powder equivalent to one tablet (250 mg) was transferred into a 100 ml volumetric flask. Initially, 50 ml of phosphate buffer (pH 7.4) 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 buffer. After suitable dilution, the drug content was estimated using Jasco V 530 UV Visible spectrophotometer at 244.3 nm for budesonide and 283 nm for domperidone. The drug content was estimated by using calibration curve.

Swelling studies

One tablet from each formulation KB, KD, KBC and Formulation KDC, 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 1 and expressed in percentage (Yeole PG *et al* 2006). 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 polysaccharide polymer 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. 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 phosphate buffer pH 7.4 for 3 h having rat small intestinal contents and finally 900 ml of phosphate buffer pH 6.8 having rat cecal contents 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 for budesonide and 283 nm for domperidone using corresponding buffers as blank. The amount of drug 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 contents 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% w/v dispersion of khaya / guar gum in water were administered for 7 days. All the rats were killed by spinal traction, 30 min 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 was carried out using USP dissolution test apparatus (XXIII), paddle type using the above said dissolution media. The paddle was rotated at 100 rpm and the medium was maintained at a constant temperature of 37 ± 0.5°C. Samples were analyzed spectrophotometrically. 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.

Mean dissolution time (MDT)

Mean dissolution time (MDT) was calculated using the equation Mockel and Lippold.

$$MDT = (n/n+1).k^{-1/n} \qquad (2)$$

Mean dissolution time (MDT) value is used to characterize the drug release rate from dosage form and indicates the drug release retarding efficiency of polymer (Mockel J E and Lippold B, 1993).

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 equation (Higuchi T 1963, cumulative percentage of drug released Vs square root of time), and zero order (cumulative percentage of drug released Vs time) pattern. Further, Korsmeyer RW and Peppas NA (1981) equation was used to analyze the data obtained from the *in vitro* release to evaluate the kinetic models and release mechanism of drug from the formulations. The Korsmeyer and Peppas equation is

$$Mt / M\infty = kt^n \quad (3)$$

Where $Mt/M\infty$ is the fraction of drug release at time t, and 'k' is a constant incorporating the properties of the macromolecular polymeric system and drug. 'n' is an exponent used to characterize the transport mechanism.

Statistical analysis

To compare the release data of all the formulations of budesonide and domperidone and to assess the statistical significance between them one way analysis of variance (ANOVA) was carried out at $P<0.0001$ significance level. Release data of formulations KB, GB, KBC and GBC were analysed between the two dissolution models, apart from comparison between compression coated and enteric coated formulations. Further, the data was also analysed for similar formulations of different drugs.

Stability study

The stability of all the formulations of budesonide and domperidone were studied at different temperatures. Three sets (12 tablets of each formulation) were wrapped individually in aluminum foil and placed in petri dish. These containers were stored at 4 ± 2°, RH 60 ± 5%, 25 ± 2°, RH 60 ± 5% and 40 ± 2°, RH 75 ± 5% for a period of 3 months. Samples were analyzed for physical changes and the drug content at regular intervals (2 weeks interval for 12 weeks) and degradation rate constant 'k' was determined (Martin A, 2005). Degradation rate constant 'k' was calculated by slope, after plotting the graph log % undecomposed drug Vs time.

RESULTS AND DISCUSSION

In-process parameters

In the present study oral colon specificity of polysaccharide polymers were investigated with the two drugs which have different solubility. Hence domperidone formulations were developed with khaya gum and guar gum as carrier and compared with similar formulations containing budesonide as drug. It was earlier reported that polysaccharide polymers 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, to investigate the effect of solubility of drugs on this effect, a weakly basic drug was used for comparison with budesonide, which is poorly soluble drug in the entire region of alimentary tract.

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 between the hardness of the tablets containing khaya gum/guar gum and core tablets, and no much difference in the hardness between compression coated and enteric coated tablets (Table 3). The higher hardness values of the compression coated tablets may be due to use of khaya gum/ guar gum.

The results of the friability of core tablets and compression coated tablets are within the permissible limits. The core tablets had higher percentage friability

Table 3: In-process parameters of the tablets

Formulation	Hardness * Kg/cm^2	Percentage Weight Variation*	Percentage Friability*	Percentage Drug Content*
Core tablets	3.16±0.859	2.680 ± 0.56	2.760 ± 0.43	100.98 ± 1.04
KB/KD	8.15±0.850	2.348 ± 0.67	0.750 ± 0.07	100.88 ± 1.03
GB/GD	7.50±0.900	2.816 ± 0.78	0.629 ± 0.09	100.66 ± 1.58
KBC/KDC	8.45±0.980	-	0.120 ± 0.03	-
GBC/GDC	7.83±0.780	-	0.125 ± 0.05	-

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

Table 4: Percentage swelling index of compression coated and enteric coated tablets of budesonide

Formulation	% Swelling index[n]				
	2 hours	**5 hours**	**8 hours**	**12 hours**	**24 hours**
KB/ KD	22.04 ± 1.78	54.63± 3.71	102.12 ± 3.67	160.65 ± 5.13	270.84 ± 5.45
KBC / KDC	21.52 ± 1.57	54.00 ± 2.89	101.61 ± 5.34	159.71 ± 4.58	267.59 ± 6.17
KD/GD	31.52 ± 1.57	66.00 ± 2.89	121.61 ± 5.34	196.71 ± 4.58	330.59 ± 6.17
KDC/GDC	29.52 ± 1.13	58.12 ± 2.12	113.43 ± 4.98	189.57 ± 5.01	312.45 ± 5.97

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

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 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 for 250 mg tablets and 10% for 450 mg tablets and not more than 2 tablets in a batch of 20 deviated from ± 5% weight variation. No significant difference in percentage swelling index was seen between different formulations (Table 4). 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.

Further, the GI transit time varies between 24-48 h in individuals, the study was carried out for 24 h. Also, from the experimental experience it was observed that maximum swelling was observed around 24 h. However, in biological system tablets may disintegrate due to the movement and the presence of microflora causes 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 is evident from the results (Table 3) that polymer has least effect on drug content.

The in-process parameter values of the tablets prepared with domperidone are comparable with that prepared with budesonide. Hence the effect of drug was not observed on the in-process parameters viz; hardness, friability, weight variation and content uniformity test (Table 3)

***In vitro* release profile**

In order to investigate the effect of solubility of the drugs on colon specificity of polysaccharide polymers (hydrophilic polymers), four formulations budesonide (formulation KB, GB, KBC and GBC) and four formulations of domperidone (formulation KD, GD, KDC and GDC) have been formulated and *in vitro* drug release studies were conducted in the pH range, which normally accounted in the GIT. 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 (Fig. 2). Dissolution studies (Fig. 1) revealed that khaya gum compression coated tablets (formulation KD) released 23.35% of drug in 2 h, whereas, guar gum compression coated tablets (formulation GD) released 29.86% of drug in 2 h. In comparison to budesonide, the release of domperidone was found to be much faster due to the differences in solubility. However, the release of domperidone reduced drastically in the basic pH, and overall release mimicked the release of budesonide. Hence, the solubility of drug also plays a significant role when these polymers are used for targeting the drugs to colon. The much faster release of basic drug in the acidic pH from the compression coated tablets is due to the high solubility of drug in acidic pH.

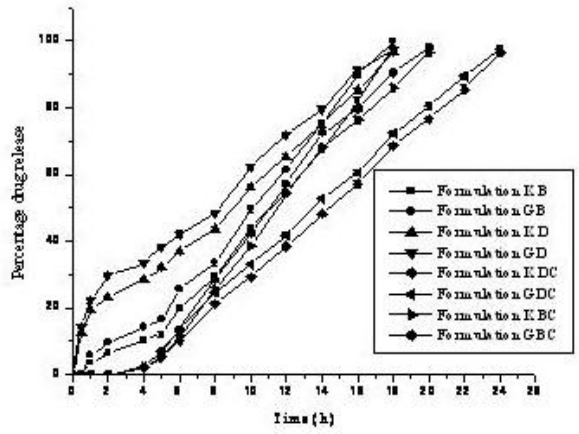

Figure 1: Release profile of formulations of domperidone in absence of rat cecal matter

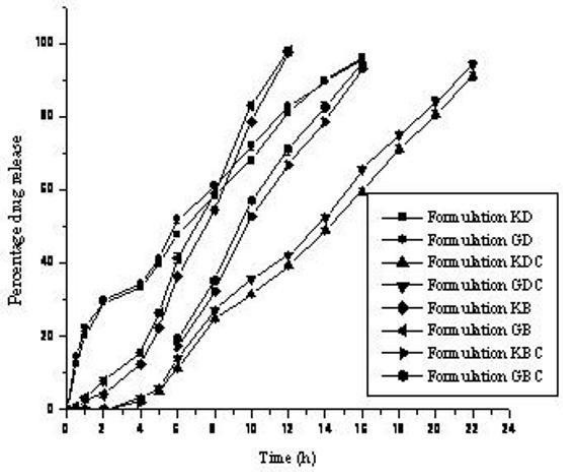

Figure 2: Release profile of formulations of domperidone in presence of rat cecal matter

Budesonide is poorly soluble drug and hence the release was found to be poor. In comparison, the formulations coated further by pH dependent polymer such as eudragit S-100, i.e., formulations KDC and GDC, showed more or less similar release profile as that of budesonide with extended release by 2 h as the drug domperidone is poorly soluble in the basic pH. Further, the release profile of domperidone did show significant difference when conducted in presence of rat cecal matter, compared to budesonide. This is due to the solubility of drug. Though, the polymer may degrade faster in presence of enzymes released by the micro-

Table 5: Comparison of release kinetics and MDT values in the absence of rat cecal content

Formulation	Zero-order r^2	First-order r^2	Higuchi's model r^2	Korsmeyer and Peppas's Model 'n' value	Mean Dissolution Time (h)
KB	0.9210	0.7241	0.8368	0.57	11.42
GB	0.9830	0.8380	0.8571	0.67	10.11
KBC	0.8930	0.8271	0.7314	0.53	11.73
GBC	0.8874	0.7991	0.7452	0.71	11.21
KD	0.9851	0.8093	0.9613	0.64	9.51
GD	0.9753	0.8162	0.9560	0.65	8.74
KDC	0.9872	0.8996	0.6973	0.64	14.17
GDC	0.9736	0.8562	0.6756	0.59	13.87

Table 6: Comparison of release kinetics and MDT values in presence of rat cecal contents

Formulation	Zero-order r^2	First-order r^2	Higuchi's model r^2	Korsmeyer and Peppas's Model 'n' value	Mean Dissolution Time (h)
KB	0.9117	0.6173	0.7954	0.53	7.52
GB	0.9512	0.6223	0.8302	0.63	7.10
KBC	0.8980	0.8173	0.6832	0.57	9.78
GBC	0.9081	0.7086	0.6579	0.78	9.12
KD	0.9713	0.9025	0.7955	0.65	8.97
GD	0.9864	0.8940	0.8242	0.63	8.13
KDC	0.9723	0.8996	0.7913	0.61	14.12
GDC	0.9475	0.8659	0.8014	0.57	13.84

bes, the poor solubility of drug (domperidone) leads to slower dissolution. Hence the impact of degradation of polymers by microflora not observed. Hypothetically, since the drug remains in unionized form in the basic region, and hence the bioavailability may improve in this region.

Mean dissolution time (MDT)

MDT value was found to be higher (11.42 h Vs 10.11 h, Table 5 and 9.15 Vs 8.44 h for formulations contaning domperidone as drug) for khaya gum compression coated tablets compared to guar gum compression coated tablets. This indicated that among the polysaccharide polymers, khaya gum found to be more efficient in controlling the drug release compared to guar gum. This result is also comparable with the swelling index of the polymers (Table 4). When compared the MDT values between the formulations of two drugs, domperidone due to its better solubility in the acidic region found to be much faster release from these polymers (9.51 h Vs 11.42 h or 8.74 h Vs 10.11 h, Table 5). Further, the MDT values of enteric coated formulations increased significantly for domperidone compared to budesonide due to difference in solubility of drugs (14.17 Vs 11.73 or 13.87 Vs 11.21).

The higher values of MDT, for enteric formulations of domperidone due to the fact that the drug is weakly basic and its release in the basic pH is poor and hence leads to slower dissolution. This may not be true when the drug is given by oral route though the *in vitro* release data indicated the faster release of drug. Because, during the release in the stomach drug will remain in the ionic form and its absorption may not be as good as its absorption from the intestine. In the basic region drug remains in the unionized form and its absorption can be expected to be better. Hence the findings of *in vitro* release profile cannot said to be related to its bioavailability. The significant differences in the MDT values of domperidone in comparison to budesonide from enteric formulations is due to the fact that the release of domperidone is totally prohibited in the acidic region, where the solubility is more and its solubility in the basic pH is very poor. Hence the MDT values found to be higher for formulations containing domperidone as drug (approximately 14 h). This indicated that, though, the MDT values are used to determine the drug release efficiency of the polymers, the solubility of the drugs too plays significant role apart from the polymer's effect in releasing the drug from the formulations.

It was also found that there is a significant difference between the MDT values (11.42 Vs 7.52 or 10.11 Vs 7.10) of formulations containing budesonide as drug (Table 5 and 6, formulation KB and GB), when the release profile was conducted in presence of rat cecal matter. However this result is not comparable with the formulations containing domperidone as drug (9.51 Vs 8.97 h or 8.57 Vs 8.13 h, Table 5 and 6). Similar result was observed with enteric formulations of domperidone (14.17 Vs 14.12 h or 13.87 Vs 13.84 h, Table 5 and 6). The possible reason could be the difference in solubilities of these two drugs. Hence, the dissolution models did not produce any impact on the MDT values of the formulations containing weakly basic drug domperidone. This indicated that, though the polymer gets fermented by the microflora of the colon, the poor solubility of the drug makes it remain undissolved and

may prolong the effect. Hence the effect of solubility of the drug is observed when the formulation was intended for colonic delivery.

Release kinetics

It was found that the formulations followed zero order kinetics to some extent. Further, the release mechanism from the formulations followed combination of diffusion and erosion as the 'n' values ranged between 0.53 and 0.78. In general the mechanism of drug release from polymeric matrices can be described by the swelling phenomenon. The solvent molecules move inside the polymeric matrix like a "front" defined at an exact speed; simultaneously, the thickness of the area increased with the time in opposite direction as solvent molecules enters. The mechanism of drug release can be described by a second phenomenon that involves the disentanglement and erosion of the polymer, where the drug release process involves the penetration of water into the tablet contaning dry polymer, hydrate and swell the polymer enabling diffusion of the drug dissolved in the tablet (Reddy KR *et al* 2003). By using Korsmeyer and Peppas model, if n= 0.45 it is Case-1 or Fickian diffusion, 0.45< n> 0.89 is for anomalous behavior or non-Fickian transport, n= 0.89 for Case 11 transport, and n> 0.89 for Super Case 11 transport. Fickian release usually occurs by molecular diffusion of the drug due to a chemical potent gradient. Case 11 relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term is also includes polymer disentanglement and erosion. In the present investigation, the release from the hydrophilic polymers (polysaccharides) followed the combination of diffusion and erosion as the 'n' values ranged from 0.53 to 0.78 as per Korsmeyer and Peppa's model (Table 5 and 6).

Statistical analysis

The release rate from different formulations of budesonide was found to be significantly different (P< 0.0001, one way ANOVA) when the release profile was conducted in absence and presence of rat small intestinal and cecal contents. However, the release profile of domperidone from the formulations was not found to be significantly different, when the dissolution was carried out in two different dissolution environments. This indicated that the effect of dissolution models on the drug release pattern was found to be significant for drugs which exhibit no significant difference in the solubility though out GIT Further, significant difference in release profile was also observed between the two drugs (KB Vs KD or GB Vs GD, KBC Vs KDC or GBC Vs GDC). This also justifies the effect of solubility of drugs on colon specificity of polymers. It was also found that the release profile of compression coated and enteric coated formulations of both the drugs is significantly different (KB Vs KBC or GB Vs GBC, KD Vs KDC or GD Vs GDC).

Stability studies

All the formulations of budesonide and domperidone, were observed for any change in colour and appearance for a period of 12 weeks. There was no change in color and appearance observed at the end of 12 weeks. The stability of the drug in the formulation was further confirmed by UV scanning and there was no spectral change observed. Drug content estimation was also done as a part of stability studies. The results of stability studies of compression coated and enteric coated tablets indicated that the formulations stored at 40° showed signs of degradation compared to lower temperature. At lower temperatures no significant change with respect to drug content at the end of 12 weeks was observed. The stability of drugs confirmed by calculating degradation rate constant 'k', and ranged from 1.6×10^{-3} to 3.0×10^{-3} at room temperature and lower. Whereas at higher temperature the "k" value ranged from 1.7×10^{-1} to 2.2×10^{-1} for both the drugs. From the data it was concluded that as the temperature increased the rate of degradation ('k' value) was also increased. However the difference within the formulations was found to be not significant. From the stability data it is concluded that all the formulations were found to be reasonably stable at room temperature and below the room temperature. However, at higher temperature the formulations degradation constant value was found to be marginally higher.

CONCLUSION

Enteric polymer coated formulations containing polysaccharides as compression coat, can be ideal for targeting the drugs to colon. The premature release of drug from enteric coated formulations by variation in intestinal pH due to certain pathological condition can be avoided when the formulation contains both enteric polymer as coating and polysaccharides as compression coat. Further, the release of drug in the acidic environment from the formulation containing polysaccharides as compression coat is also dependent upon the solubility of drug in the acidic pH. The present investigation revealed that basic drugs are not the ideal candidates to target to the colon from compression coated polysaccharide based polymers. Their high solubility in the acidic pH makes them vulnerable to release the drug faster from polysaccharides based compression coated formulations as these polysaccharides are hydrophilic in nature. However, if the basic drugs are well protected from being released in the acidic environment, extended release may be observed in the colon as indicated by the MDT values, due to their poor solubility in the basic region.

ACKNOWLEDGEMENT

The authors are grateful to Nitte University, Mangalore and RGUHS Bangalore, for providing the financial support and necessary facilities to carry out this study.

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