Original Article

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An Investigation into the Characteristics of Natural Polysaccharide: Polymer Metoprolol Succinate Tablets for Colonic Drug Delivery

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Abstract

Colon-specific drug delivery systems based on a polysaccharide: polymers blend viz. guar gums, Kollicoat MAE 30 DP were evaluated using *in vitro* methods. *In vitro* drug release studies have shown that prepared formulations in the form of compression coat applied over metoprolol succinate (MS) core tablets protected the drug from being released under conditions mimicking mouth to colon transit. The prepared tablets were compression coated with polysaccharide: polymers blend to give protection in the stomach. The coated tablets were tested *in vitro* for their suitability as colon specific drug delivery systems. The drug release studies were carried out in simulated stomach environment (pH 1.2) for 2 h followed by small intestinal environment at pH 6.8. The result demonstrates that matrix tablets formulated using polysaccharide: polymers blend was unable to prevent the release of drug in upper part of GIT, whereas, compression coated tablets of drug with polysaccharide: polymers blend at different weight ratios (CT1;1.75:0.75, CT2;1.5:1, CT3;1.25:1.25) were shown promising results. The compression coated MS tablets coated with CT1 did not degrade in simulated colonic fluids and showed only 8.03% and 57.39% drug released in the first 6 h and 24 h respectively. When used in different concentrations CT2 and CT3 tablets showed 10.05% & 64.98% and 9.78 &85.73% drug released in the first 6 h and 24 h, respectively. The above study shows that polysaccharide: polymers blend could be successfully used as a rate controlling membrane, for colon targeting of water soluble drugs in preference to guar gum when used in the various concentrations. Additionally, formulations developed with guar gum and Kollicoat MAE 30 DP would be highly site specific since drug release would be at a retarded rate till microbial degradation or polymer solubilization takes place in the colon.

Keyword: Polysaccharide, Matrix tablets, Simulated colonic fluids, Site-specific, Solubilization.

INTRODUCTION

Decades before colon was considered as a site for water reabsorption and residual carbohydrate fermentation. However, it is currently being viewed as a site for drug delivery. Colonic drug delivery is not only restricted to treatment of local disorders but also for systemic drug delivery. Until recently, oral drug delivery systems for colon targeting have attracted a great deal of interest for the local treatment of a variety of local and systemic diseases[1-3] and for improving systemic absorption of drugs susceptible to enzymatic digestion in the upper gastrointestinal tract[4]. Various approaches have been reported to develop new methodologies for site-specific drug release[5-6]. This part of GIT is also being considered as a site for administration of protein and peptide drugs[7]. This is because colon transit time may last for upto 78 h, which is likely to increase the time available for drug absorption. Moreover, colon provides a less hostile environment for drugs due to low diversity and intensity of digestive enzymatic activities, and a near

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neutral pH. Additionally, considering that this site is more responsive to absorption enhancers, its suitability as a site for drug administration appears promising. Further, colonic delivery of drugs may be extremely useful when a delay in drug absorption is required from a therapeutic point of view e.g. in case of diurnal asthma, angina, arthritis, etc[8].

Various systems had been developed for the purpose of site-specific drug delivery to the colon which includes a) Enzyme controlled release systems[9-10] b) Time-dependent formulations[11] c) Systems developed with pH sensitive polymers[12] d) Bacteria responsive drug delivery[13] e) Pressure responsive delivery[14-15]. Any one or a combination of the above approaches is utilized to achieve colon specific drug delivery. Analyzing the marketed products however, shows a preference for using enteric polymers, being the simplest and most viable technique for the above purpose[12]. As these systems effectively resist drug release under acidic conditions of the stomach, but a considerable amount of drug may be released in the small intestine before it reaches the colon. Also, as the pH-difference between the small and large intestine is not very pronounced[16].

Colon site-specific drug delivery may be achieved by different approaches. Among, the approach based on a combination of pH-dependent and time-controlled release mechanism seems encouraging. pH-ependent release can be assured by enteric coating and drug release can be delayed further for a predetermined time during transit through the small intestine. Time-controlled release system may be soluble coating, swellable, oral matrix type, which can resist the release of majority of drug from the formulation for an additional 3 h (i.e. the usual small intestinal transit time) and can deliver drug primarily to the colon.

Various polysaccharides/polymers are conventionally used in the tablet formulations to retard drug release. These have been used either as matrices or as a rate controlling membrane. For matrices, usually, a high concentration of polymer is required. Alternatively, these can be used as binders in tablets. A solution of these polysaccharides/polymers as binders probably on drying enables the granules to be coated by them[17-18]. Different polysaccharide/polymer and their concentration thus affect drug release from the prepared tablet. Based on the above assumption, three different polysaccharides namely, guar gum, xanthan gum and a pH sensitive polymer were selected for the present study.Metoprolol succinate is a selective β_1 receptor blocker used in treatment of several diseases of the cardio-vascular system, especially hypertension. Metoprolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches[19]. It is freely insoluble in water, freely soluble in acetone, soluble in alcohol. Metoprolol undergoes a-hydroxylation and O-demethylation as a substrate of the cyto-chrome liver enzymes CYP2D6[20] and a small percentage by CYP3A4. It is selective, moderately lipophilic drug without intrinsic sympathomimetic activity (ISA). Due to its short half-life, therefore must be taken at least twice daily or as a slow-release preparation.

Present study was aimed to formulate a dosage form which was enteric coated to prevent drug release in the stomach and had an additional lag phase in the formulation to retard drug release in the small intestine. Though enteric coated systems with such lag phases have been developed earlier, but being relatively complex systems, their large scale manufacturing requires a lot of technological advancement and skills[11,21]. So, an attempt was made to formulate a dosage form with matrix and compression coated system using natural (biodegradable) gums that retards the release of drug in upper GIT and gets degraded by vast microbial flora present in colon for successful colon specific drug delivery which could be formulated easily, using the usual tableting techniques and usual tableting ingredients, with just modification in the method of processing of the ingredients.

MATERIALS

Metoprolol succinate (MS) was a generous gift from Cadila Healthcare Pvt. Limited (Ahmadabad) India. Guar gum, Avicel pH 102, Ac-Di-Sol, sodium starch glycolate, maize starch, magnesium stearate and talc were obtained as gift samples from Rajesh Chemicals, Mumbai, India. Kollicoat MAE 30 DP (KCDP) was obtained as gift sample from BASF Mumbai. All other ingredients used in the preparation and coating of tablets were of pharmacopoeial grades.

METHODS

Preparation of matrix tablets

Matrix tablet of metoprolol succinate containing 43.75 % of guar gum and 18.75% of Kollicoat MAE 30 DP (KCDP) were prepared by wet granulation method as described below. Microcrystalline cellulose (MCC) was used as diluent and a mixture of magnesium stearate and talc (3:2 w/w ratio) was used as lubricant. Figure 1 shows infrared spectra of metoprolol succinate, guar gum and Kollicoat MAE 30DP. The composition of the matrix formulation containing 100 mg of metoprolol is shown in Table 1a. Guar gum was sieved (<250 µm) separately and mixed with metoprolol(<150 µm) and MCC (<250 µm). The powders were blended and granulated with 10% maize starch paste. The wet mass was passed through a mesh (1680 µm) and granules were dried at 50ºC for 2h. The dried granules were passed through a mesh (1190 µm) and these granules were lubricated with a mixture of talc and magnesium stearate (3:2 w/w ratio). The lubricated granules were compressed at a compression force of 4500-5500 kg using 11 mm round, flat and plain punches on a single station tableting machine (M/s Cadmach Machinery Co. Pvt. Ltd., India). Compressed matrix tablets were tested for their hardness, drug content, and drug release characteristics with a suitable number of tablets for each test. The hardness of the matrix tablets was determined by using Monsanto hardness tester (M/s Harrisons Pharma Machinery Private Limited, New-Delhi).

Table 1a. Composition of metoprolol succinate matrix tablet containing guar gum: Kollicoat MAE 30 DP (KCDP)

Ingredients	mg per tablet		
	MT1	MT2	MT3
Metoprolol succinate	100	100	100
Guar gum	175	150	125
Kollicoat MAE 30 DP	75	100	125
Microcrystalline cellulose	50	50	50
Starch (added as paste)	45	45	45
Magnesium stearate	3	3	3
Talc	2	2	2
Total weight	450	450	450

The core tablet formulation consisted of metoprolol succinate, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and talc. All the above mentioned ingredients were firstly weighed and mixed in the geometric fashion. Then mixture equivalent to 100 mg of metoprolol succinate (125 mg) was weighed and then compressed by single station Cadmach tablet punching machine using 7 mm flat punches, optimizing the hardness and die cavity of the machine, so that the tablets will be of uniform hardness and with minimal weight variation. The composition of the matrix formulation used in the study containing 100 mg of metoprolol is shown in Table 1b.

Table 1b. Core tablet formulation of metoprolol succinate

Ingredients	mg per tablet
Metoprolol succinate	100
Microcrystalline cellulose	20
Sodium starch glycolate	3
Magnesium stearate	0.5
Talc	1.5
Total weight	125

Compression coating of core tablet

40% weight of coating mixture then kept in die cavity and then core tablet was placed on it in centered position and then remaining 60% of coating mixture was added to cavity and compressed in to tablets, optimizing the hardness and die cavity of the machine. So that the tablets will be of uniform hardness and with minimal weight variation. Their compositions are shown in Tables 2a, 2b.

Table 2a. Compression coating formulations metoprolol succinate with guar gum (GG) and Kollicoat MAE

Formulation	Drug: GG: KC_{DP}
Metoprolol succinate	100
Microcrystalline cellulose	20
Sodium starch glycolate	3
Magnesium stearate	0.5
Talc	1.5
Total weight	125

Table 2b. Composition of compression coating formulations of metoprolol succinate with guar gum and Kollicoat MAE30DP

Ingredients	mg per tablet		
	CT1	CT2	CT3
Guar gum	175	150	125
Kollicoat MAE30DP	75	100	125
Microcrystalline cellulose	45	45	45
Magnesium stearate	3	3	3
Talc	2	2	2
Total weight	300	300	300

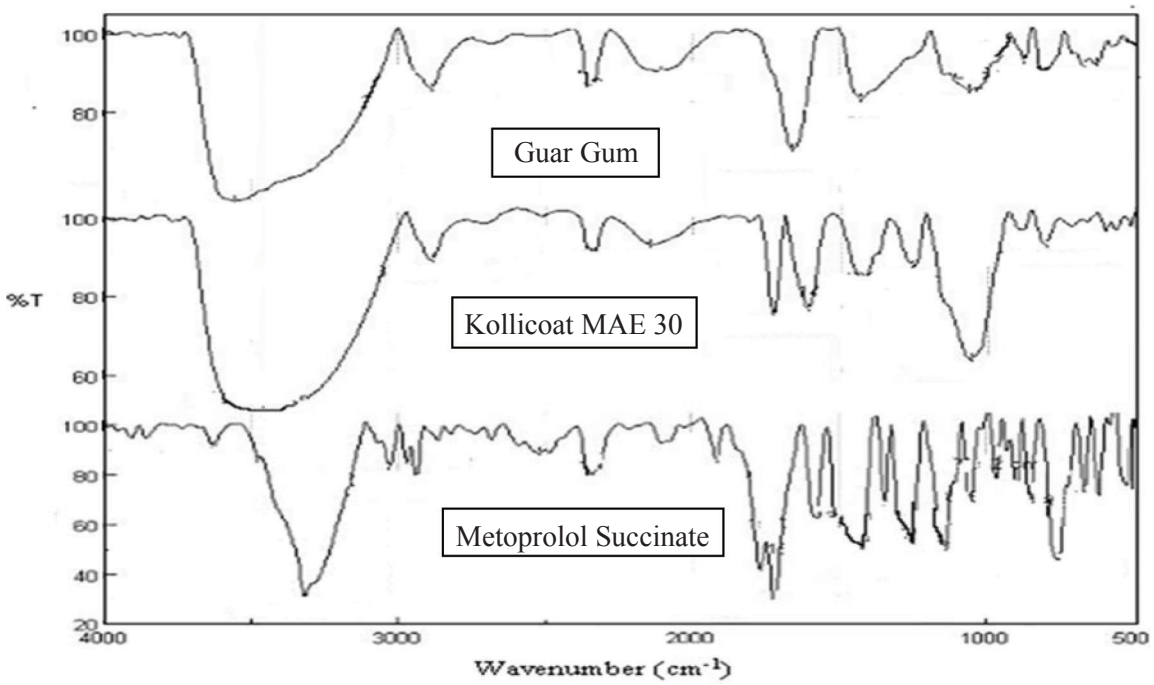

Figure 1. Infrared spectra of metoprolol succinate, guar gum and Kollicoat MAE 30DP.

Evaluation of tablet properties

Tablets were subjected to evaluation of properties (as shown in Table 3) including drug content uniformity, weight variation, tablet hardness, friability, and thickness and *in vitro* drug release studies

Table 3. Properties of metroprolol succinate tablets

Formulation	Hardness‡ (kg/cm2)	Friability‡ (%)	Thickness* (mm)	Weight variation† (mg)	Drug content* (%)
MT1	5.8±0.2	0.37±0.2	3.85±0.02	411±9	98.04±0.05
MT2	5.8±0.3	0.35±0.3	3.91±0.03	409±11	97.13±0.06
MT3	5.7±0.3	0.41±0.4	3.87±0.00	413±8	99.40±0.04
CT1	6.2±0.2	0.43±0.3	3.93±0.04	428±9	97.33±0.03
CT2	6.4±0.2	0.41±0.4	3.86±0.02	420±11	100.21±0.04
CT3	6.4±0.3	0.43±0.2	3.95±0.04	430±9	101.03±0.02

*All values are expressed as mean ± S.E. n = 5
‡ All values are expressed as mean ± S.E. n = 6
† All values are expressed as mean ± S.E. n = 20

In vitro drug release studies

The compression-coated tablets of metoprolol succinate (MS) were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. These studies were carried out using a USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C). The tablets were tested for drug release for 2 h in 0.1 N HCl (900 ml) as the average gastric emptying

time is about 2 h. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3 h. At the end of the time periods, samples each of 5 ml were taken, suitably diluted and analyzed for MS 222 nm using a double beam UV/VIS spectrophotometer (JASCO V 530). The susceptibility of guar gum coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 ml of pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents. The caecal contents were obtained from male albino rats (supplied by Ghosh, Calcutta, India, weighing 150-200 g) after pre-treatment for 7 days with guar gum dispersion. Earlier studies have shown that the presence of 4% w/v rat caecal contents in pH 6.8 obtained after 7 days of pre-treatment of rats with 1 ml of 2% w/v aqueous dispersion of guar gum provide the best condition for *in vitro* evaluation of guar gum. 30 min before the commencement of drug release studies, five rats were killed by spinal traction. The abdomen were opened, the caecal were isolated, ligated at both ends, dissected and immediately transferred into pH 6.8 phosphate buffer, previously bubbled with CO_2. The caecal bags were opened, their contents were individually weighed, pooled and then suspended in phosphate buffer to give a final caecal dilution of 4% w/v. As the caecum is naturally anaerobic, all these operations were carried out under CO_2. The drug release studies were carried out in USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modification. A beaker (capacity 150 ml, internal diameter 55 mm) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which was, in turn, in the water bath of the apparatus. The tablets were placed in the baskets of the apparatus and immersed in the dissolution added to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes. The volume was made up to 10 ml with phosphate buffer, centrifuged and the supernatant was filtered through a bacteria-proof filter and the filtrate was analyzed spectrophotometrically for MS content at 222 nm as described above. The above study was carried out on all the MS tablets coated with different coat formulation CT1, CT2, CT3 and also without caecal matter in pH 6.8 phosphate buffer (control).

Table 4. Properties of metroprolol succinate tablets

Specification	Standard values
Apparatus	USP dissolution apparatus 1
Speed	100 rpm
Volume of media	900 ml (pH 1.2)
	900 ml (pH 7.4)
	900 ml (pH 6.8)
Dissolution media used	pH 1.2
	pH 7.4
	pH 6.8 with 4% of fresh rat caecal content.
Stirrer	Basket type
Aliquot taken at each time interval of 1 h	5 ml
Temperature	37±0.5 °C

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for MS using guar gum and Kollicoat MAE 30 DP (KC_{DP}) 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[22-23]. Earlier guar gum matrix tablets released about 21% of the drug (indomethacin) in the physiological environment of stomach and small intestine, but released majority of its drug content in the physiological environment of colon[24]. However, the release of such a small percentage of drug from the surface of the matrix tablets in the physiological environment of stomach and small intestine is a serious consideration for drugs showing deleterious effects on stomach and small intestine (for example, anticancer drugs in the treatment of colon cancer). In such a situation, it was suggested to apply guar gum as a compression coat over the drug core tablet [25]. In this direction, compression coated 5-aminosalicylic acid tablets were developed for colon targeting [26-29]. The drug delivery system targeted to colon should remain intact in stomach and small intestine, but should release the drug in colon.

Matrix tablets of metoprolol succinate

The matrix tablets were prepared by applying maximum force of compression and the hardness of tablets was found to be in the range of 5.7-6.4 kg. Metoprolol Succinate (MS) tablets containing GG: KCDP in weight ratio of 1:1.75:0.75, 1:1.5:1, 1:1.25:1.25 were prepared, and subjected to drug content uniformity and *in vitro* drug release studies. The matrix tablets were found to contain 97.13-101.03% of the labelled amount of MS indicating uniformity of drug content.

The matrix tablets were subjected to *in vitro* drug release studies in 0.1 M HCl (2 h), pH 7.4 phosphate buffer (3 h) and simulated colonic fluids (rat caecal content medium at 4% w/v level after 7 days of enzyme induction, 19 h). It was reported earlier that rat caecal content medium at 4% w/v level after 7 days of enzyme induction provide the best conditions for assessing the susceptibility of guar gum to colonic bacterial degradation[24]. When the matrix tablets were subjected to *in vitro* drug release studies, MS tablets containing MT1, MT2, MT3 remained intact and slightly swollen at the end of 5 h. When matrix tablets formulation MT2, MT3 subjected to dissolution. The percent MS released was found to be 16.27±1.3 and 18.40±1.2 where as in next 19 h of dissolution study it was 60.81±1.7 and 67.82±2.6 respectively. On exposure to the dissolution fluids, the gum gets hydrated and forms a viscous gel layer around the tablet that slows down further seeping-in of the dissolution fluids towards the core of the tablets.

The release of less percentage of MS from formulation MT1 and MT2 (52.94±1.9% and 60.81±1.7%) in 0.1 M HCl, pH 7.4 phosphate buffer and phosphate buffer 6.8 (control) after 24 h of dissolution study indicates that the drug was not able to diffuse out of the formulations. This may be due to the increased concentration of KCDP, which results in increased path length due to formation of viscous gel layer with more thickness.

Hence, further studies on the *in vitro* dissolution of the formulations in simulated colonic fluids (rat caecal contents medium) were not carried out on formulations MT1, MT2 and MT3 as they also released almost 15.25 to 18.40 % of its drug in physiological environment of stomach and small intestine. The results, thus, show that the matrix formulations of MS containing MT1, MT2, MT3 (67.82±2.6%, 60.81±1.7% and 52.94± 1.9%) of GG:KCDP failed to control the drug release in the physiological environment of stomach and small intestine. Hence, it was planned to control the release of MS by preparing compression-coated tablets at the same GG:KCDP ratio. The results are shown in Table 5 and Figure 2.

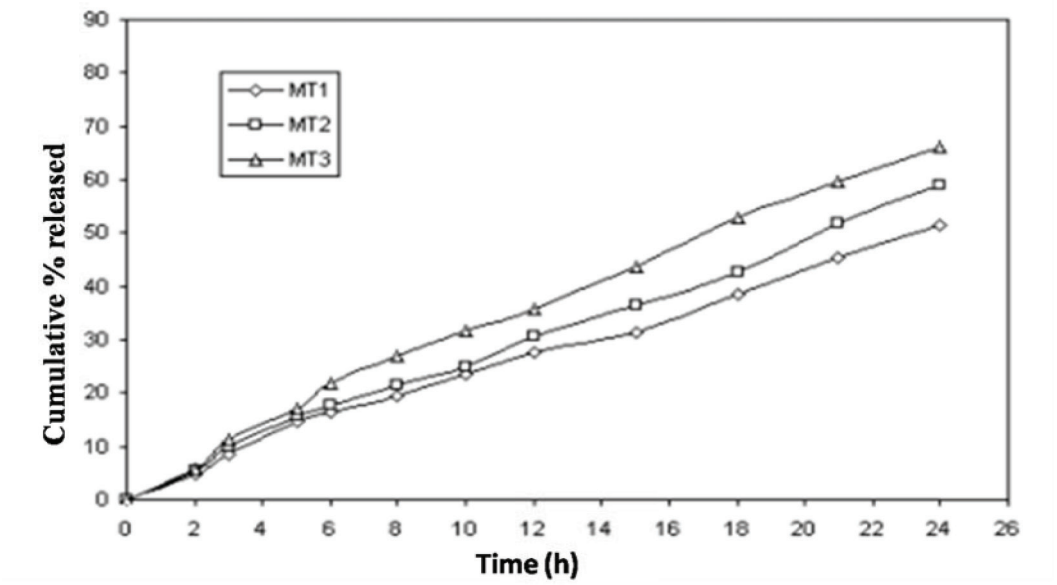

Figure 2. Percent released of MS from matrix tablets containing MT1, MT2, and MT3 in 0.1 M HCl (2 h), pH 7.4 buffer (3 h) and pH 6.8 buffer (19 h)

Table 5. Percent released of MS from matrix tablets containing MT1, MT2, and MT3 in 0.1 M HCl (2 h), pH 7.4 buffer (3 h) and pH 6.8 buffer (19 h). Each value represents mean ± S.D.

Time (h)	Cumulative % released		
	MT1	MT2	MT3
2	4.67±0.8	5.37±0.8	5.73±0.9
3	8.64±0.9	9.80±0.9	11.36±0.7
5	15.25±1.1	16.27±0.8	18.40±0.9
6	16.48±1.2	17.89±1.1	21.87±1.2
8	19.48±1.3	21.58±1.2	26.93±1.4
10	23.48±1.5	24.89±1.5	31.86±1.6
12	27.49±2.4	30.58±2.6	35.90±2.8
15	31.49±2.6	36.48±2.7	43.57±2.6
18	38.46±2.5	42.48±2.8	52.89±2.9
21	45.27±3.4	51.67±3.5	59.67±3.7
24	52.94±3.8	60.81±3.8	67.82±3.9

Compression coated MS tablets

In view of the unsuccessful delivery of the GG:KCDP matrix tablets of MS in the physiological environment of colon, it was essential either to prevent or minimize the release of MS in the physiological environment of colon until the guar gum present in the formulation (CT1, CT2 and CT3) upon by colonic bacteria. For this reason it was planned to apply guar gum and Kollicoat MAE 30 DP as a compression coat over the fast disintegrating MS core tablets. The fast disintegration of MS core tablets is

necessary to ensure fast release of the drug from the tablets soon after the degradation of the guar gum coat by the colonic bacteria. Kollicoat MAE 30 DP by increasing path length helps to prevent the release of MS in simulated gastric and intestinal media.

Fast-disintegrating MS core tablets were prepared by incorporating super disintegrant such as sodium starch glycolate. The hardness of the core tablets of MS was found in the range of 3.0-3.5 kg. The core tablets of MS were also found to comply with the friability test since the weight loss was found less than 0.59 %. The core tablets were found to disintegrate within 30 s showing the required fast disintegration characteristics. The combined action of the superdisintegrant (sodium starch glycolate) and microcrystalline cellulose (used as diluent and direct compression filler) might have contributed to such a fast disintegration. Thus the core tablets of MS formulated in the study were found to have the required characteristics for colon targeting in the form of a GG:KCDP compression coat over the drug core.

The core tablets of MS prepared as above were compression coated with a coat formulation containing various quantities of guar gum and xanthan gum. The cumulative amount of MS released from tablets coated with coat formulations containing CT1, CT2 and CT3 (1.75:0.75, 1.5:1, 1.25:1.25 of GG: KCDP) was found to be less than 4% after 5 h of the dissolution study in simulated gastric and intestinal fluids. Thus, guar gum and Kollicoat MAE 30 DP in the form of a compression coat, is capable of protecting the drug from being released in the physiological environment of stomach and small intestine. To assess the integrity of the coats, drug release studies were carried out without the addition of rat caecal contents to pH 6.8-phosphate buffer. At the end of the 24 h of the dissolution study, all the tablets coated with coat formulations CT1, CT2 and CT3 were found intact and the mean percent drug released was 25.73±0.8%, 26.98±0.5% and 28.55±1.0%, respectively. This indicates that until the coat is degraded, the GG:KCDP will not permit the release of the bulk of the drug present in the core. The results are shown in Table 6 and Figure 3.

Table 6. Mean percentage of MS released from compression coated tablets (n=3) containing GG:KCDP coat in the formulation (CT1, CT2, CT3) in dissolution study without rat caecal contents

Time	Cumulative % released		
(h)	CT1	CT2	CT3
2	0.67	0.83	0.96
3	1.91	2.57	2.81
5	2.56	3.29	3.61
6	4.79	6.82	7.60
8	7.07	8.83	9.62
10	8.30	10.09	11.12
12	11.34	12.53	14.46
15	14.91	18.97	19.88
18	18.06	22.65	24.21
21	21.79	23.89	26.36
24	25.73	26.98	28.55

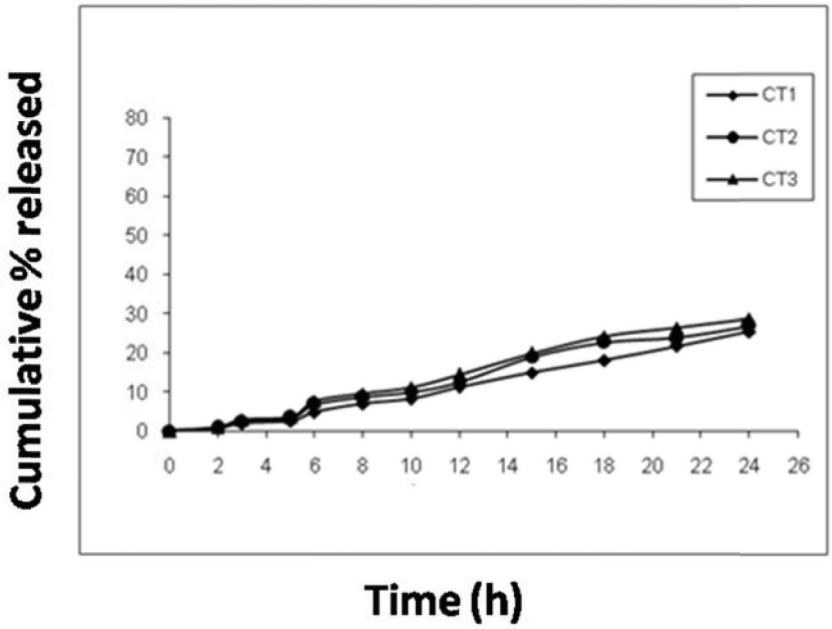

Figure 3. Mean percentage of MS released from compression- coated tablets (n=3) containing of GG:KCDP coat in the formulation (CT1, CT2, CT3) in dissolution study without rat caecal contents

The drug delivery systems targeted to the colon should not only protect the drug from being released in the physiological environment of stomach and small intestine, but also have to release the drug in colon. Hence, *in vitro* drug release studies were carried out in pH 6.8 phosphate buffer containing 4% w/v of rat caecal contents[24]. When the *in vitro* dissolution studies were carried out in the presence of rat caecal content medium, the percent drug released from MS tablets coated with coat formulation CT1 was found to be only 57.93±0.8% and the coat remained intact (Figure.4). A significant difference ($p>0.001$) was observed in the amount of MS released at the end of 24 h of the dissolution study with rat caecal content medium when compared to the dissolution study without rat caecal contents. The presence of lesser amount of Kollicoat MAE 30 DP (75 mg) CT1 might not have allowed complete release of drug during the time period of testing.

The percent drug released from MS core tablets coated with coating formulation CT2 was found to increase from 6 h onwards indicating the commencement of disruption of the hydrated gum:KCDP coats. The percentage of drug released from CT2 formulation is shown in Figure 4. The percentage of drug released after 24 h of testing was 64.98± 2.3% and the tablet coat was found to be broken at one point making way for the release of the drug. A significant difference ($p<0.001$) was observed in the amount of MS released at the end of 24 h of the dissolution study with rat caecal content medium when compared to the dissolution study without rat caecal contents. In case of tablets coated with coat formulations CT3, an increase in percent drug released was observed from 6 h onwards, and at the end of 24 h of dissolution study. 85.73 ±4.1% of MS was released (Figure 4). A significant difference ($p<0.001$) was observed in the amount of MS released at the end of 24 h of the dissolution study with rat caecal content medium when compared to the dissolution study without rat caecal content. The coat (CT3) was almost degraded in the presence of rat caecal contents thereby releasing the drug into the dissolution medium. Since the KCDP content of coat formulation CT1 (75 mg) was lesser compared to coat formulations

CT2 (100 mg) and CT3 (125 mg) and the coat might have been completely hydrated and subsequently form smallest path length among all three formulations for movement of MS from core tablet towards the dissolution medium and resulting in the release of about 85.73±4.1% of MS. The results show that tight control of drug release from compression coated formulation CT2 and CT3 might have facilitated the colonic bacterial action on swollen guar gum:KCDP and resulted in the degradation of the formulation thereby releasing the drug in the physiological environment of colon.

The compression coated formulation CT3 was completely degraded in simulated colonic fluids whereas CT2 formulation partially degraded in simulated colonic fluids. The results of the study indicate that MS tablets compression coated with either CT2, CT3 (1.5:1, 1.25:1.25 of GG: KCDP) would be potential formulations in delivering the drug to the colon.

The MS compression coated formulation CT3 released almost 85.73±4.1% of its MS at the end of 24 h of the dissolution study. The formulation CT2 also released about 64.98±2.3% of its MS content in the physiological environment of colon. It is clear from these results that formulation CT3 could target MS to colon. The CT2 tablets are also considered as potential formulations for targeting of MS to colon because of the fact that the human caecal contents would be far more than what was used in the present study. On increasing the proportion of Kollicoat MAE 30 DP in coat just by an increment of 25 mg (CT1), only 57.39±1.1% of the drug was released at the end of 24 h of dissolution study. The gel strength of the swollen coat of Kollicoat MAE 30 DP might be too high and prevented the drug release from the formulation. The colonic bacterial action of the rat caecal medium might not be sufficient to enter into a high strength gel barrier of the swollen CT1 compression coated formulation. Unless the coat of guar gum degrades, the drug release does not occur. Even in humans, in spite of higher caecal contents, the complete degradation of the CT1 may not be possible because of such a high quantity of Kollicoat MAE 30 DP in the coat formulation. However, the relative potential of the formulations CT2 and CT3 needs to be evaluated in human volunteers. The results are shown in Figure 4 and Table 7.

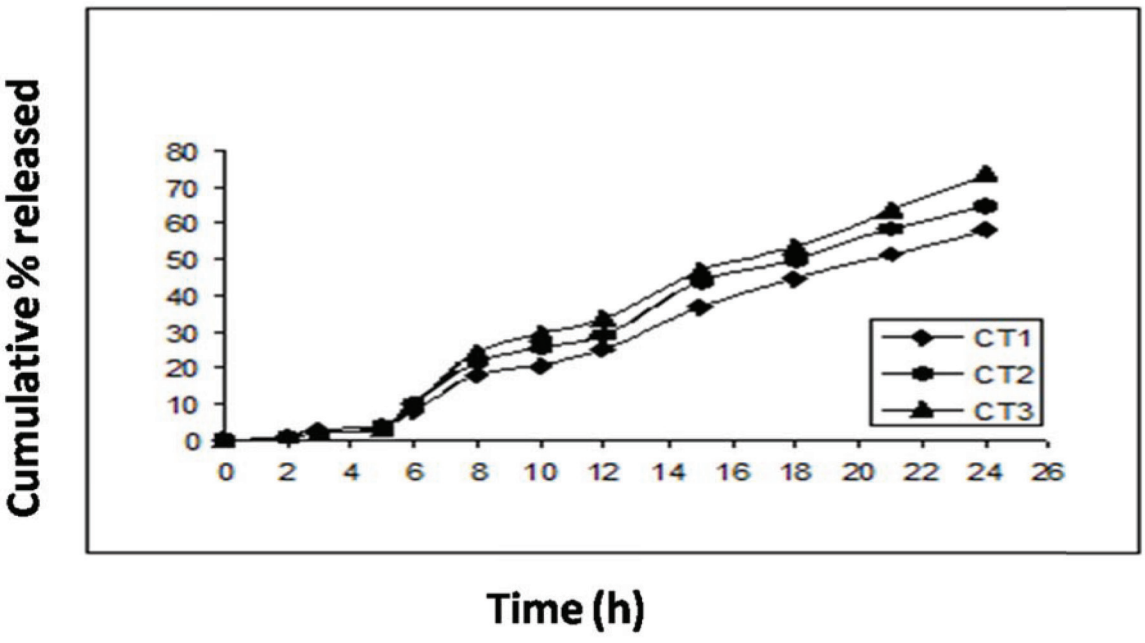

Figure 4. Mean (±S.D.) percentage of MS released from compression-coated tablets (n=3) containing of guar gum: KCDP coat in the formulation (CT1, CT2, CT3) in dissolution study with rat caecal contents

Table 7. Mean percentage of MS released from compression- coated tablets (n=3) containing of GG:KCDP coat in the formulation (CT1, CT2, and CT3) in dissolution study with rat caecal contents

Time (h)	Cumulative % released		
	CT1	CT2	CT3
2	0.84	0.70	0.79
3	2.76	2.08	2.11
5	3.68	3.44	3.15
6	8.03	10.05	9.78
8	17.89	21.59	24.29
10	20.48	25.59	29.49
12	24.99	28.89	33.49
15	36.49	43.59	46.89
18	44.59	49.68	53.19
21	51.27	58.49	63.49
24	57.39	64.98	85.73

Stability studies[30-31]

The stability studies are essential to determine whether any changes occur in the physiochemical properties of dosage form with the passage of time. The accelerated stability studies were carried out in incubator maintained at 40°C and 75±5% RH. Sample of 10 tablets from formulation CT3 were kept in the incubator for 45 days and after specified time they were analyzed for the drug content and the release pattern was also studied.

The results obtained were as follows.

There was no change in the physical appearance of the tablet.

The total drug content was

Formulation	Drug content (%)	
	Prior to stability study	After stability study
CT3	99.62	99.14

The release pattern of the drug was studied (as shown in Figure 5) by dissolution studies in same way as done previously. The results obtained was compared with the previous data, the comparative graph is as follows.

From the graph, it was observed that the drug release pattern after stability study was nearly the same with little difference.

Thus the formulation showed the characteristics of stable dosage form with no change in the physiochemical characteristics and release pattern.

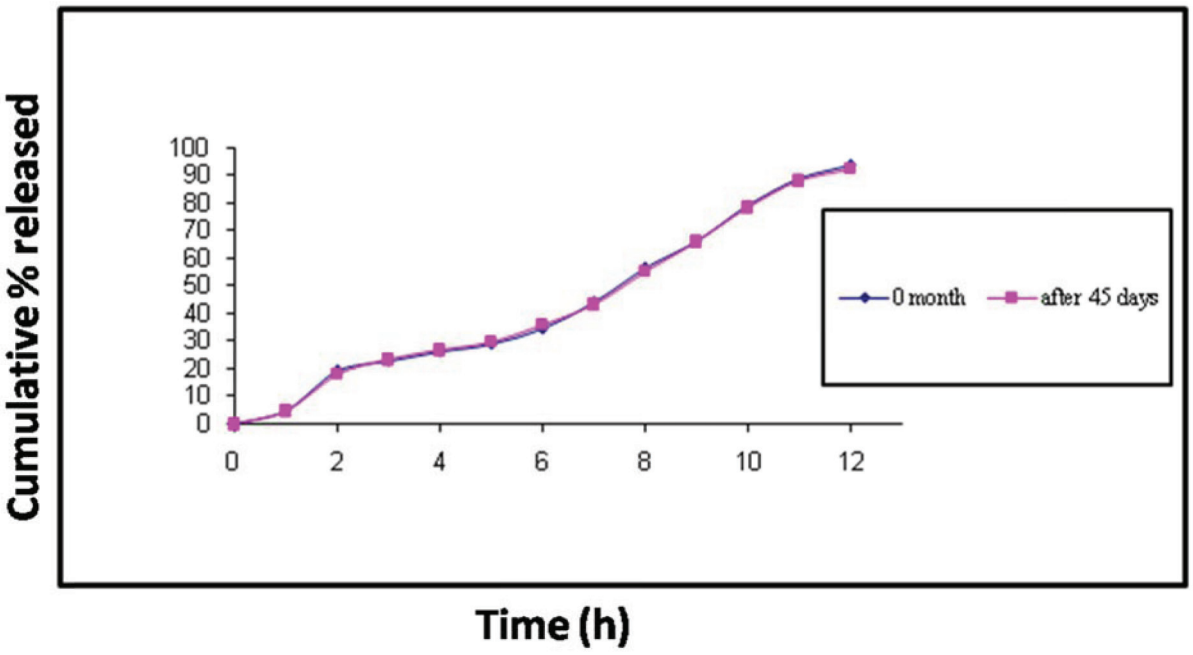

Figure 5. Release profile of metoprolol succinate tablets after storage at 40˚C and 75±5% RH.

CONCLUSION

The present investigation was carried out to develop colon targeted drug delivery systems for MS for an effective and safe therapy of hypertension. Matrix tablets of metoprolol succinate with MT1, MT2, MT3 (1.75:0.75, 1.5:1, 1.25:1.25 weight ratio) as a release controlling matrix of guar gum and Kollicoat MAE 30 DP formulation failed to release the drug in the physiological environment of colon. In view of this result, alternative colon targeted drug delivery systems were developed which could release minimal quantity of metoprolol succinate until colonic bacteria act upon the formulation. Fast disintegrating metoprolol succinate core tablets were compression coated with coat formulation containing various quantities of guar gum and Kollicoat MAE 30 DP in different weight ratios (1.75: 0.75, 1.5:1, 1.25:1.25). The compression coated metoprolol succinate tablets coated with CT1 did not degrade in simulated colonic fluids where as the formulations coated with CT2 and CT3 degraded in dissolution medium containing rat caecal contents there by releasing about 64.98% and 85.73% of the drug, respectively. It appears that compression coated metoprolol succinate tablets compression coated with either CT2 or CT3 (1.5:1, 1.25:1.25 w/w) are most likely to provide targeted delivery of metoprolol succinate to the colon.

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