Research Article

Compression-Coated Tablet for Colon Targeting: Impact of Coating and Core Materials on Drug Release

Siddhartha Maity[1] and Biswanath Sa[1,2]

Abstract. This work was envisaged to develop compression-coated tablets using a blend of Ca^{+2} ion cross-linked carboxymethyl xanthan gum (CMXG) and sodium alginate (SAL) for delayed release of immediate pulse release tablets of prednisolone (PDL) in the colon without the need of colonic bacterial intervention for degradation of the polysaccharide coat. The core tablets containing PDL and other compatible excipients were prepared by direct compression method and subsequently compression coated with different ratios of CMXG and SAL. Long T_{lag}, the time required to restrict the drug release below 10%, and short T_{rap}, the time required for immediate release following the T_{lag}, were considered as suitable release parameters for evaluation of colon targeting of PDL tablets. Among the various compression coats, a blend of CMXG and SAL in a ratio of 1.5:3.5 provided T_{lag} of 5.12 ± 0.09 h and T_{rap} of 6.50 ± 0.05 h. The increase in microcrystalline cellulose (MCC) and crospovidone (CP) in the core tablets did not change T_{lag} significantly although decreased the T_{rap} marginally. Inclusion of an osmogen in the core tablets decreased the T_{lag} to 4.05 ± 0.08 h and T_{rap} to 3.56 ± 0.06 h. The increase in coat weight to 225 mg provided a reasonably long T_{lag} (6.06 ± 0.09 h) and short T_{rap} (4.36 ± 0.20 h). Drug release from most of the formulations followed the Hixson-Crowell equation and sigmoidal pattern as confirmed by the Weibull equation. In conclusion, tablets, compression coated with CMXG and SAL in a ratio of 1.5:3.5 and having 225-mg coat weight, were apparently found suitable for colon targeting.

KEY WORDS: colon targeting; compression coating; drug release; prednisolone; release kinetic.

INTRODUCTION

Colon targeting of drugs for the treatment of colon-related diseases such as Crohn's disease, ulcerative colitis, inflammatory bowel syndrome, colorectal cancer, amebiasis, *etc.* has become one of the thrust areas in pharmaceutical research (1). When compared with conventional oral dosage forms, colon-targeted drug delivery systems offer potential advantages like delivery of high local drug concentration at the afflicted site of the colon to produce optimum therapeutic action and reduction in systemic adverse effects associated with premature release and subsequent absorption of drugs from the upper gastrointestinal tract (g.i.t.) (2–4).

Pharmaceutical approaches, which have been adopted for colon targeting of drugs, include pH-sensitive system, time-dependent release system, and microbially triggered system which includes prodrug and polysaccharide-based system. pH-sensitive systems exhibit unpredictable site specificity of drug release because of inter- and intrasubject variation and almost similar pH values of small intestinal and colonic fluids (5). A time-dependent system seems difficult for accurate prediction of site for drug release because of wide variation in gastric

retention time (6) though the small intestinal transit time (3 ± 1 h) is relatively constant and less variable (7). Prodrugs based on azo polymers are specifically reduced by azoreductase enzymes. However, they are expensive and their safety is questionable (8). Microbially triggered systems are based on compression coating of immediate release tablets with natural polysaccharides which are degraded by anaerobic microflora of the colon (5,9). However, various factors may quantitatively change the composition of the human gut ecosystem (10,11). Moreover, a larger amount of coat is required to prevent premature drug release due to higher hydrophilicity of the polysaccharides (12). On the other hand, thicker coating, although minimizes precolonic release, induces sustained release following a reasonable lag time instead of burst release of drugs in the absence of specific enzymes or cecal content (13–15). A general and indeed a more rational approach is, therefore, to develop a compression-coated tablet, the coat of which should erode slowly enough to prevent or at least to minimize the precolonic release and then to provide an immediate burst release of drugs in the colon irrespective of enzymatic metabolism of the polysaccharides by colonic microflora. For such a drug delivery system, T_{lag}, the time required to prevent or at least restrict the drug release to a minimum (say <10%), should be long usually 6 h (inclusive of 2 h gastric empting time in an empty stomach and 3 h small intestinal transit time and 1 h buffer time for any delay in transit), and T_{rap}, the time required for immediate pulse

[1] Division of Pharmaceutics, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, 700032, India.
[2] To whom correspondence should be addressed. (e-mail: biswanathsa2003@yahoo.com)

release in the absence of colonic enzyme or cecal content following the T_{lag}, should be short (say 4–6 h), and thus, the release pattern should conform to a sigmoidal curve.

Although several polysaccharides such as guar gum, pectin, sodium alginate, locust bean gum, chitosan, boswellia gum, and xanthan gum have been used as compression-coating material (16–20), carboxymethyl xanthan gum (CMXG), neither alone nor in combination with other polysaccharides, has been explored to assess its suitability for the development of compression-coated colon-targeted tablets. In a previous study, we evaluated Ca^{+2} ion cross-linked CMXG (Ca-CMXG) matrix tablets for colon delivery of prednisolone (PDL) (21). That study revealed that although Ca-CMXG matrix tablets released considerably less amount of drug in the initial 5 h, none of the tablets was able to produce rapid and complete release in the following 5 h, and thus, Ca-CMXG matrix tablets were found unsuitable as colon-targeting device. In another study, in which we evaluated the swelling and erosion characteristics of Ca-CMXG matrix tablets, it was observed that the increase in the amount of Ca^{+2} ion increased the erosion of the matrix (22). Considering the high release retarding ability of Ca-CMXG and higher erosional characteristics at higher Ca^{+2} ion level, it was reasonable to examine whether Ca-CMXG, either alone or in combination with other polysaccharide, could be used as a compression-coating material in developing colon-targeted tablet.

In this study, core tablets of PDL for immediate pulse release were developed and subsequently compression coated with Ca-CMXG with or without sodium alginate. *In vitro* release of PDL from the resulting compression-coated tablets was evaluated in a dissolution medium devoid of any enzyme or simulated colonic fluid. The intention of this study was to develop a compression-coated tablet that can restrict the premature drug release to or below 10% for at least 6 h and thereafter provide almost a complete release within 4–6 h. Prednisolone has been chosen as a model drug because of its local pharmacological effect in colonic diseases (10).

MATERIALS AND METHODS

Materials

PDL was obtained from Mepro Pharmaceuticals, Mumbai, India. CMXG, having a degree of substitution of 0.8, was synthesized in our laboratory. Sodium alginate (SAL), $CaCl_2$, $2H_2O$ ($CaCl_2$), microcrystalline cellulose (MCC, PH 102), polyplasdone XL (crospovidone, CP), trisodium citrate (TSC), magnesium stearate (MS), and trisodium orthophosphate dodecahydrate (TSP) were purchased commercially. All other reagents and solvents of analytical grade were used throughout the study.

Preparation and Characterization of CMXG

Conversion of XG to CMXG and its characterization have been reported elsewhere (22). In brief, a required amount of XG was sprinkled slowly for 30 min in alkaline solution at 0–8°C. After complete hydration, 45% *w/v* monochloroacetic acid solution was added slowly at 15–18°C and the temperature was increased to 75°C. After 1 h, the mass was washed repeatedly with 80% *v/v* methanol solution, and finally, the pH of the mixture was made neutral with glacial acetic acid. The resulting CMXG was dried at 45–50°C to constant weight. Formation of CMXG was ascertained by Fourier transform infrared (FTIR), DSC, XRD, ^{1}H-NMR, and elemental analyses.

Preparation of the Core Tablet

Core tablets having a crushing strength of about 4 kg were prepared by direct compression method. PDL and various amounts of excipients such as MCC, CP, MS, and TSC were passed through a #60 BS screen, blended manually, and compressed into tablets using a flat face 5.5-mm punch in a 10 station rotary minipress tablet machine (RIMEK, Karnavati Engineering Ltd., Gujarat, India). The composition of the core tablets is shown in Table I. Fifty tablets of each formulation were prepared in duplicate.

Preparation of the Compression-Coated Tablet

Granules containing different ratios of CMXG and SAL and having size #18 to #22 mesh (BS screen) were prepared by wet granulation method with the aid of a required amount of $CaCl_2$ solution and were used as compression-coating material. To prepare compression-coated tablets of crushing strength of about 6 kg, 40% of the granules were placed in 8-mm die, the core tablet was placed centrally in the die cavity, and the remaining 60% of granules were poured in the die cavity and finally compressed using 8-mm punch. The composition of the compression-coated tablets is shown in Table II. Fifty tablets of each formulation were prepared in duplicate.

Physical Characteristics of the Tablets

Weight Variation

Twenty core tablets and compression-coated tablets were weighed individually in an electronic pan balance (XB 600M-C, Precisa, Switzerland). The weight of each tablet was compared with the respective average weight of the tablets.

Crushing Strength

The crushing strength of the core tablets and compression-coated tablets was determined using a Monsanto type tablet hardness tester (Campbell Electronics, Mumbai, India), and the average value of ten determinations was reported.

Thickness

The thickness of the core tablet and compression-coated tablet was measured with a Digimatic Caliper (CD-6″CS, Mitutoyo Corporation, Japan), and the average of ten determinations was calculated.

Friability

Ten core tablets and ten compression-coated tablets were weighed and placed in a plastic drum of a friabilator (EF2,

Table I. Composition and Physical Properties of the Core Tablets

Code	Composition of core tablets (mg)				Weight of core tablets (mg) (mean±SD, $n=20$)	Drug content (mg) (mean±SD, $n=10$)	Tablet thickness (mm) (mean±SD, $n=10$)	Tablet friability (%)
	MCC	CP	TSC	PDL				
C1	55	4	0	5	64.47±2.14	5.03±0.25	2.82±0.025	0.72
C2	75	4	0	5	84.65±1.44	4.79±0.17	3.04±0.024	0.71
C3	90	4	0	5	99.29±2.03	5.06±0.15	3.97±0.043	0.89
C4	55	9	0	5	70.16±2.35	4.77±0.15	2.95±0.033	0.64
C5	55	14	0	5	75.82±1.61	4.79±0.18	3.03±0.034	0.96
C6	55	9	5	5	75.93±1.64	4.81±0.11	2.84±0.047	0.90
C7	55	9	10	5	80.51±1.74	5.11±0.10	2.95±0.033	0.79
C8	55	9	20	5	90.54±1.84	4.86±0.20	3.29±0.036	0.93
C9	55	9	10	10	86.01±1.30	9.67±0.17	3.03±0.055	0.75
C10	55	9	10	15	90.77±2.16	14.95±0.12	3.22±0.039	0.77

MCC microcrystalline cellulose, *CP* crospovidone, *TSC* trisodium citrate, *PDL* prednisolone

Electro Lab, Mumbai, India). After 100 revolutions, the tablets were deducted with a soft brass and reweighed. The percentage of weight loss was calculated.

Drug Content

A core tablet was crushed in a glass mortar and transferred quantitatively with methanol in a stoppered conical flask. The flask was shaken in a mechanical shaker for 4 h. The mixture was filtered and an aliquot, following suitable dilution, was analyzed at 243 nm using a microplate spectrophotometer (Multiskan Go, Thermo Scientific, USA). The drug content was determined using a calibration curve constructed in methanol. The drug content of each of the ten core tablets was compared with the average drug content of the tablets.

Fourier Transform Infrared Analysis

The FTIR spectra of PDL and PDL-loaded core tablet containing all the excipients (MCC, CP, TSC, and MS) were recorded in a FTIR spectrophotometer (Perkin Elmer, RX-1, UK). The samples were mixed with KBr and converted into pellets using a hydraulic press. The spectra were taken in the wave number region of 4000–400 cm^{-1}.

In Vitro Drug Release Study

In vitro drug release study was carried out in USP-II tablet dissolution rate test apparatus (TDP-06P, Electro Lab, Mumbai, India) at $37\pm0.5°C$ with 100 rpm speed under sink condition following the method described in Indian Pharmacopoeia 2010 (23) for modified release tablet with slight modification. The compression-coated tablets of each formulation were immersed in 700 ml HCl solution of pH 1.2 (gastric pH), and the study was carried out for 2 h. Thereafter, 200 ml of 0.2 (M) trisodium orthophosphate dodecahydrate solution was added quickly and pH was adjusted using a pH meter (Orion 2 Star, Thermo Scientific, Singapore) to 7.4 (small intestinal pH),

and the study was carried out for 3 h in 900 ml solution of pH 7.4. After 5 h, the pH of the dissolution medium was adjusted to pH 6.8 (colonic pH) by adding 5-ml 2 (M) HCl, and the study was continued up to 14 h in 905 ml of dissolution medium. During the release study, 5-ml aliquot was withdrawn from the dissolution medium at a predetermined time and replaced with 5 ml of the fresh respective fluid warmed at 37°C. The aliquots were filtered through Whatman (no. 1) filter paper. The absorbance was measured spectrophotometrically at 248 nm for both acid solution of pH 1.2 and buffer solutions of pH 7.4 and 6.8. The amount of drug released from the tablet was determined using calibration curves drawn in the respective medium.

Viscosity Measurement

Two percent (*w/v*) dispersions of CMXG/SAL/CaCl$_2$ in different ratios, simulating the compression-coating material, were prepared in acid solution of pH 1.2 and kept for 48 h. The viscosities of the solutions were measured in a rheometer (Anton Parr MCR102, Austria, Europe) using a cone and plate apparatus (D-CP/3, diameter 40 mm, gap between the cone and plate 0.08 mm).

Scanning Electron Microscopic Study

Compression-coated tablets before and at different periods of the dissolution study were collected, dried, and mounted onto stubs using double-sided adhesive tape and sputter coated with gold using a sputter coater (S150, Edward, UK). The coated tablets were observed under a scanning electron microscope (JSM-5200, Jeol, Japan) at ×30 magnification. The acceleration voltage used was 10 kV.

Data Treatment

To understand the mechanism of the drug dissolution from the various compression-coated tablets, the dissolution/release data after the lag period (T_{lag}) were fitted in various

Table II. Composition, Physical Properties, and Release Parameters of Compression-Coated Tablets

Code	Core tablets (weight in mg)	Ratio of coating material CMXG	SAL	Weight of coating material (mg)	Weight of compression-coated tablets (mg) (mean±SD, n=20)	Tablet thickness (mm) (mean±SD, n=10)	Tablet friability (%)	T_{lag} (h) (mean±SD, n=6)	T_{rap} (h) (mean±SD, n=6)
CC1	C1(65)	5	0	200	264.21±3.39	4.51±0.040	0.79	9.52±0.05	–
CC2	C1(65)	2.5	2.5	200	264.58±2.71	4.42±0.034	0.68	8.25±0.06	–
CC3	C1(65)	2	3	200	264.05±2.76	4.41±0.033	0.86	5.71±0.06	7.25±0.12
CC4	C1(65)	1.5	3.5	200	264.00±2.62	4.42±0.033	0.90	5.12±0.09	6.50±0.05
CC5	C1(65)	0	5	200	264.79±2.72	4.46±0.034	0.86	0.03±0.001	0.53±0.02
CC6	C2(85)	1.5	3.5	200	285.32±1.67	4.60±0.029	0.56	5.12±0.07	6.42±0.08
CC7	C3(100)	1.5	3.5	200	299.84±2.75	4.89±0.028	0.83	5.13±0.06	6.30±0.11
CC8	C4(70)	1.5	3.5	200	270.32±2.21	4.54±0.032	0.88	5.12±0.08	4.88±0.21
CC9	C5(75)	1.5	3.5	200	275.00±1.80	4.59±0.032	0.65	5.16±0.06	4.49±0.13
CC10	C6(67)	1.5	3.5	200	275.21±2.10	4.42±0.022	0.65	4.36±0.08	4.55±0.07
CC11	C7(80)	1.5	3.5	200	279.89±2.13	4.60±0.024	0.64	4.09±0.07	3.56±0.09
CC12	C8(90)	1.5	3.5	200	290.53±2.20	4.70±0.028	0.72	3.89±0.11	3.52±0.04
CC13	C9(85)	1.5	3.5	200	284.89±2.28	4.59±0.028	0.77	4.12±0.05	3.51±0.06
CC14	C10(90)	1.5	3.5	200	289.89±1.76	4.73±0.018	0.62	4.05±0.08	3.56±0.06
CC15	C10(90)	1.5	3.5	175	265.21±1.72	4.10±0.029	0.64	2.25±0.04	3.38±0.05
CC16	C10(90)	1.5	3.5	225	315.05±2.25	5.15±0.020	0.73	6.06±0.09	4.36±0.20
CC17	C10(90)	1.5	3.5	250	340.05±2.72	5.49±0.017	0.56	6.59±0.07	8.30±0.25

CMXG carboxymethyl xanthan gum, *SAL* sodium alginate

equations, such as zero order Eq. (1), 1st order Eq. (2), and Hixson-Crowell Eq. (3) (24).

$$Q_t = K_0 t \qquad (1)$$

where Q_t is the amount of drug released in time t, and K_0 is the zero order release rate constant.

$$Q_t = Q_0 \cdot e^{-K_1 t} \qquad (2)$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet, and K_1 is the first order release rate constant.

$$W_0^{1/3} - W_t^{1/3} = K_s t \qquad (3)$$

where W_0 is the initial amount of the drug in the formulation, W_t is the remaining amount of the drug in the formulation at time t, and K_s is the constant incorporating surface to volume ratio.

In addition, to examine which dissolution curves were sigmoidal in shape, the release data were fitted in Weibull Eq. (4) (24) which is as follows:

$$m = 1 - \exp\left[-(t - T_{\text{lag}})^{\beta} / \alpha \right] \qquad (4)$$

where m is the accumulated fraction of the drug in dissolution medium at time t, α is the time scale of the process, T_{lag} is the lag period before the onset of dissolution or release process, and β is the shape parameter which characterizes the curve as either exponential ($\beta=1$) (case 1); sigmoid, S-shaped with upward curvature followed by a turning point ($\beta>1$) (case 2); or parabolic, with a higher initial slope and after that consistent with the exponential ($\beta<1$) (case 3).

Statistical Analysis

The effect of various formulation parameters on drug release characteristics such as time required for 10% release (T_{lag}) and rapid release (T_{rap}) following the T_{lag} was statistically compared by analysis of variance (one-way ANOVA) with the aid of GraphPad Prism (Version 3.0). Difference was considered significant when $p < 0.05$.

RESULTS

The composition and physical properties of the core tablets of PDL prepared with various amounts of MCC and CP with or without TSC are shown in Table I. The weight of the tablets (C1, C4–C6) weighing less than 80 mg did not vary by more than 10% of the average weight. The weights of the other tablets weighing between 80 and 250 mg were found confined within ±7.5% of the average weight. The amount of PDL in each of the tablets was within ±15% of the labeled potency. Friability of the tablets was less than 1%. Thus, the physical properties of the core tablets complied with the limits of variation prescribed in Indian Pharmacopoeia. Moreover,

the thickness of the tablets varied within ±5% of the average thickness. All the core tablets having a crushing strength of 4 kg disintegrated within 30 s.

The composition and physical properties of the compression-coated tablets having a crushing strength of 6 kg are shown in Table II. The weight and friability of the tablets were, respectively, within ±5% and less than 1% and complied with the requirement of Indian Pharmacopoeia. In addition, the thickness of the tablets did not vary by more than ±5% of the average thickness.

The FTIR spectra of PDL and core tablets containing maximum amounts of all the excipients are shown in Fig. 1. The spectrum of PDL exhibited peaks at 3496, 3455, and 3356 cm^{-1} for three –OH groups, 1609 cm^{-1} for diene, and 1654 and 1710 cm^{-1} for 3,20-dione, which were considered for the identification of PDL. The spectrum of the core tablets containing PDL demonstrated the above peaks on the same wave numbers.

The release of PDL from the core tablet in dissolution medium of pH 6.8 was rapid and 95–99% of the loaded drug was released within 15 min (data not shown). The release profiles of the drug from various compression-coated tablets are shown in Fig. 2. Tablet CC1 which was coated with Ca^{+2} ion cross-linked CMXG released only 5.19±0.11% and 21.04± 1.37% drug, respectively, in 7 and 14 h.

Substitution of CMXG with an increasing amount of SAL in the coat, as in tablets CC2 to CC4, increased the release of the drug. Tablet CC5, which was compression coated with Ca^{+2} ion cross-linked SAL, released the drug rapidly within 45 min. Table II compares the values of T_{lag}, the time required to release <10% of the loaded drug, and T_{rap} ($T_{90-10\%}$), the time required for rapid pulse release after the T_{lag}, of the tablets coated with cross-linked CMXG and SAL in different ratios. The T_{lag} value for tablet CC1 which was coated with only cross-linked CMXG was 9.52±0.05 h. Substitution of CMXG with an increasing amount of SAL decreased the values of both T_{lag} and T_{rap}. Tablet CC5 which was coated
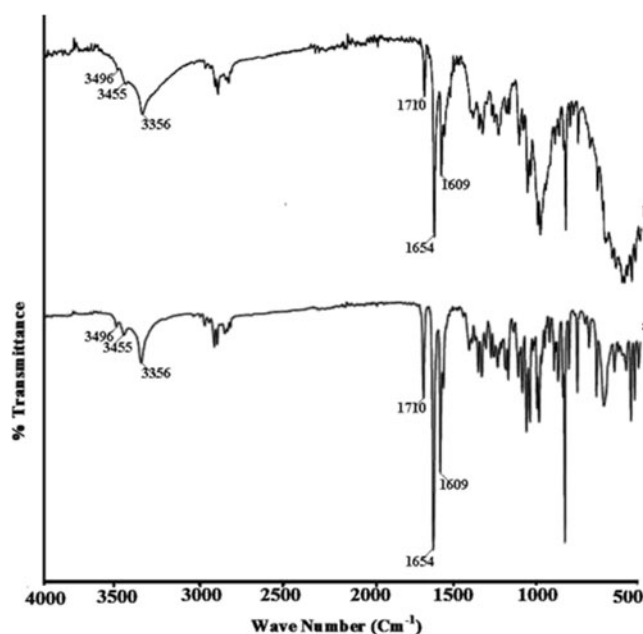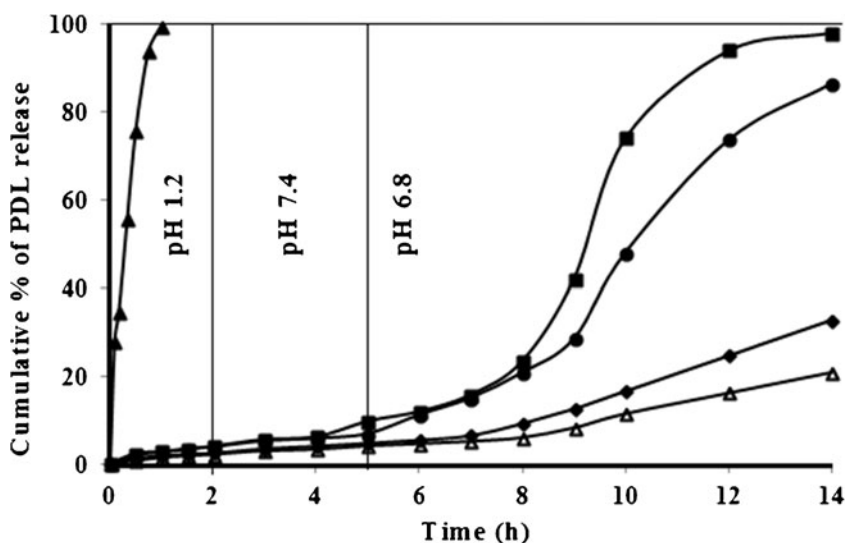

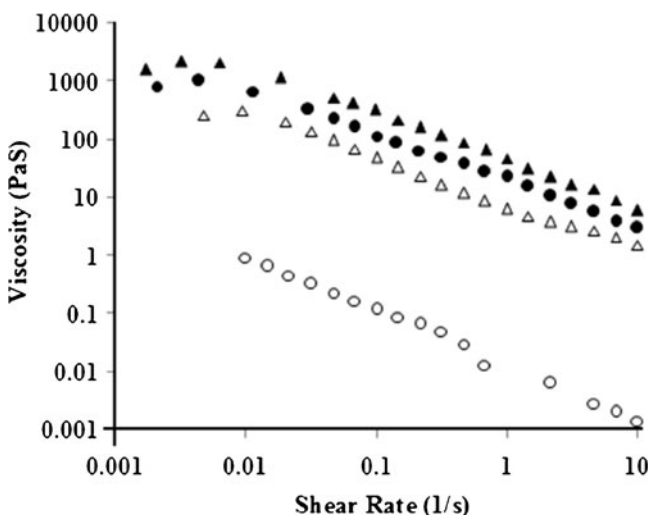**Fig. 1.** FTIR spectra of *a* PDL and *b* PDL-loaded core tablet

Fig. 2. Effect of coating material on cumulative % of PDL release from compression-coated tablet. *Key*: CC1, *empty triangle*; CC2, *filled diamond*; CC3, *filled circle*; CC4, *filled square*; CC5, *filled triangle*. Maximum SD (±2.56, *n*=6)

with cross-linked SAL alone exhibited very short T_{lag} (0.03± 0.001 h) and T_{rap} (0.53±0.02 h).

The viscosity of various polymeric solutions containing CaCl$_2$ in acid solution of pH 1.2 is shown in Fig. 3. The viscosity of CMXG solution was very high. Substitution of CMXG with an increasing amount of SAL decreased the viscosity of the bipolymeric gel layer, and the viscosity of the SAL solution was the lowest.

Keeping the composition of the compression-coated material (CMXG/SAL=1.5:3.5) fixed, the effect of variation in the core composition on drug release profiles was studied. The effect of the increase in the amount of MCC in the core tablets (CC4, CC6, and CC7) is shown in Fig. 4. The increase in the amount of MCC from 55 to 75 mg in the core tablet made the drug release faster, although further increase in MCC to 90 mg
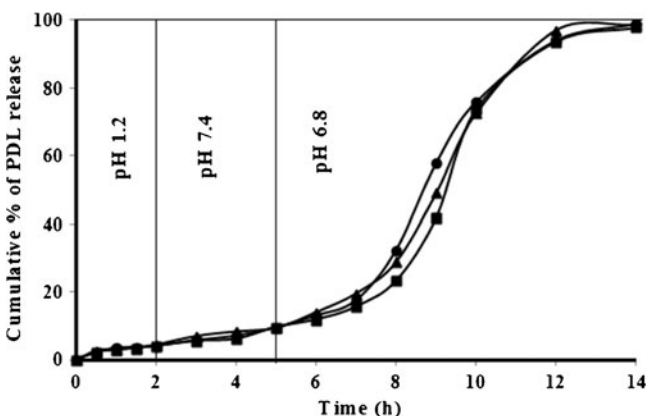
did not increase the drug release. Comparison of area under the curves (AUCs) of % drug release *versus* time profiles of tablets CC6 and CC7 by *t* test did not reveal any significant difference (*p*>0.05). When T_{lag} of tablets CC4, CC6, and CC7 were compared with analysis of variance (one-way ANOVA) test, no significant change (*p*>0.05) was observed, although T_{rap} of the tablets tended to decrease marginally but significantly (*p*<0.05) with the increase in the amount of MCC.

The effect of CP in the core tablets on drug release profiles (Fig. 5) and T_{lag} and T_{rap} was investigated with tablets CC4, CC8, and CC9. The increase in the amount of CP in the core tablets increased the release of the drug after the T_{lag} period. Moreover, the value of T_{rap} decreased significantly (*p*<0.05), although no significant change (*p*>0.05) in T_{lag} was evident (Table II).

The effect of the inclusion of TSC as an osmogen in the core tablets on drug release profiles (Fig. 6) and T_{lag} and T_{rap} was studied with tablets CC10, CC11, and CC12. The drug release from the tablets containing TSC was much faster than

Fig. 3. Viscosity profiles of various blends of coating polymers in acid solution of pH 1.2. *Key*: CC1, *filled triangle*; CC3, *filled circle*; CC4, *empty triangle*; CC5, *empty circle*

Fig. 4. Effect of MCC in core on cumulative % of PDL release from compression-coated tablet. *Key*: CC4, *filled square*; CC6, *filled circle*; CC7, *filled triangle*. Maximum SD (±2.46, *n*=6)
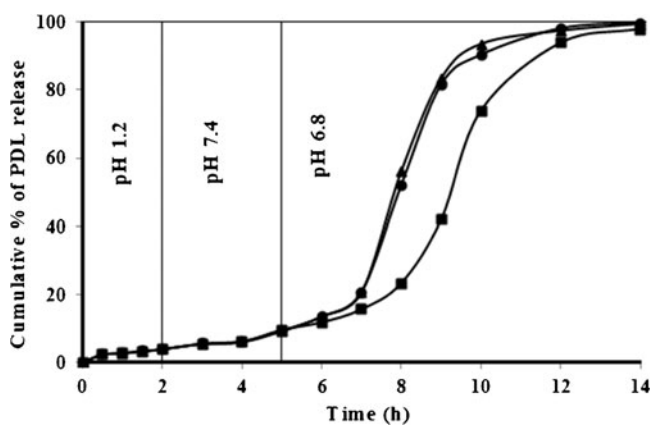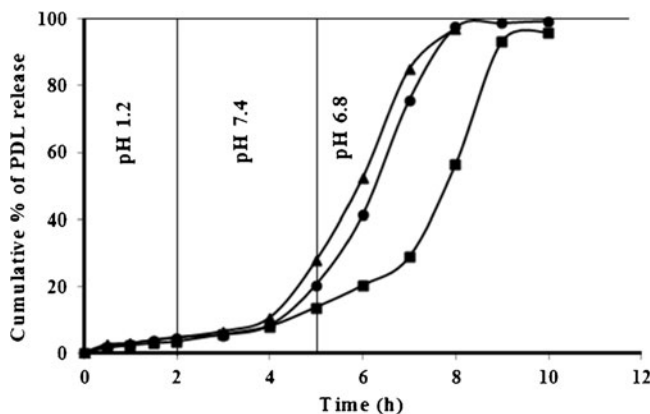
Fig. 5. Effect of CP in core on cumulative % of PDL release from compression-coated tablet. *Key*: CC4, *filled square*; CC8, *filled circle*; CC9, *filled triangle*. Maximum SD (±3.28, $n=6$)

Fig. 7. Effect of PDL load on cumulative % of PDL release from compression-coated tablet. *Key*: CC11, *filled circle*; CC13, *filled square*; CC14, *filled triangle*. Maximum SD (±4.19, $n=6$)

that from a similar tablet (CC8) without containing TSC (Fig. 5). Further, the inclusion of the osmogen not only reduced T_{rap} but also decreased T_{lag} considerably. The larger the amount of TSC, the shorter were the T_{lag} and T_{rap} (Table II).
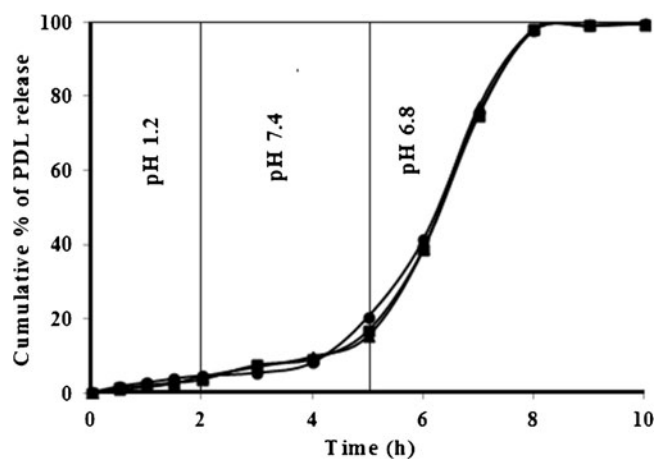
As the dose of PDL may vary depending upon the severity of the diseases (25), the effect of variation in dose strength on the drug release behavior from the bipolymeric (CMXG/SAL=1.5:3.5) compression-coated tablets (CC11, CC13, and CC14) containing MCC (55 mg), CP (9 mg), and TSC (10 mg) was studied. The increase in the amount of PDL from 5 to 15 mg in the core tablets (CC11, CC13, CC14) did not produce any significant change ($p<0.05$) either in drug release profiles (Fig. 7) or in T_{lag} and T_{rap} values (Table II).

The effect of the increase in the coat weight (175 to 250 mg) on the drug release (Fig. 8) and T_{lag} and T_{rap} was studied with tablets CC14 to CC17. The tablet (CC17) coated with the highest amount of polymers did not release the drug completely in 14 h. A decrease in coat weight provided faster drug release. Moreover, T_{lag} and T_{rap} were found to decrease from 6.59±0.07 to 2.25±0.04 h and 8.30±0.25 to 3.38±0.05 h, respectively (Table II).

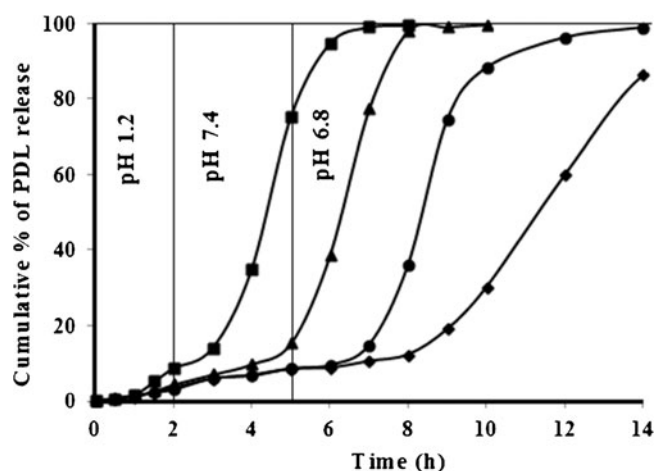The state of the tablet (CC16) before dissolution and at different time periods during dissolution was assessed by

observing the dried tablets in a scanning electron microscope (SEM). Figure 9a revealed the presence of a compact coat around the core tablet before dissolution. After 2 h of exposure in acid solution, the surface of the tablet appeared somewhat uneven (Fig. 9b). The coat eroded to a significant amount, and the core became visible after 6 h (Fig. 9c) although it did not disintegrate. At the end of 8 h (Fig. 9d), the core appeared less dense and many pores and fissures developed in the core tablet. After 10 h, the tablets disintegrated completely.

The release data from the end of the lag time up to 70% of drug release from each of the compression-coated tablets were fitted in zero order, 1st order, and Hixson-Crowell equations. The best fit of the curves was judged from the values of linear regression coefficients (r) which are shown in Table III. The results demonstrated that the release of PDL from CC1, CC2, CC12, and CC17 tablets followed the zero order kinetic and that from the remaining tablets was governed by the Hixson-Crowell model. Data treatment in Weibull equation

Fig. 6. Effect of TSC in core on cumulative % of PDL release from compression-coated tablet. *Key*: CC10, *filled square*; CC11, *filled circle*; CC12, *filled triangle*. Maximum SD (±3.74, $n=6$)

Fig. 8. Effect of coat weight variation on cumulative % of PDL release from compression-coated tablet. *Key*: CC14, *filled triangle*; CC15, *filled square*; CC16, *filled circle*; CC17, *filled diamond*. Maximum SD (±4.43, $n=6$)
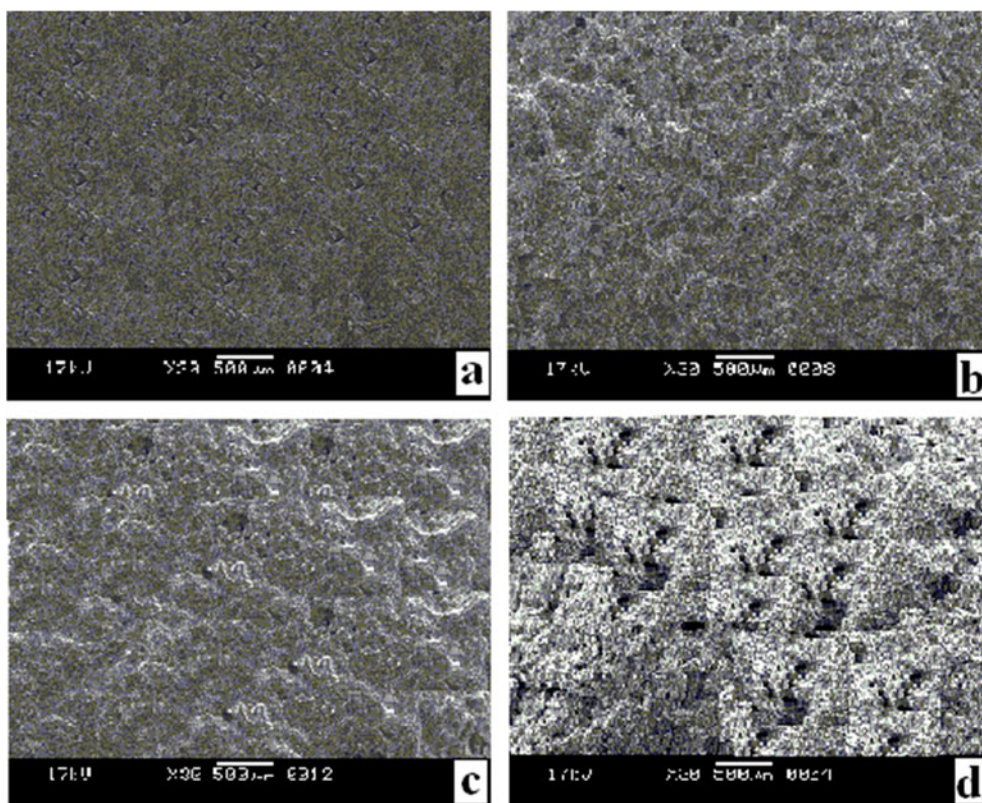
Fig. 9. Scanning electron micrographs of compression-coated tablets: before dissolution (**a**) and at different time periods (**b** 2 h, **c** 6 h, and **d** 8 h) during the dissolution study

revealed that the release profiles of PDL from tablets CC1, CC2, CC3, CC5, CC12, and CC17 were not sigmoidal as the values of shape parameter (β) were <1. However, the release profiles of the drug from other tablets were sigmoidal as the values of β>1.

DISCUSSION

Initially, the core tablets of PDL were prepared by direct compression method using MCC and CP as common excipients. MCC is a versatile excipient in direct compression

Table III. Fitting of PDL Release Data After T_{lag} in Different Kinetic Models

Code	Zero order model (r)	1st order model (r)	Hixson-Crowell model (r)	Weibull model		
				β	$\log\alpha$	(r)
CC1	0.998	0.990	0.971	0.279	−0.830	0.965
CC2	0.999	0.998	0.965	0.528	−0.833	0.974
CC3	0.935	0.888	0.981	0.840	−0.703	0.799
CC4	0.873	0.801	0.988	1.623	−1.059	0.895
CC5	0.995	0.984	0.996	0.929	+0.539	0.912
CC6	0.943	0.908	0.988	1.616	−0.973	0.936
CC7	0.928	0.870	0.995	1.572	−0.958	0.904
CC8	0.934	0.900	0.983	1.737	−0.877	0.961
CC9	0.926	0.901	0.959	1.668	−0.823	0.950
CC10	0.915	0.845	0.995	1.468	−0.771	0.819
CC11	0.929	0.886	0.972	1.849	−0.645	0.967
CC12	0.983	0.868	0.965	0.883	−0.241	0.859
CC13	0.980	0.939	0.994	1.923	−0.696	0.966
CC14	0.980	0.937	0.995	2.063	−0.782	0.976
CC15	0.965	0.918	0.997	1.885	−0.667	0.979
CC16	0.969	0.922	0.998	1.635	−0.732	0.979
CC17	0.990	0.921	0.955	0.964	−0.810	0.791

r correlation coefficient, α the time scale of the dissolution process, β the shape parameter

method of tablet preparation as it acts as both a bulking agent and dry binder and provides compressibility to the tablets that disintegrates rapidly (26). CP was included in the core tablet as a superdisintegrant to facilitate rapid disintegration once the coat is removed to expose the core tablet in aqueous fluid. The core tablets disintegrated within 30 s irrespective of the amount of MCC and CP. The crushing strength of the core tablet was kept constant at 4 kg to avoid excessive increase in hardness of the core tablets following double compression with the coating polymers. Excessive increase in crushing strength may prolong the disintegration time (27) due to decrease in porosity (28). Moreover, the crushing strength of 4 kg was sufficient enough to restrict the friability below 1% as specified in official compendia. The physical properties of both the core and compression-coated tablet were within pharmacopoeial limits.

The compatibility of PDL with all the excipients in the core tablets was evaluated using FTIR study. The characteristic peaks of the drug in the core tablets were located at almost the same wave numbers as those found with the drug alone, and generation of no new peak or abolition of any of the existing peaks was noted. This confirmed the absence of any drug-excipient interaction.

The colon-targeted drug delivery system should not release the drug in the upper g.i.t. up to 5 h following which the complete drug release should be achieved at the desired site (29). It implies that drug release should conform to a slow-fast sigmoidal release pattern. Two release parameters *viz.* T_{lag} and T_{rap} appear to be important to achieve this type of release pattern. T_{lag} is the time required to prevent or minimize the precolonic drug release and should be long usually 6 h, and T_{rap} is the time required to provide immediate pulse release which should be small usually 4–6 h. T_{rap} represents the steepness of the release phase and can be calculated from $T_{90-10\%}$. Many polysaccharides either alone or in combination have been used as compression-coating materials to achieve colon-specific drug release. Among these, pectin and guar gum have been studied extensively. However, pectin coat alone has been found insufficient to protect the core from premature release due to its higher aqueous solubility and poor mechanical strength, and a larger amount of pectin is required to prevent precolonic release (13,30,31). Similar findings have been reported with guar gum used as compression-coating material (8,32,33). Alternately, calcium cross-linking of carboxyl groups of pectin and SAL has been reported to decrease the aqueous solubility of native polysaccharides and/ or strengthen the gel layer through the formation of an "egg-box" configuration leading to a more controlled release (34–36). In general, although these polymers in a higher amount effectively cut down the precolonic release, immediate pulse release was not evident. Instead, following the lag period, the drug was released slowly in a sustained release fashion over a longer period of time. The present study was envisaged to shorten the postlag release time so as to achieve high local drug concentration in the colon. About 95–99% drug was released from the core tablets within 15 min (data not shown). Rapid release indicates that the release from the core tablets was not a rate-limiting step (37,38). A number of variables both in the core tablets and composition of the compression coat may be a determinant factor in achieving slow-fast type sigmoidal drug release pattern. In this study, initially, the

composition of the coat was optimized using various ratios of CMXG and SAL both cross-linked with Ca^{+2} ion. Coating with cross-linked CMXG alone provided a long T_{lag}; however, complete drug release could not be achieved within 14 h. Release of PDL from a Ca^{+2} ion cross-linked CMXG matrix tablet has been reported to be incomplete even after 10 h (21). Substitution of CMXG with an increasing amount of SAL increased the drug release with a decrease in both T_{lag} and T_{rap}. On the other hand, cross-linked SAL alone was found unsuitable as a compression-coating material as the drug was completely released within 45 min with a very short T_{lag} and T_{rap}. When CMXG is brought in contact with water, the interaction between many hydrophilic groups of CMXG and water leads to the formation of a viscous polymer solution around the tablet surface (21,39). Cross-linking of CMXG with Ca^{+2} ion further restricts the mobility of the polymer chain resulting in the formation of a true gel layer around the tablet surface (34) and reduces the macromolecular mess size (19). This in turn decreases the water penetration velocity through the coat (22). Hindrance in seepage of water through the coat shielded the core tablets from disintegrating and liberating the drug. A similar finding in indomethacin release has been reported from Ca^{+2} ion cross-linked pectin coat (37).

The viscosity of the gel layer can be reduced to enhance water permeation by incorporating a more hydrophilic and low viscous polymer in the coat. Compression coating of the core tablet with SAL provided comparatively faster drug release due to higher hydrophilicity and low viscosity of SAL gel (17,40). To decrease the viscosity of the gel layer and enhance water permeation through the coat, CMXG was substituted with Ca^{+2} ion cross-linked SAL. The fall in viscosity of the gel layer due to substitution of CMXG with an increasing amount of SAL was ascertained by measuring the viscosity of the aqueous solution of CMXG, SAL, and $CaCl_2$ in ratios simulating the ratios used in compression coat. Figure 3 demonstrated that the viscosity of Ca^{+2} ion containing CMXG solution was the highest. Substitution of CMXG with an increasing amount of SAL decreased the viscosity, and the solution of SAL exhibited the lowest viscosity. The decrease in the viscosity of the gel layer increased the permeation of water and made the coating polymer to hydrate, dissolve, and/ or erode rapidly. Following dissolution and/or erosion of the coat, the core tablets come in contact with the aqueous solution, disintegrate, and liberate the drug. The higher the amount of SAL, the faster was the drug release and the shorter were the values of T_{lag} and T_{rap}. As tablet CC5, coated with SAL alone, was unable to protect the core from rapid drug release, and tablets CC1, CC2, and CC3, prepared with a higher proportion of CMXG in the coat, produced exceedingly long T_{lag} and T_{rap}, tablet CC4 compression coated with CMXG/SAL in a ratio of 1.5:3.5 was considered optimum for further study.

Keeping the coat composition (CMXG/SAL=1.5:3.5) fixed, the composition of the core tablets was manipulated to investigate the effect on drug release profiles, T_{lag} and T_{rap}. The increase in the amount of MCC in the core did not produce any significant change in T_{lag} and marginally decreased the T_{rap} values. On the other hand, the increase in the amount of CP considerably reduced the T_{rap} values, although T_{lag} values were found virtually the same (Table II). MCC is considered as a versatile excipient in tablet

manufacturing by direct compression method as it acts as both a bulking agent, dry binder, and disintegrating agent for tablets and also provides compressibility to the matrix (26). MCC facilitates the penetration of water into the core by wicking action and exerts hydrostatic pressure to disintegrate the tablets (41). The increase in the amount of MCC decreased the T_{rap} marginally. Probably, a decrease in disintegration time with a higher amount of MCC might have compromised with the increase in compressibility of the core matrix. On the other hand, the increase in CP considerably decreased the T_{rap} value when compared with MCC. CP is regarded as a superdisintegrating agent and is more powerful than MCC concerning the disintegration of tablets. It should, however, be noted that T_{lag} was not apparently changed due to the increase in the amount of either MCC or CP. It is reasonable to assume that the time taken by the compression-coating material to dissolve/or erode might be almost same, and slight seepage of water through the gel layer was not sufficient to explode the core. Inclusion of TSC as an osmogen considerably reduced both T_{lag} and T_{rap} values. The larger the amount of TSC, the shorter were the values of T_{lag} and T_{rap} (Table II). Even slight seepage of water through the gel layer may develop high osmotic pressure in the core that acts radically outwards to rupture the coat or surrounding membrane (42). The lag time of drug release from compression-coated ethyl cellulose tablets has been reported to decrease markedly due to the presence of NaCl as osmogen in the core tablets (43).

The mechanism of drug release from compression-coated tablets is not well documented. The nature and amount of the polysaccharide coat as well as the composition of the core appears decisive in elucidating the drug release mechanism. When a polysaccharide coat comes in contact with water, a gel layer is formed around the core. A strong gel, formed either due to the nature of the polymer or its presence in a large amount, reduces swelling, hinders penetration of water, and may promote erosion of the coat (44,45). Slow penetration of water dissolves the drug in the core slowly providing long T_{lag} and T_{rap}. Probably, preferential erosion over swelling of the coat results in zero order drug release (45). Cross-linked CMXG forms a stronger gel than SAL as evidenced from the viscosity as displayed in Fig. 3. The presence of a higher proportion of CMXG in tablets CC1 and CC2 and a higher amount of total polymer as in CC17 probably induced erosion-controlled zero order release after T_{lag}. On the other hand, low gel strength produced by a higher proportion of SAL, as in tablets CC3, CC4, and CC5, and the presence of lower coat weight, as in tablets CC14, CC15, and CC16, allowed the coat to dissolve somewhat rapidly, exposing the core to the dissolution medium and allowing the release of the drug following the Hixson-Crowell model. At a particular coat composition, the increase in MCC, CP, and TSC in the core probably made the coat to fracture exposing the core in the dissolution medium rapidly and allowing the liberated drug to dissolve following the Hixson-Crowell model. The tablets having very high or low T_{lag} and T_{rap} values (CC1, CC2, CC3, CC5, CC12, and CC17) did not display a sigmoidal release pattern that was substantiated from the shape parameter (β) which was not greater than 1. However, other compression-coated tablets released the drug in a sigmoidal pattern ($\beta > 1$).

Tablet CC16 consisting of MCC (55 mg), CP (9 mg), TSC (10 mg), and PDL (15 mg) in the core and compression coated with 225 mg of a blend of Ca-CMXG and SAL in a ratio of 1.5:3.5 appeared to provide an optimum drug release profile for colon targeting. The surface topography of tablet CC16 during different stages of the dissolution study was evaluated by SEM. The change in the state of the tablet surface corroborated well with the drug release profile. The surface of the compression-coated tablet was compact and smooth before dissolution (Fig. 9a). After 2 h of exposure in acid solution of pH 1.2, the surface of the tablets appeared rough/uneven due to slow erosion of the coating material taking place during dissolution. The core tablet was still covered with a considerable amount of coating material and, hence, was not visible (Fig. 9b). Consequently, the amount of drug released in 2 h was very less (about 3%). Figure 9c shows the state of the tablet after 6 h of dissolution. Although the core tablet became visible after 6 h of dissolution study (Fig. 9c), it did not show any sign of disintegration probably due to the presence of the gel layer around the core tablet that prevented a significant amount of the drug to be released. The figure of the drug release profile (Fig. 8) showed that only 10% of the drug was released in 6 h. After 8 h (Fig. 9d), the gel layer almost eroded making somewhat a better contact between the core tablet and water. As a result, the core tablet tended to bulge out and appeared less dense, and many pores and fissures became evident on the surface of the core indicating the beginning of disintegration. At this point, a somewhat larger amount of the drug (about 36%) was released. The tablet disintegrated completely after 10 h and liberated about 90% of the drug. Thus, the compression-coating material eroded slowly and minimized the premature drug release up to 6 h. After the T_{lag} (about 6 h) of drug release, the coating material eroded completely, exposed the core tablet to the aqueous dissolution medium, and induced almost complete release within the next 4 h.

CONCLUSION

A novel compression-coated tablet was developed using a blend of polysaccharides for colon targeting of prednisolone. The composition of both the coating polymers and the core tablet was found critical to achieve a prolonged T_{lag} (about 6 h) for minimization of the drug release in the upper g.i.t. and a shorter T_{rap} for rapid release of the drug in the colonic region following the T_{lag}. In vitro drug release study revealed that the coating of the core tablet with neither CMXG nor SAL alone was suitable for colon targeting of the drug. A blend of CMXG and SAL in a ratio of 1.5:3.5 was able to provide a reasonably long T_{lag} and short T_{rap}. Inclusion of osmogen in addition to common disintegrants in the core tablet and the increase in coat weight resulted in the development of a compression-coated tablet that appeared to achieve the desired values of T_{lag} and T_{rap}. This type of compression-coated tablet appears to be suitable for colon

targeting of prednisolone even in the absence of colonic fluid/colonic bacterial enzymes.

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