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Original Article

FACTORS INFLUENCING DELAYED RELEASE FOLLOWED BY RAPID PULSE RELEASE OF DRUGS FROM COMPRESSION COATED TABLETS FOR COLON TARGETING

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ABSTRACT

Objective: This work was undertaken to develop colon targeted tablets that can minimize premature release of ibuprofen (IBP) and metronidazole (MNZ) in a lag period of 7h during which the tablets are likely to remain in the upper gastro-intestinal tract, and produce rapid pulse release within 1-5 h after the lag period when the tablets could be located in the colon with or without intervention of colonic microflora.

Methods: Core tablets of ibuprofen and metronidazole containing different amounts of tri-sodium citrate (TSC) as osmogen were compression coated with locust bean gum (LBG) and carboxymethyl LBG (CMLBG). *In vitro* drug release studies were performed in a dynamic pH shift condition with or without rat cecal matters. The release of the drugs were also monitored at different hydrodynamic conditions.

Results: *In vitro* release studies revealed that increase in the amount of TSC, decrease in coat-weight and change in hydrodynamic conditions influenced the drug release considerably. While LBG coated tablets under the stated conditions failed to provide complete release of the drugs in 12 h, CMLBG coated tablets produced complete release rapidly in the post lag period minimizing the release in the initial 7 h. Presence of rat cecal matter in dissolution medium further accentuated the release of the drugs from CMLBG compression coated tablets in the post lag period.

Conclusion: The study revealed that tablets containing appropriate amount of osmogen in the core and compression coated with suitable amount of CMLBG may be suitable for colon targeting of drugs even in the absence of colonic microflora.

Keywords: LBG, CMLBG, Osmogen, Rat cecal content, *In vitro* dissolution

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INTRODUCTION

Development of colon-targeted drug delivery systems intended for administration through oral route has become the most challenging task to the pharmaceutical researchers because of the possibility of premature drug release in the upper gastrointestinal tract (g.i.t.) before reaching the colon. Colon specific dosage forms are of immense importance for the treatment of colon-related diseases such as Crohn's disease, ulcerative colitis, inflammatory bowel syndrome and colorectal cancer [1], as they provide high local drug concentration at the afflicted site of colon, and thereby, produce optimum therapeutic response and reduce the emergence of adverse drug-effects associated with premature drug release and subsequent absorption through the upper g.i.t. [2-5].

As the gastric residence time of tablets ranges from 0.5 h to about 2 h and small intestinal transit time of about 3 h is fairly constant [6], the time required for a tablet dosage form to reach colon may be considered as 5 h. Adding a buffer time of 2 h due to further variation in transit time if any, the strategy for designing a colon-targeted dosage form should be to prevent or minimize premature drug release (below 10 %) for a period of 7 h (lag period) following which the drug should be released rapidly and completely within 7-12 h (post lag time) to provide high local concentration of drug in colon.

Various methods such as coating with pH-sensitive polymers, time-dependant release systems, compression coating with bio-degradable polysaccharides have been developed for achieving colon targeting of drugs [7]. Principally these dosage forms consist of a reservoir system in which an immediate release core is covered with a suitable barrier coating to protect the drug release in lag period. The barrier may be a pH-sensitive polymer such as methacrylic acid and methylmethacrylate copolymers [8] or a polysaccharide degradable by colonic microflora [9,10]. The rationale of compression coating of tablets with polysaccharides for colon targeting of drugs is that large number of anaerobic bacteria present in the human colon secrete various enzymes to degrade polysaccharides which are not digested in the upper g.i.t. [11]. Although the composition of human gut ecosystem may be altered by various factors [12], microbially triggered systems which are based on compression coating of an immediate release tablet with a biodegradable polysaccharide have been investigated extensively [13-17]. However, available literatures indicate that after a satisfactory lag period, the drugs from compression coated tablets are released in the colon in a sustained release manner rather than in a rapid pulse release fashion [13-16].

Osmotic pressure controlled drug delivery systems with several modifications have been developed. When a tablet consisting of a core of an osmotically active drug, or a core of osmotically inactive drug in combination with an osmotically active salt and surrounded by a semi permeable membrane is brought into contact with water, the release of the drug takes place through an orifice at a constant rate due to osmotic pressure difference. In the absence of orifice, imbibed water develops hydraulic pressure inside the tablet until the core ruptures and the contents are released [18]. It is therefore possible that presence of an osmotically active salt (osmogen) in the core of a compression coated tablet may induce complete release of the drug rapidly in the post lag period. In addition, variable environment of human gut system in colon-related diseases may alter the hydrodynamic condition and subsequently, affect the drug release behavior from compression coated tablets in both lag and post lag time periods.

The objective of the present work was to develop locust bean gum (LBG) and carboxymethyl locust bean gum (CMLBG) compression coated tablets of ibuprofen (IBP) and metronidazole (MNZ) containing different amounts of osmogen in the core and polysaccharides in the coat, and to evaluate the effect of osmogen, coat weight and hydrodynamic condition on in vitro release behavior of drugs during the lag and post lag periods. The effect of microbial flora on the drug release in the post lag period was examined using rat cecal matter in dissolution medium. LBG and CMLBG were selected as polysaccharides for compression coating as LBG is susceptible to

degradation by colonic microflora [19, 20]. Details of CMLBG synthesis from LBG through a base catalyzed reaction with monochloroacetic acid, and its characterization have been reported elsewhere [21]. IBP and MNZ have been used in this study as model drugs.

MATERIALS AND METHODS

Materials

Locust bean gum (LBG), mol. wt. 310 000 (Sigma-Aldrich Corporation, USA) and all other analytical grade reagents were obtained commercially and used as received. Carboxymethyl locust bean gum (CMLBG) having a degree of substitution 0.65±0.05 was synthesized in our laboratory. Ibuprofen (IBP), metronidazole (MNZ), HPMCE15, avicel PH 102 (avicel), crosspovidone (CP), sodium starch glycolate (SSG), magnesium stearate (MS) and tri-sodium citrate (TSC) were obtained as gift samples from Caplet India Ltd, Kolkata.

Preparation of core tablets

IBP core tablets containing 2.5 to 10 % w/w TSC were prepared by a two-step process. Initially, dummy granules (# 20-# 30 mesh BS screens) were prepared using avicel, 50 % of total SSG, (intragranular disintegrant) and required amount of 2.5% w/v HPMCE15 solution by wet granulation method. Subsequently, the dried (at 60 °C) granules were mixed thoroughly with IBP (# 60 mesh), remaining 50 % of SSG (extra granular disintegrant), MS and required amount of TSC, and compressed using a 6 mm flat face punch in a tablet machine (RIMEK, Karnavati Engineering Ltd., Gujarat).

Conventional wet granulation method was followed for the preparation of MNZ core tablets containing 2.5 to 10 % w/w TSC. Required amounts of MNZ (# 60 mesh), avicel, and 50 % of CP were blended uniformly and wet granulated with 3% w/v HPMCE15 solution. The dried (60 °C) granules (# 20-# 30 mesh) were mixed with remaining CP, MS and required amount of TSC, and compressed into tablets using 6 mm flat face punch in the tablet machine. The average weight and crushing strength of both IBP and MNZ core tablets were adjusted to 150 mg and 2.5 to 3 kg respectively. The composition of the core tablets are shown in table 1.

Table 1: Composition and drug release from core tablets

Code of core tablets	IBP (mg)	MNZ (mg)	Dummy granules (mg)	avicel (mg)	SSG (mg)	CP (mg)	MS (mg)	TSC (mg)	% of drug release in 10 min*
I_1	100		41.00		3.75		1.5	3.75	92.30±2.14
I_2	100		37.25		3.75		1.5	7.50	96.81±1.93
I_3	100		29.75		3.75		1.5	15.0	100±1.28
M_1		100		38.75		6.0	1.5	3.75	90.07±0.98
M_2		100		35.0		6.0	1.5	7.50	92.81±0.91
M_3		100		27.5		6.0	1.5	15.0	98.04±1.89

*mean±SD (n=6), IBP-ibuprofen; MNZ-metronidazole; avicel-avicel PH 102; SSG-sodium starch glycolate; CP-cross povidone; MS-magnesium stearte; TSC-trisodium citrate.

Preparation of compression coated tablets

Granules of LBG and CMLBG for compression coating of core tablets were prepared separately by wet granulation method using water as granulating fluid following the method described for carboxymethyl xanthan gum compression coated tablets [22]. 40 % of the dried (at 60 °C) granules were placed in a 10 mm die, the core tablet was placed in the centre manually, remaining 60 % granules were placed over the core tablet and compressed with 10 mm flat face punch in the tablet machine. The variation in the formula for the preparation of compression coated tablets was as follows:

1) Keeping the coat weight constant at 350 mg, the amount of TSC in the core tablets was varied from 2.5 to 10 % w/w.

2) Keeping the amount of osmogen constant at 10 %, coat weight was varied from 250-300 mg.

IBP and MNZ core tablets were compression coated with LBG and CMLBG following the above general method and the composition of the tablets are shown in table 2.

Evaluation of tablets

Weight variation test and friability test of core and compression coated tablets were performed following the methods described in USP 27/NF 22 [23]. The weight of the tablets were measured in an electronic pan balance (Precisa, XB 600 M-C, Switzerland) and friability was determined using a friabilator (EF 2, Electrolab, Mumbai). Hardness of core and compression coated tablets were measured using Monsanto type hardness tester (Monsanto, Cambell Electronics, Mumbai).

Disintegration time test of core tablets was conducted in phosphate buffer (PB) solution of pH 6.8 [24] at 37±2° C in a disintegration time test apparatus (ED 2L, Electrolab, Mumbai).

Drug contents in core tablets were determined in the following way

IBP content: An IBP core tablet was powdered in a glass mortar and transferred quantitatively with phosphate buffer (PB) solution of pH 7.4 [24] into a stoppered conical flask. After shaking in a mechanical shaker for 24 h, the mixture was filtered through Whatman filter paper (pore diameter 11 µm). An aliquot from the filtrate was diluted with the buffer solution and analyzed at 222 nm in a spectrophotometer (Shimadzu, UV, 2450, Japan). The concentration of drug was determined from the calibration curve drawn in PB solution (pH 7.4), and IBP content in the tablet was determined by the usual process.

MNZ content: For the determination of MNZ in a core tablet, the drug from the powdered tablet was extracted in HCl solution of pH 1.2 (acid solution) as described above and analyzed spectrophotometrically at 278 nm.

In vitro drug release study

USP II tablet dissolution rate test apparatus (TDP-06P, Electro Lab, Mumbai) was used to determine the *in vitro* release of drugs from various tablets. The temperature of the dissolution medium was maintained at 37±0.5 °C and paddle speed was fixed at 75 rpm. The release study of the drugs from the core tablets were performed in PB solution of pH 6.8 and the same from the compression coated tablets were conducted under dynamic pH shift condition following the method described in USP 27/NF 22 for delayed release formulation [25] with slight modification. The drug release was monitored for 2 h in 700 ml acid solution of pH 1.2 (simulating the gastric pH) after which the solution pH was increased to 7.4 (small intestinal pH) by adding 200 ml 0.2 (M) trisodium phosphate solution and adjusting quickly with 0.2 (M) NaOH/HCl solution, and the release study was continued upto 5 h. Finally, the pH of the dissolution medium was decreased to pH 6.8 (colonic pH) adding 5 ml 2 (M) HCl solution, and the drug release was monitored upto 12 h. In all cases, change in pH of the medium was checked with a pH meter (Orion 2 star, Thermo Scientific, Singapore). During the dissolution study, aliquots were removed at pre-scheduled times and immediately replenished with the same volume of fresh respective medium kept at 37 °C. Filtered and diluted aliquots were analyzed spectrophotometrically. IBP samples in acid solution, PB solution (pH 7.4) and PB solution of pH 6.8 were analyzed at 220

nm, 222 nm, and 222 nm respectively. MNZ was analyzed at 278 nm, 319 nm, and 319 nm respectively in acid solution, PB solution (pH 7.4) and PB solution of pH 6.8. The amounts of drugs released were calculated using the respective calibration curves constructed in different media.

***In vitro* drug release study with rat cecal content**

In vitro drug release study in presence of rat cecal content was performed following the method described elsewhere [26] with slight modification. Male whister Albino rats having body weight 250 to 300 g were purchased from an authorized breeder and kept in animal house under the recommended conditions of the Animal Ethical Committee of the institution (AEC/PHARM/1601/01/2016). The animals were maintained on normal diet (water-soaked Bengal gram) and water. 3 ml 2 % w/v dispersion of LBG in water was administered to the animals orally through a teflon tubing for 7 d. 30 min prior to the experiment, the rat was sacrificed and its abdomen was opened. The cecal bag after ligating at both ends was dissected and opened. The content was weighed, homogenized in a homogenizer (KMH 1321, Electrocrafts, Mumbai) and added in 200 ml PB solution (pH 6.8) to get a final concentration of 4% w/v. The medium was maintained throughout at 37±0.5 °C under nitrogen gas. A compression coated tablet, after *in vitro* dissolution study in acid solution for 2 h and PB solution (pH 7.4) for 3 h, was immersed in PB solution (pH 6.8) containing the rat cecal content, and the release was continued for an additional 7 h. Samples from the dissolution bath were collected at pre-scheduled times and replenished immediately with the same volume of PB solution (pH 6.8). Withdrawn samples were diluted suitably and centrifuged (Sigma 3K30, Singapore) at 10 000 rpm for 30 min. The supernatant was collected, filtered through a bacteria proof filter paper (0.2 µm, 47 mm diameter, PALL Corporation, Mumbai), and analyzed spectrophotometrically.

Statistical analysis

% of drug released at different times as well as the area under the curves (AUCs) of % drug release versus time profiles, which were calculated using trapezoidal rule, were subjected to one way analysis of variance (ANOVA) using Graph Pad Prism 7 software. *P<0.05 was considered as significant difference.

RESULTS AND DISCUSSION

The compositions of IBP core tablets (I_1 to I_3) and MNZ core tablets (M_1 to M_3) containing 100 mg of the respective drugs are shown in table 1. To avoid any thermal decomposition of IBP (M. P. 79.42 °C), the IBP core tablets, each weighing 150 mg, were prepared by a two step process wherein dummy granules prepared by wet granulation method were compressed with IBP and other excipients directly. MNZ core tablets were prepared following the conventional wet granulation method. The average weights of IBP and MNZ core tablets varied from 148.30±0.45 mg to 149.32±0.41 mg, and 148.20±0.41 mg to 148.80±0.30 mg respectively. IBP and MNZ contents in the respective core tablets were found to vary from 97.93±0.3 mg to 99.30±0.31 mg, and 98.72±0.28 mg to 98.91±0.35 mg. All the tablets having a crushing strength of 2.5 to 3 kg exhibited less than 1 % friability and disintegrated within 2 min. *In vitro* release of IBP in PB solution of pH 6.8 from the core tablets containing different amounts of TSC, used as osmogen, varied from 92.30±2.14 % to 100±1.28 % for 10 min, and in the same time span, MNZ release from the core tablets varied from 90.07±0.98 % to 98.04±1.89 % (table 1). The higher the concentration of TSC, the higher was the drug release. Rapid release of the drugs from the core tablets indicated that the drug release was not dissolution rate limited [27].

To study the effect of varying amounts of TSC on *in vitro* drug release from compression coated tablets, the core tablets containing 2.5 % to 10 % w/w TSC were compression coated with 350 mg of LBG (composition shown in table 2). The average weights of IBP and MNZ compression coated tablets varied from 500.26±0.28 mg to 501.09±0.41 mg, and 501.16±0.18 mg to 502.18±0.68 mg respectively. The friability of the tablets having hardness of 4.5 to 5 kg was less than 1 %. *In vitro* drug release from compression coated tablets was studied in a dynamic pH shift condition simulating the pH conditions prevailing in g.i.t.. The amounts of IBP and MNZ released at 2 h, 7 h and 12 h from LBG compression coated tablets were taken out from the drug release profiles and have been shown in table 2. The results showed that keeping the coat weight constant at 350 mg, increase in the amount of TSC in the core tablets tended to increase the release of IBP and MNZ. Statistical analysis in the form of one way ANOVA of the % of drug released at different times as well as the area under the curves (AUCs) of the release profiles of IBP and MNZ demonstrated significant difference (*P<0.05) in release of the drugs with increase of TSC. Although premature release within a lag period of 7 h was considerably less at each of the TSC concentrations, the post lag release was unsatisfactory as the maximum amount of IBP release in 12 h was only 4.47±0.73 % for the tablets containing the highest amount of TSC. The release of MNZ from LBG compression coated tablets containing increasing amounts of TSC in the core followed the same pattern. Although, the release of the drug was considerably less in the lag period of 7 h, the maximum amount of drug released in 12 h was only 3.85±0.98 % from the tablet containing highest amount of TSC (table 2).

Table 2: Composition and effect of osmogen and coat weight on release of drugs from LBG compression coated tablets

Compression coated tablet	Core tablet	Coat weight of (mg) LBG	Average weight (mg) of compression coated tablets	% of drug release[a] in		
				2h	7h	12h
Effect of osmogen						
L_1I_1	I_1	350	500.26±0.28	0.33±0.18	2.14±0.61	3.56±0.43
L_1I_2	I_2	350	501.06±0.19	0.41±0.21	2.45±0.32	3.82±1.36
L_1I_3	I_3	350	501.09±0.41	0.64±0.32	2.89±0.51	4.47±0.73
Statistics[b]				*P<0.05	*P<0.05	*P<0.05
L_1M_1	M_1	350	502.18±0.68	0.25±0.54	1.03±2.79	3.08±0.91
L_1M_2	M_2	350	501.16±0.31	0.33±0.24	1.34±0.14	3.34±0.73
L_1M_3	M_3	350	501.16±0.18	0.41±0.75	1.60±0.67	3.85±0.98
Statistics[b]				*P<0.05	*P<0.05	*P<0.05
Effect of coat weight						
L_1I_1	I_3	350	501.09±0.41	0.64±0.18	1.73±0.51	4.47±0.73
L_1I_2	I_3	300	447.71±0.32	1.04±0.21	3.12±0.67	5.70±0.91
L_1I_3	I_3	250	401.23±0.20	1.77±0.32	4.58±1.34	7.55±1.29
Statistics[b]				*P<0.05	*P<0.05	*P<0.05
L_1M_1	M_3	350	501.16±0.18	0.41±0.54	1.60±0.67	3.85±0.97
L_1M_2	M_3	300	451.20±0.41	0.50±0.24	2.14±0.25	4.59±0.31
L_1M_3	M_3	250	398.21±0.23	0.98±0.75	2.79±0.31	5.59±0.71
Statistics[b]				*P<0.05	*P<0.05	*P<0.05

[a]mean±SD (n=6), [b]One way analysis of variance (ANOVA) revealed significant difference (*P<0.05).

Keeping the amount of TSC constant at 10 %, coat weight of LBG was reduced from 350 to 250 mg, and the amounts of drug released at different time periods are shown in table 2. Decrease in coat weight was found to increase the release of both drugs significantly (*P<0.05). Moreover, statistical analysis in the form of one way ANOVA of the area under the curves (AUCs) of the release profile of each of the drugs demonstrated significant difference (*P<0.05). However, even at the lowest coat weight (250 mg), the release in the post lag period was unsatisfactory as the maximum amount of IBP and MNZ release were respectively 7.55±1.29 % and 5.59±0.71 % in 12 h (table 2). This indicates that LBG coat was unsuitable to provide complete drug release in the designated post lag period of 7-12 h.

The effect of changes in the amounts (2.5 to 10 %) of TSC on *in vitro* release of IBP and MNZ from the tablets compression coated with 350 mg of CMLBG was studied under the similar conditions adopted for LBG compression coated tablets. The average weights of CMLBG compression coated IBP and MNZ tablets having hardness 4.5 to 5 kg and friability less than 1 % varied from 348.97±0.34 mg to 350.23±0.41 mg and 349.18±0.32 mg to 351.02±0.43 mg respectively. The results of drug release study have been shown in fig. 1 which demonstrated that increase in the amount of TSC from 2.5 to 10 % increased the release of IBP from 27.09±0.31% to 63.15±0.34 %, and that of MNZ from 32.21±0.58 % to 40.86±0.68 % in 12 h although in all the cases the maximum amounts of drug release during the lag period of 7 h were below 10 % (6.97±0.63 % IBP and 5.53±0.55 % MNZ from tablets containing 10 % TSC in the core). It was further noted that the change in drug release as a function of the amount of TSC during the lag period was marginal although after the lag time of 7 h, sudden pulse release of the drugs was observed, the amount of which was dependent on the concentration of TSC. However, complete release of neither IBP nor MNZ could be achieved in 12 h.

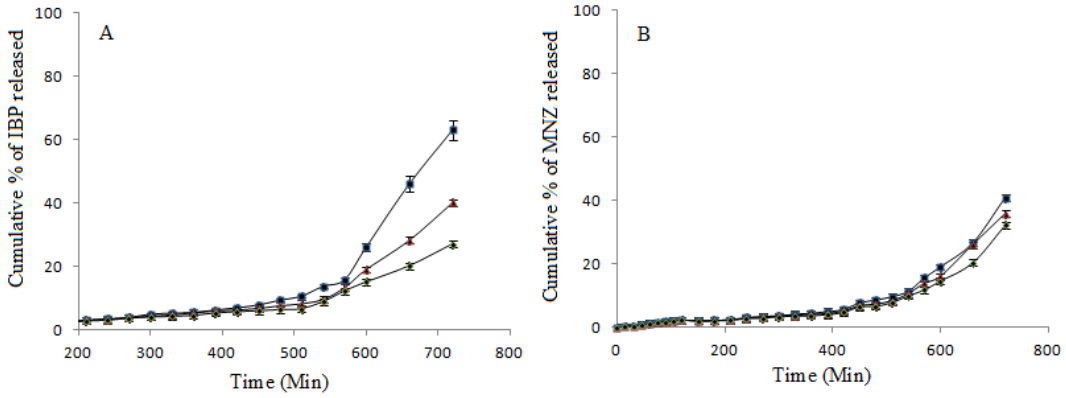

Fig. 1: Effect of TSC in the core tablets on release of (A) IBP and (B) MNZ from CMLBG (350 mg) compression coated tablets. Key: TSC concentration: (♦) 2.5 % w/w, (▲) 5% w/w, (■)10 % w/w. Maximum SD (A) (±2.38, n = 6) (B) (±1.98, n = 6)

Keeping the amount of TSC fixed at 10 % in core tablets, the amount of CMLBG coat was decreased from 350 mg to 250 mg, and the resultant effect on drug release have been shown in fig. 2. While the tablets compression coated with 350 mg of CMLBG released respectively 63.15±0.32 % IBP and 40.86±0.45 % MNZ in 12 h, the tablets compression coated with 250 mg of CMLBG released respectively 100±0.31 % and 95.61±0.44 % of IBP and MNZ in 12 h. Although decrease in CMLBG coat weight marginally increased the drug release above the cut off value of 10 % during the lag period of 7 h (11.49±0.41 % of IBP and 11.12±0.31 % of MNZ from the tablets having 250 mg coat weight), after the lag period almost complete release of the drugs were achieved in 12 h.

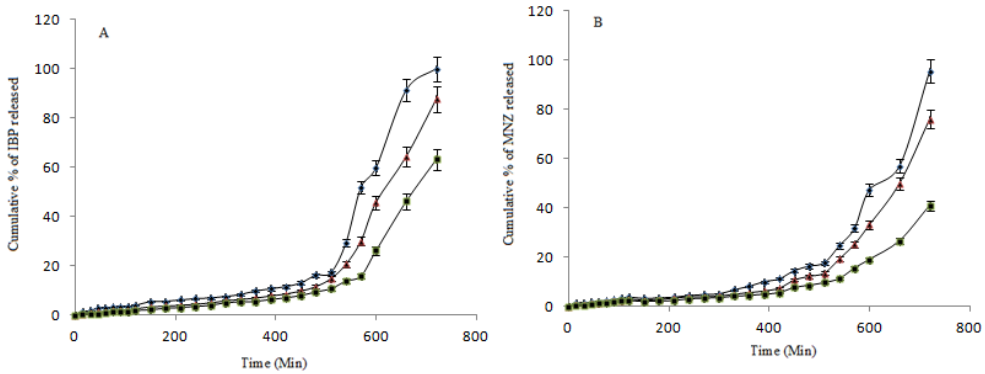

Fig. 2: Effect of coat weight of CMLBG on release of A) IBP and B) MNZ from tablets containing 10 % w/w of TSC in the core tablet. Key: coat weight: (♦) 250 mg, (▲) 300 mg, (■)350 mg. Maximum SD (A) (±3.08, n = 6) (B) (±2.18, n = 6)

The results indicate that the amount of osmogen in the core tablet, nature of polysaccharide used to coat the core and the coat weight are some of the determinant factors in controlling the release of drugs in both the lag and post lag periods. When a tablet compression coated with a polysaccharide is brought in contact with aqueous medium, the coat hydrates and forms a gel layer on tablet surface. The gel layer may be a strong elastic gel or a viscous solution depending on the nature of polysaccharide. During the dissolution study, seepage of water through the gel layer into the osmogen containing core develops osmotic pressure which acts radially outwards to rupture the core or the surrounding membrane [28]. However, the amount of ingressed water depends on the viscosity and strength of the gel layer. It has been reported that while LBG forms a strong elastic gel layer of high yield strength in

contact with water, CMLBG produces a viscous gel layer of low yield strength [21]. Probably slow seepage of water through the elastic gel layer of LBG failed to develop sufficient osmotic pressure even in the presence of 10 % osmogen in the core for rupturing the LBG coat and to expose the core in dissolution medium. This resulted in exceedingly low drug release. On the other hand, comparatively faster seepage of water through the viscous gel layer of CMLBG produced osmotic pressure which was sufficient enough to break apart the CMLBG coat and consequently produced higher release of the drugs. Moreover, the higher the osmogen concentration, the higher is the osmotic pressure. Consequently, increase in osmogen concentration in the core produced higher drug release. Decrease in the amount of polymer produces a gel layer of lower viscosity and yield strength which allow rapid and higher penetration of water into the core. This results in a rapid buildup of osmotic pressure to break apart the CMLBG coat quickly inducing faster release of drugs. Consequently, as the coat weight was decreased, the release of the drugs in the post lag period increased.

The motility of g.i.t. has been reported to be altered in various colonic diseases [29]. To study the effect of altered gastrointestinal motility on drug release from compression coated tablets, *in vitro* drug release was examined in different hydrodynamic conditions. IBP and MNZ release from tablets containing 10 % osmogen in the core and compression coated with 250 mg LBG was studied by changing the speed of the paddle of the dissolution apparatus, and the results are shown in fig. 3A and 3B.

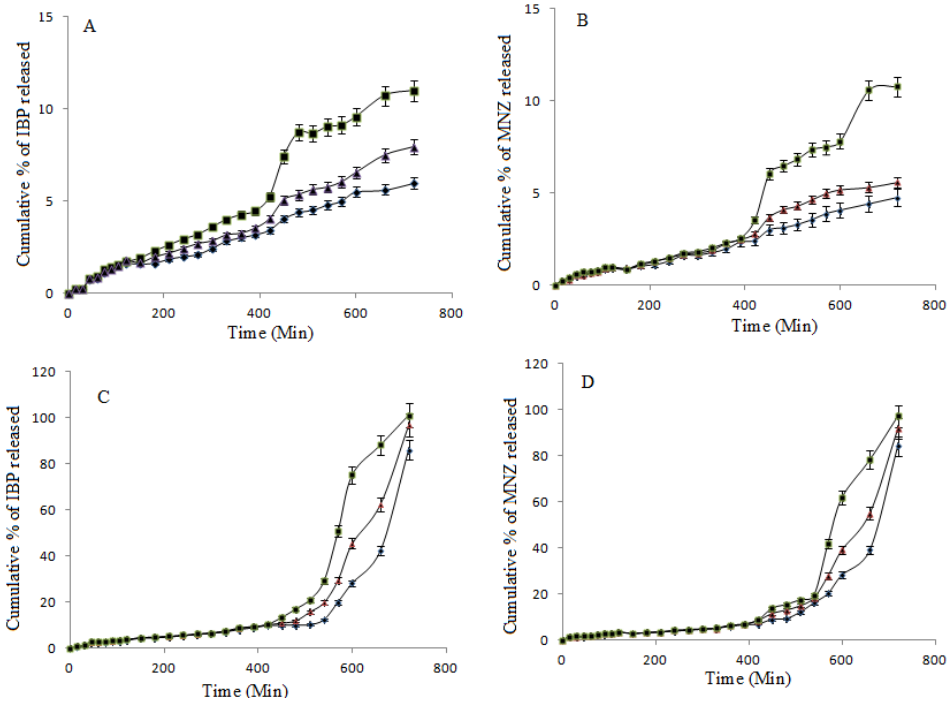

Fig. 3: Effect of stirring speed of paddle on release of (A) IBP and (B) MNZ from LBG (250 mg) compression coated tablets containing 10 % w/w TSC in core and effect of stirring speed of paddle on release of (C) IBP and (D) MNZ from CMLBG (250 mg) compression coated tablets containing respectively 2.5 % w/w and 5 % w/w TSC in core tablets. Key: (♦) 50 rpm, (▲) 75 rpm, (■) 100 rpm. Maximum SD (A) (±2.17, n = 6) (B) (±1.39, n = 6) (C) (±1.97, n = 6) (D) (±3.67, n = 6)

Increase in paddle speed from 25 rpm to 100 rpm tended to increase the release of both drugs, although the amounts of release of the drugs in 12 h were exceedingly less. Similarly, release of IBP and MNZ from tablets containing respectively 2.5 % and 5 % TSC in the core and compression coated with 250 mg CMLBG were found to increase with increase in stirring speed of the paddle (fig. 3C and 3D). Increase in drug release both in lag and post-lag periods were significant (*P<0.05). Effects of change in hydrodynamic condition on drug release from matrix tablets have been reported in various literatures. It has been stated that increase in stirring speed of paddle/basket makes the drug transport independent of stagnant boundary layer effect [30, 31], and increases the mass transfer and decreases the film thickness [32]. Increase in stirring speed may also induce erosion of the matrix made up of low molecular weight polymer due to greater attrition at the swelling/dissolution fronts leading to increase in release rates [33]. As LBG forms a strong elastic gel layer in contact with water, erosion of the coat during the dissolution process may be less. It may, therefore, be assumed that decrease in film thickness at higher agitation speed increased the influx of water into the core, although to a less extent, leading to increase in drug release from LBG coated tablets. On the other hand, CMLBG which forms a viscous gel in aqueous medium might have undergone erosion to a greater extent with increase in stirring speed leading to faster penetration of water. As a result high osmotic pressure, which was developed in the core, was sufficient to rupture the CMLBG coat at late hours inducing higher drug release.

In vitro drug release study in presence of rat cecal content

The success of colon-targeted tablets compression coated with polysaccharides rely on the fact that polysaccharides are not digested by the enzymes present in the upper g.i.t. but are degraded by the enzymes of the colonic microflora [4]. Regular consumption of polysaccharides induces large amount of colonic microflora in humans [34]. Rats which are used in laboratory experiments are usually fed with water-soaked Bengal gram which may not induce sufficient microflora in colon [26]. Most of the researchers have fed rats with solution/dispersion of polysaccharides of interest to induce microflora. The period of feeding and the amount of rat cecal content to be used in dissolution medium are the two important factors to be considered during the experiment. Addition of 4 % w/v rat cecal matter, obtained after administering 1 to 2 % w/v aqueous dispersion/solution of polysaccharide in rat for 7 d, into dissolution medium appears to be optimum for evaluation of compression coated tablets for colon delivery of drugs [16, 35-37]. In the present study, since LBG was found unsuitable as compression coating material, CMLBG compression coated tablets were subjected to *in vitro* drug release study in the presence of rat cecal matter. Release of IBP from CMLBG (250 mg) compression coated tablets (containing 2.5 %

osmogen in the core) in absence and presence of rat cecal matter have been compared in fig. 4 A. It was found that while 100±2.32 % IBP was released in 8 h in dissolution medium containing rat cecal matter, 96.85±0.32% IBP was released in 12 h in the absence of rat cecal content. Similar trend was observed for CMLBG compression coated MNZ tablets. Complete release of MNZ in presence of rat cecal content was achieved in 9 h while 91.71±0.34% release was obtained in 12 h in absence of rat cecal content (fig. 4B).

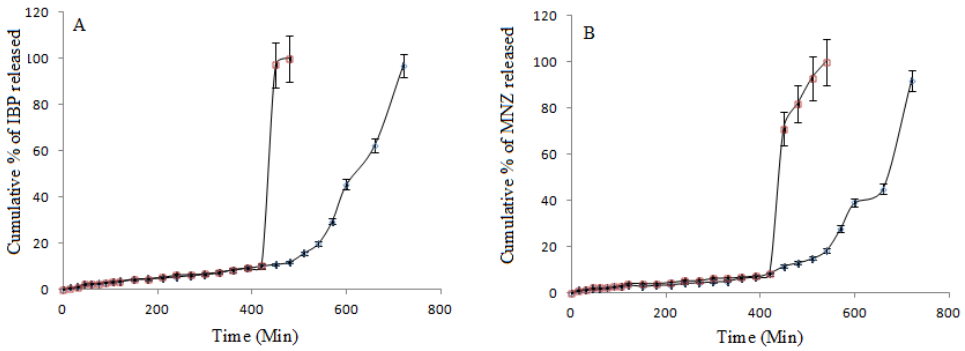

Fig. 4: Release of (A) IBP and (B) MNZ in release medium in absence (◊) and presence (□) of rat cecal matter from CMLBG (250 mg) compression coated tablets containing respectively 2.5 % w/w and 5 % w/w of TSC in core. Maximum SD (A) (◊) = (2.07±, n = 3), (□) (1.05±, n = 3) (B) (◊) = (1.97±, n = 3), (□) (0.89±, n = 3)

CONCLUSION

IBP and MNZ core tablets containing varying amounts of TSC in the core and compression coated with different amounts of LBG or CMLBG were prepared. *In vitro* drug release studies revealed that inclusion of osmogen in the core tablet compression coated with CMLBG minimized the premature release of IBP and MNZ upto a lag period of 7 h following which a rapid pulse release of the drugs were achieved in the post lag period of 7-12 h. However, under the identical experimental conditions, similar formulations compression coated with LBG failed to provide complete drug release. In addition, hydrodynamic conditions influenced the drug release to some extent. Minimization of premature drug release upto 7h and complete release in the post lag period of 7-12 h were achieved both in the absence and presence of colonic fluid although the presence of colonic fluid decreased the post-lag time for complete release. It is concluded that tablets containing appropriate amount of osmogen in the core and compression coated with suitable amount of CMLBG may be suitable to provide desired drug release pattern for colon targeting of drugs.

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CONFLICTS OF INTERESTS

Any opinion, finding and conclusions or recommendations expressed in this material are those of the authors and therefore the authors report no declaration of interest.

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