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Research Article

Preparation and Evaluation of Diclofenac Sodium Tablet Coated with Polyelectrolyte Multilayer Film Using Hypromellose Acetate Succinate and Polymethacrylates for pH-Dependent, Modified Release Drug Delivery

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Abstract. Polyelectrolyte multilayer (PEM) film formed due to the electrostatic interaction between oppositely charged polyelectrolytes is of considerable interest because of their potential applications as both drug carriers and surface-modifying agents. In this study, *in vitro* studies were carried out on polyelectrolyte complexes formulated with Eudragit E (EE) and hypromellose acetate succinate (HPMCAS). The complexes of EE and HPMCAS were formulated by non-stoichiometric method. The prepared IPCs were investigated using Fourier transform infrared spectroscopy. Diclofenac sodium (DS) tablets were prepared and were coated with polymer solution of HPMCAS and EE to achieve pH-dependent and sustained-release tablets. Tablets were evaluated for their physical characteristics and *in vitro* drug release. The results of pharmacokinetic studies in rabbits showed that the selected formulation (F6) exhibited a delayed peak plasma concentration and marked sustained-release effect of drug in the *in vivo* drug release in comparison with marketed tablet. The suitable combination of PEM film based on EE and HPMCAS demonstrated potential candidate for targeted release of DS in the lower part of the gastrointestinal (GI) tract.

KEY WORDS: eudragit E; hypromellose acetate succinate; multilayer film; polyelectrolyte; Polyelectrolyte complex.

INTRODUCTION

Recently, the oral colon-specific delivery system had attracted immense interest due to its various advantages. The advantages of targeting drugs to the colon are the following: (1) drugs can be delivered locally to treat inflammatory bowel diseases or systemically to deliver proteins and peptides, (2) to reduce the adverse effects and degradation of drugs in the upper gastrointestinal tract, and (3) to increase the bioavailability and efficacy of some drugs, especially drugs that degrade in the stomach and intestine or undergo first-pass metabolism (1). The fundamental objective of oral colon-specific delivery is to protect drugs in the upper gastrointestinal tract and deliver them directly into the colon. There are several approaches for targeting drugs to colon, and each approach represents a distinct system in terms of design. Some colonic delivery systems utilize one or more triggering mechanisms to release the drug, such as gastrointestinal transit time-dependent delivery (2–5), pH-sensitive polymers (6), bacterial concentration, and pressure (7).

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug, widely used to control pain and for the treatment of rheumatic arthritis (8). The conventional immediate-release DS tablets make the drug immediately available for absorption in upper gastrointestinal (GI) tract resulting in local GI toxicity (9). It has been reported that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa (10). DS is well adsorbed in the colon (11), and thus, colon-specific release can be used for the treatment of widespread inflammatory bowel diseases. For colon-targeted drug release, enteric polymers are commonly used as they are able to release the drug at a particular pH. The pH-sensitive copolymers, such as methacrylic acid/methylmethacrylate copolymers and Eudragit® types L (EL) and S (ES), dissolve in aqueous media at pH 6 and 7, respectively, which may be equivalent to drug release in the distal ileum (12). Hypromellose acetate succinate, also known as hydroxypropyl methylcellulose acetate succinate (HPMCAS), is an enteric polymer developed by Shin-Etsu Chemical Co., Ltd., Japan. This enteric polymer is soluble in aqueous media at a pH higher than 5.5, owing to the presence of carboxyl groups. Three different grades of HPMCAS (AS-LF, AS-MF, and AS-HF) are commercially available which are classified according to the ratio of succinoyl substitution to acetyl

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substitution (SA ratio). The SA ratio is highest in AS-LF, whereas AS-HF has the lowest SA ratio (13).

Over the past few years, a growing interest in polyelectrolyte complexes (PECs) has led to the formulation and characterization of systems involving a variety of anionic and cationic polymers: EL and gelatin (14), EL-ES (15), Eudragit® E (EE)-EL (16), EE-sodium alginate (17), chitosan (CS)-alginate, CS-carrageenan (18), CS-polygalacturonic acid (19), and CS-carboxymethyl cellulose (20). Margulis *et al.* investigated the potential use of a new CS/Eudragit® L100-55 interpolyelectrolyte complex in colon-specific drug delivery systems (DDS) and compared with the individual polymers using swellability testing. The PECs showed more stable swellability profiles during 24 h under simulated intestinal tract conditions, indicating their suitability for use in colon-specific drug delivery (21). However, to date, there are no reports of the use of the HPMCAS and EE as interpolyelectrolyte complex in colon-targeted DDS.

Recently, there has been increasing interest in developing polyelectrolyte multilayer (PEMs) films that carry drugs for biomedical applications. Further, PEMs prepared by layer-by-layer (LbL) adsorption method could be used for a more controlled delivery due to the ability of varying the number of layers and other properties of the film which affect drug delivery (22). In this study, an attempt has been made to formulate a dosage form which was enteric coated to prevent the drug release in the stomach and had an additional lag phase to ensure drug release in the lower part of the GI tract. HPMCAS was used as enteric polymer, and EE was used to provide the additional lag phase. Further this study was designed to investigate the formation of PEC between EE and HPMCAS, to characterize the product formed, and to evaluate its performance as a matrix for pH-dependent and sustained release of drug, using DS as a model drug.

MATERIALS AND METHODS

Materials

DS was obtained from Mylan Laboratories Limited (Hyderabad, India) as a gift sample. EE was purchased from Evonik Röhm GmbH (Darmstadt, Germany), and HPMCAS was purchased from Shin Etsu, Japan. Mannitol, microcrystalline cellulose, croscarmellose sodium, citric acid, hydroxypropyl cellulose, and magnesium stearate were obtained as a gift sample from Mylan Laboratories Limited (Hyderabad, India).

Methods

Preparation of Core Tablets

Various formulations (Tables I and II) were studied based on different polymer coating type and levels. Drug and intragranular materials were passed through #30 mesh sieve and mixed together for 10 min in a polybag. The blend was granulated using 5% (*w*/*v*) solution of hydroxypropyl cellulose in water, and wet granules were dried in an oven at 60°C for 1–2 h. Dried granules were sifted through #30 sieve and further mixed with croscarmellose sodium in a polybag for 5 min. Magnesium stearate (0.95% *w*/*w*, previously passed through #60 mesh sieve) was added into the above powder blend and mixed in a polybag for 5 min. Lubricated blend was compressed with average weight of 160 mg on a rotary tablet punching machine (Kambert machinery, Ahmedabad, India) fitted with 7.0-mm round-shaped standard concave punches with corresponding die to provide a desirable hardness. The amount of DS in core tablets was kept constant at 50 mg while the amount of other excipients was varied.

Physical Evaluation of the Core Tablets

Formulated tablets were subjected to the following physical characterization studies. Tablet weight variation was calculated by measuring the weight of ten tablets, and the results are expressed as mean values ± SD. The hardness of the matrix tablets was examined for ten tablets of each batch using a hardness tester (Dr. Schleuniger, Germany). Tablet thickness was examined for ten tablets of each batch using an electronic digital caliper. Tablet disintegration time was tested using the disintegration test apparatus (Electrolab, Mumbai). Water kept at 37°C was used as a medium, and six tablets from each lot were evaluated. Friability of the tablet was measured in a friability tester (EF-1W, Electrolab, Mumbai, India). Tablets were weighed initially and rotated at 25 rpm for 4 min, and the samples were then reweighed. The percentage friability was calculated using the following equation:

$$F\% = (W1 - W2)/\, W1 \times\ 100\% \qquad (1)$$

where *F*% represents the percentage weight loss and *W1* and *W2* are the initial and final tablet weights, respectively.

Preparation of Polymer-Coated Tablets

The core tablets were further coated with pH-dependent polymer EE or HPMCAS using pan coating method. Ten percent *w*/*v* EE polymer solution was prepared in isopropyl alcohol, and 10% *w*/*v* HPMCAS polymer solution was prepared in acetone. The polymer solution was plasticized with triethyl citrate (10% *w*/*w*, with respect to dry polymer). The core tablets were coated using the polymer solution to achieve different coating buildup by using a perforated pan coater (Freund coater, Model 0.65L, Japan). The operative coating conditions for the coating process are as follows: air inlet temperature 30–45°C, air outlet temperature 28–40°C, atomizing pressure 0.2 kg/cm^2, and pan speed 5–10 rpm, and coating solution was sprayed onto the tablets at a flow rate of 0.5–1.0 mL/min.

Determination of the Optimum Ratio Between EE-HPMCAS (Turbidity Measurements)

The EE/HPMCAS ratio in the complex was examined by monitoring the transmittance of the solution at a wavelength of 420 and 620 nm using an ultraviolet (UV) spectrophotometer. An aqueous 0.1% EE solution in 0.1 N HCl and 0.1% solution of HPMCAS in pH 6.8 phosphate buffer were used. Both the solutions were mixed in different ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4), and each mixture was shaken vigorously. The pH of the polymer mixtures was adjusted to about 4 and then left to stand for about 2 h before measuring the transmittance as a function of the various mixing ratios (EE/HPMCAS).

Table I. Compositions of Diclofenac Sodium Double-Layer Polymer-Coated Tablets

Ingredients	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)
Intragranular				
Diclofenac sodium	50.0	50.0	50.0	50.0
Mannitol	84.5	80.75	77.0	64.5
Croscarmellose sodium	3.0	3.0	3.0	3.0
Microcrystalline cellulose	15.0	15.0	15.0	15.0
Hydroxypropyl cellulose	3.0	3.0	3.0	3.0
Citric acid anhydrous	–	3.75	7.5	20.0
Extragranular				
Croscarmellose sodium	3.0	3.0	3.0	3.0
Magnesium stearate	1.5	1.5	1.5	1.5
Polymer coating 1				
Eudragit EPO	3.0	3.0	3.0	3.0
Triethyl citrate	0.3	0.3	0.3	0.3
Polymer coating 2				
Hypromellose acetate succinate	5.9	5.9	5.9	5.9
Triethyl citrate	0.6	0.6	0.6	0.6

Preparation of EE–HPMCAS Complex (PEC)

EE in 0.1-N HCl solution (3% *w*/*v*) and HPMCAS in pH 6.8 phosphate solution (3% *w*/*v*) were mixed. EE solution was added slowly to the HPMCAS solution under stirring condition, and the mixture was then stirred for a period of 1 h at a speed of 800 rpm with a magnetic stirrer. The precipitate formed was filtered and washed several times with water to remove any non-complexed polymeric material. The precipitate was dried in hot air oven, and the dried complex was ground with a grinder. The powder was passed through sieve no. 30 and used for further study.

FT-IR Spectroscopy

EE and HPMCAS, at 1:1 weight ratio, were physically mixed using a mortar and pestle. PEC was analyzed by Fourier Transform infrared (FT-IR) spectroscopy according to the KBr disk method using a PerkinElmer FT-IR spectrometer (USA). For comparative purposes, FT-IR analysis was also performed on pure EE, pure HPMCAS, and physical mixture of the polymers. The compressed disks were scanned over 400 to 4000 cm^{-1} at ambient temperature using an accumulation of four runs in each sample with the resolution of 4 cm^{-1}, and characteristic peaks were recorded and evaluated by using spectrum software.

Table II. Compositions of Diclofenac Sodium Triple-Layer Polymer-Coated Tablets

Ingredients	F5 (mg/tab)	F6 (mg/tab)
Intragranular		
Diclofenac sodium	50.0	50.0
Mannitol	77.0	74.5
Croscarmellose sodium	3.0	3.0
Microcrystalline cellulose	15.0	15.0
Hydroxypropyl cellulose	3.0	3.0
Citric acid anhydrous	7.5	10.0
Extragranular		
Croscarmellose sodium	3.0	3.0
Magnesium stearate	1.5	1.5
Polymer coating 1		
Hypromellose acetate succinate	2.9	2.9
Triethyl citrate	0.2	0.3
Polymer coating 2		
Eudragit E	2.9	2.9
Triethyl citrate	0.3	0.3
Polymer coating 3		
Hypromellose acetate succinate	3.0	3.0
Triethyl citrate	0.3	0.3

In Vitro Drug Release

In vitro drug release testing from tablets was conducted according to the USP 27 apparatus two specifications using a dissolution apparatus (Electrolab, Mumbai, India). The dissolution testing for DS tablets was conducted in 1000 mL of pH 6.8 phosphate buffer or 750 mL of 0.1 N HCl (pH 1.2) for 2 h, and further, pH of the medium was changed to 6.8 using 250 mL of 0.20 M trisodium phosphate dodecahydrate. During dissolution testing, the medium was maintained at 37±0.5°C. The paddles were rotated at a speed of 50 rpm. Tablets were placed into dissolution medium, and aliquots of 10 mL were withdrawn from the dissolution apparatus at different time intervals and filtered through a nylon syringe filter (0.45 μm). The drug content was determined spectrophotometrically at a wavelength of 276 nm. At each time of withdrawal, 10 mL of fresh medium was replaced into the dissolution flask. The mean of three determinations was used to calculate the drug release from each of the formulation. The release kinetics of selected formulation was described by finding the best fit of the data (fraction of drug released *versus* time) to distinct mathematical functions: zero-order, first-order, Higuchi, and Hixson–Crowell models (23). Moreover, in order to gain some insight into the drug release mechanism, Korsmeyer–Peppas semi-empirical model was applied (24). The model with the highest correlation coefficient was considered to be the best-fitting one.

***In Vivo* Drug Release**

The *in vivo* pharmacokinetic parameters were assessed using the literature method (25) according to which rabbits of either sex weighing 2–3.5 kg maintained on normal diet were

used for this study. The study was performed in accordance with the ethical principles that have their origin in the declaration of Helsinki and was approved by the animal ethical committee of Albino Research and Training Institute, Hyderabad (Protocol no. ARTI/CPCSEA/051-2014). The coated tablets (F6) from batches selected as best after *in vitro* dissolution studies were administered to the rabbits. Voveran®50 GE tablets were also administered as reference to compare the drug release. Animals (n=3, for each group) were fasted overnight for 12 h and then administered a tablet (test or reference) after which blood was collected at 1, 2, 4, 6, 8, 10, 12, and 24 h. The obtained blood was centrifuged at 5000 rpm for 10 min to separate the plasma.

HPLC Analysis of Plasma Samples

Plasma samples were cyclomixed for 10 min by adding 0.5 mL of acetonitrile to extract the drug and subjected to centrifugation at 8000 rpm for 20 min, the supernatant was collected by using micropipette, the samples were filtered through 0.45-μm filters, and 20 μL of the samples was injected into HPLC system (Waters, Milford, MA). The mobile phase was a mixture of acetate buffer of pH 4.0 and acetonitrile in ratio of 40:60 *v*/*v*, respectively. The mobile phase used was pumped at a flow rate of 1.0 mL/min. The chromatography was performed at room temperature (25±2°C) on an analytical column with C_{18} bonded phase (4.6×250 mm, 5 μm). The dual absorbance detector was built into the chromatograph and operated at 278 nm. The retention time was about 4.8 min. The DS concentration was calculated by the absolute calibration method. A representative chromatogram is provided in Fig. 1.

Pharmacokinetic Parameters

The maximum plasma concentration (C_{max}) and the time required to reach maximum plasma concentration (T_{max}) after oral administration were directly determined from the plasma concentration–time curves. Also, the area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0–24}$) was calculated using trapezoidal rule. All results are represented as means±SD. Paired t test was used for comparison of pharmacokinetic parameters (C_{max} and $AUC_{0–24}$) between test and reference formulations. A value of $p<0.05$ was considered to be significant.

RESULTS AND DISCUSSION

The aim of the study was to formulate DS-loaded delayed-release tablets, film coated with the combination of EE and HPMCAS polymer solutions for possible pH-dependent colonic targeted delivery. We have earlier reported that PEC complex based on EE and HPMCAS can be effectively used as a matrix former and sustained drug release can be obtained by using different polymer ratios and their concentrations (26). By taking this platform with certain changes, in this study, the effect of EE in combination with HPMCAS polymer has been studied to see whether PEC film can form by LbL coating method which will give better delayed-release and targeted release profile for the selected drug. The results are discussed below as per the test. From the studies in this research work, it can be said that PEC film can effectively be employed to formulate delayed- and sustained-release tablets.

Turbidity Measurements

Turbidity measurement is a simple and direct indicator for PEC formation, accompanied by drastic changes of the system turbidity of the solution (27). The change in transmittance as a function of the weight ratio of EE/HPMCAS was measured to determine the composition of the PEC, as shown in Fig. 2. The EE solution and the HPMCAS solution were transparent prior to mixing. With addition of EE solution to HPMCAS solution, the turbidity increased rapidly up to a EE/HPMCAS mass ratio of 0.43, resulting in the abrupt increase in turbidity of the mixture. However, the transmittance decreased as the ratio was changed from 0.43 to 1.5. The change in transmittance was not significant at higher ratios. It appears that the excess EE did not react with HPMCAS because of the saturation of the electrostatic interaction sites of EE by that of HPMCAS. As the EE/HPMCAS ratio was changed from 0.43 to 1.5, there is no significant increase in transmittance which confirms the poor formation of PEC. The transmittance results clearly show that the complexation mass ratio of EE with HPMCAS was 0.43 (3:7).

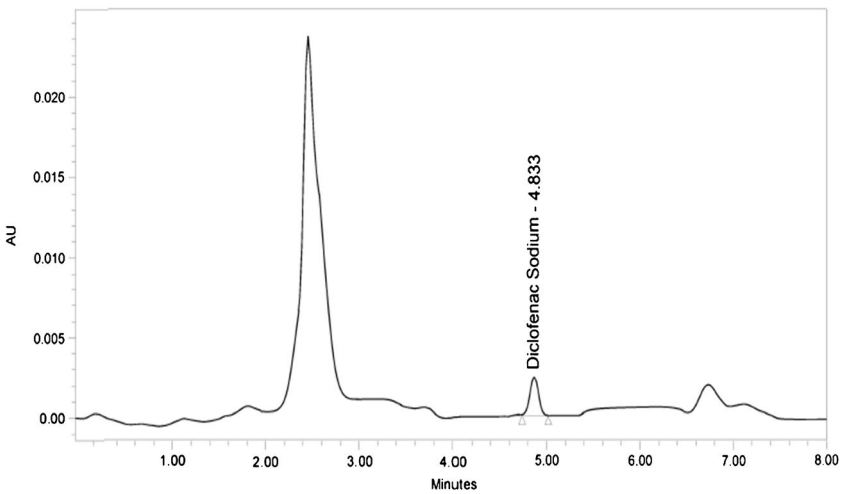

Fig. 1. Representative HPLC chromatogram of DS plasma analysis

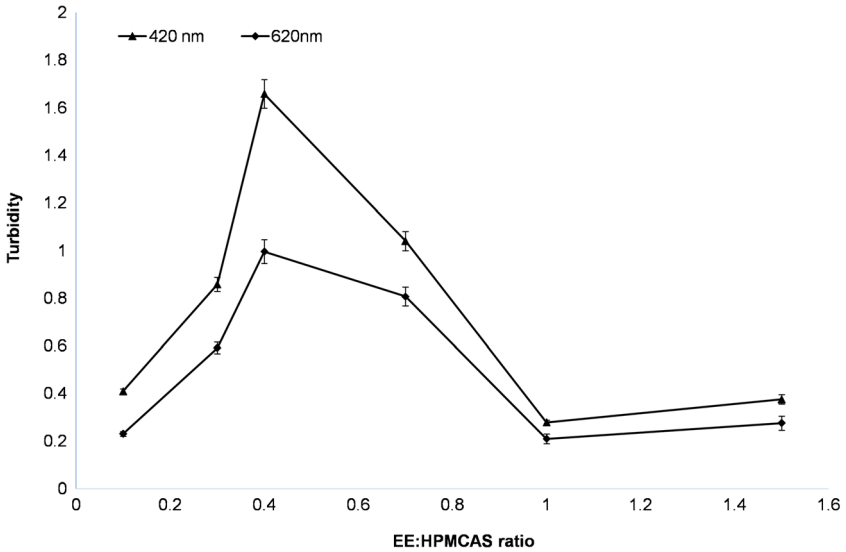

Fig. 2. Turbidimetric titration curve for the polymer solutions of EE and HPMCAS

FT-IR Spectroscopic Analysis

The FT-IR spectrum of pure polymers, physical mixture of pure polymers, and PEC mixture is depicted in Fig. 3. We have earlier characterized and reported the PEC mixture of EE-HPMCAS. In brief, the spectrum of HPMCAS polymer exhibited characteristic absorption peaks at 1064 cm^{-1} due to C–O stretch of cyclic ethers group; 1400–1350 cm^{-1} due to C–O–C stretching, 1750 cm^{-1} due to C═O stretching, and 3400 cm^{-1} due to polyhydroxy group (–OH group) (Fig. 3 (b)) (28). The spectrum of EE (Fig. 3 (a)) exhibited the characteristic bands of the ester groups at 1150–1190, 1240, and 1270 cm^{-1}, as well as the C═O ester vibration at 1730 cm^{-1}. In addition, CHX vibrations can be observed at 1385, 1450–1490, and 2950 cm^{-1}. Also, the spectrum of EE exhibited a characteristic absorption band at 2770 and 2820 cm^{-1} which corresponds to the absorption by dimethylamino groups and in agreement with data presented in the product specifications of Evonik (29). The physical mixture samples showed the bands for both components (Fig. 3 (c)). It may be noticed that the FT-IR spectrum of PEC is different from the rest of the spectra. Figure 3 (d) shows that the absorption band at 1728 cm^{-1} was weaker for the PEC sample than for the pure (co)polymers. This provided evidence that number of protonated carboxylic acids in the HPMCAS is decreased. The two bands of absorption at 2770 and 2824 cm^{-1} were considerably reduced for the PEC. This might be due to the interaction of protonated dimethylamino group of EE with the carboxylate group of anionic polymers. The FT-IR spectrum demonstrated the formation of PEC similar to those published in the literature (30).

Physical Evaluation of Core Tablets

DS core tablets were evaluated for their physical properties. The weight variation, thickness, hardness, disintegration time, and friability are shown in Table III. The results show that all formulations had low weight variation, indicating that

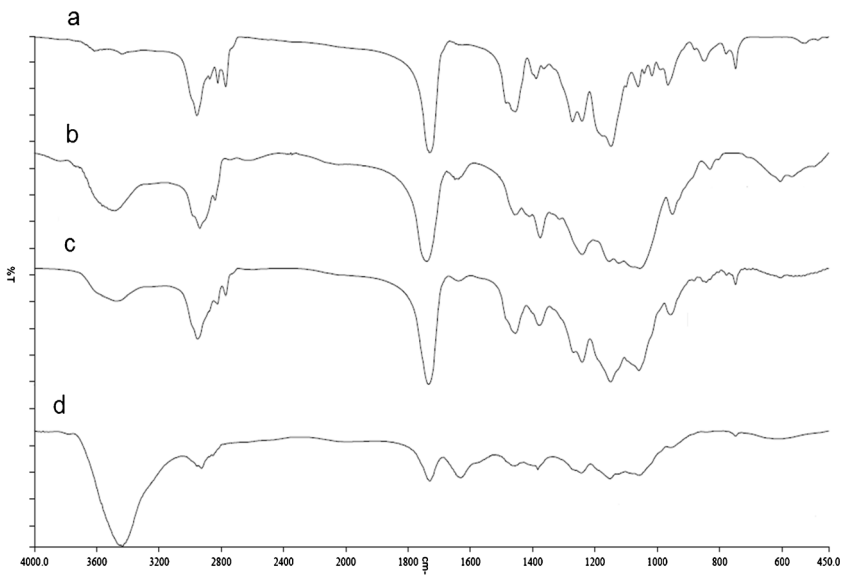

Fig. 3. FT-IR spectrum of pure polymer *a* EE, *b* HPMCAS, *c* physical mixture of EE and HPMCAS, and *d* PEC of EE/HPMCAS

Table III. Physical Properties of DS Core Tablets (with±SD)

Tablet physical parameters	F1	F2	F3	F4	F5	F6
Average weight of core tablets (mg) (n=10)	160.3±1.3	160.2±1.6	160.5±0.9	160.9±1.1	160.5±1.4	159.7±1.3
Hardness (kp) (n=10)	7.9±0.6	8.3±0.5	8.5±0.6	8.2±0.7	7.8±0.9	8.4±0.8
Disintegration time (min) (n=6)	6–9	8–10	7–10	8–10	7–10	8–10
Thickness (mm) (n=10)	3.85±0.01	3.81±0.01	3.83±0.01	3.85±0.01	3.83±0.01	3.82±0.01
Friability (%)	0.10	0.12	0.17	0.15	0.11	0.10

DS diclofenac sodium

wet granulation method is an acceptable method. The hardness of all formulations was moderately high enough to carry through the coating process.

Drug Release from Polymer-Coated Tablets

DS tablets (coated and uncoated) were evaluated for drug release using USP apparatus II-paddle dissolution apparatus. The release of DS from the uncoated tablets (for F1 formulation) was 100% within 1 h of exposure to 1000 mL of pH 6.8 dissolution medium indicating the immediate-release nature from the core tablets. When core tablet of F1 formulation was coated with films comprising of 2% *w*/*w* EE and 4% HPMCAS or of 4% *w*/*w* EE and 4% HPMCAS, the drug release observed is 1 and 0.9% after 2 h at pH 1.2, and after pH change from 1.2 to 6.8, only 32 and 14% of drug release was observed (Fig. 4) over a period of 5 h. Lower release (<10%) in the pH 1.2 medium indicated that the level of polymeric coating is sufficient enough to prevent the drug release in the stomach. Drug release was found to be less than 5% when dissolution was carried out directly in 1000 mL of pH 6.8 buffer for F1 formulation. The possible reason for the lower drug release could be due to the interaction of cationic polymer (EE) and anionic polymer (HPMCAS) and formation of low-soluble film around the core tablet.

Effect of Citric Acid Concentration

To further accelerate the drug release, it was decided to include the pH modifier like citric acid in the tablet core formulation. Inclusion of citric acid will modify the microenvironmental pH of the formulation and will be helpful to further increase the drug release rate. The concentration of citric acid included in the formulation was varied at different levels (3.75 mg (F2), 7.5 mg (F3), and 20 mg (F4) per tablet), and their effect on the drug release was studied. The drug release was found to be less than 10% in 0.1-N HCl dissolution medium for F2, F3, and F4 formulations, indicating that citric acid levels did not alter the enteric properties of the HPMCAS. However, when the pH of the dissolution medium was changed from pH 1.2 to 6.8, there was a significant difference in the drug release pattern. From Fig. 5, it can be observed that the drug release was rapid and 100% release was observed at 3-h time point for the F4 formulation with 20 mg of citric acid whereas the drug release was found to be more gradual, and prolonged drug release was observed for the F2 and F3 formulations containing lower amount of citric acid. Drug release was found to be rapid and complete for reference and F4 formulation when dissolution was carried out directly at pH 6.8 buffer whereas incomplete drug release was observed for F1, F2, and F3 formulations (Fig. 6). This indicated that drug release can be altered very well using different concentration of citric acid based on the desired drug release profile.

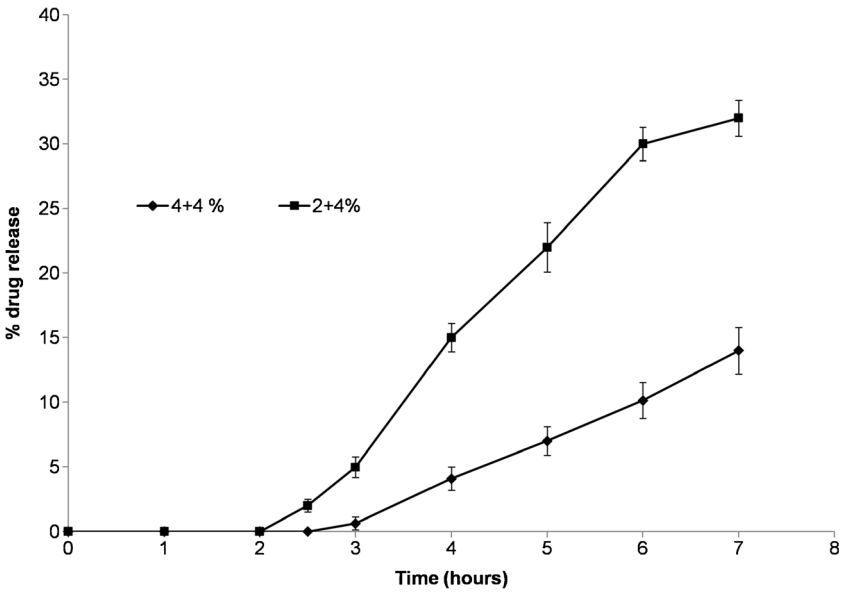

Fig. 4. Dissolution profile of DS tablet F1 formulation with different levels of polymer coating in 0.1 N HCl followed by pH 6.8 buffer

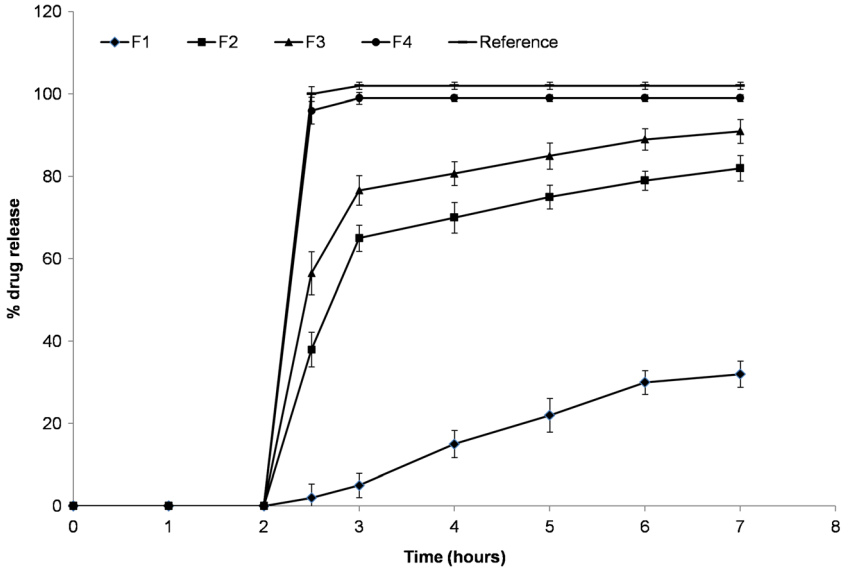

Fig. 5. Dissolution profile of DS tablet F1–F4 formulations and reference tablet in 0.1 N HCl followed by pH 6.8 buffer

Drug Release from Polymer-Coated Tablets by LbL Method

PEM polymer thin films prepared by layer-by-layer (LbL) adsorption of oppositely charged polymers have been used for the targeted drug delivery. In this research work, PEM films on DS core tablets were prepared by LbL adsorption method using cationic (EE) polymeric solution and anionic (HPMCAS) polymeric solution. DS core tablets containing 7.5 mg of citric acid (F5) and 10 mg of citric acid (F6) were prepared and further coated with different polymer coating solutions to get about 2% *w*/*w* HPMCAS coating buildup (first layer) followed by 2% *w*/*w* EE (second layer) and 2% *w*/*w* HPMCAS (third layer) (Table II). Polymer-coated tablets were further evaluated for drug release using USP apparatus II-paddle dissolution apparatus and compared with the reference gastro-resistant tablets. The drug release after 2 h at pH 1.2 was found to be less than 2% for both reference and test formulations and indicated that the level of polymer coating is sufficient enough to prevent the drug release in the stomach. However, when the pH of the dissolution medium was changed from pH 1.2 to 6.8, there was a significant difference in the drug release pattern. The drug release from the reference formulation was found to be rapid and complete drug release was observed within 1 h in pH 6.8 buffer (Fig. 7). However, for both F5 and F6 formulations, the drug release was found to be more gradual and prolonged drug release was observed. The possible reason for the slower drug release could be due to the interaction of cationic polymer (EE) and anionic polymer (HPMCAS) and formation of low-soluble film around the core tablet. The dissolution profile was found to be similar for F5 and F6 formulations (f_2>50).

Kinetic Analysis of Release Data

To describe the kinetics of drug release from the selected formulation (F6), release data was analyzed according to different kinetic equations. The data was analyzed by the

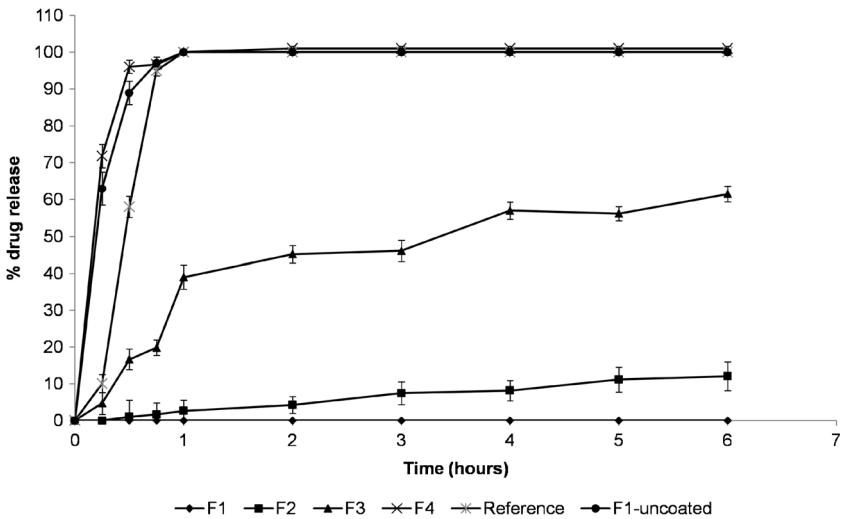

Fig. 6. Dissolution profile of DS tablet F1–F4 formulations and reference tablet in pH 6.8 buffer

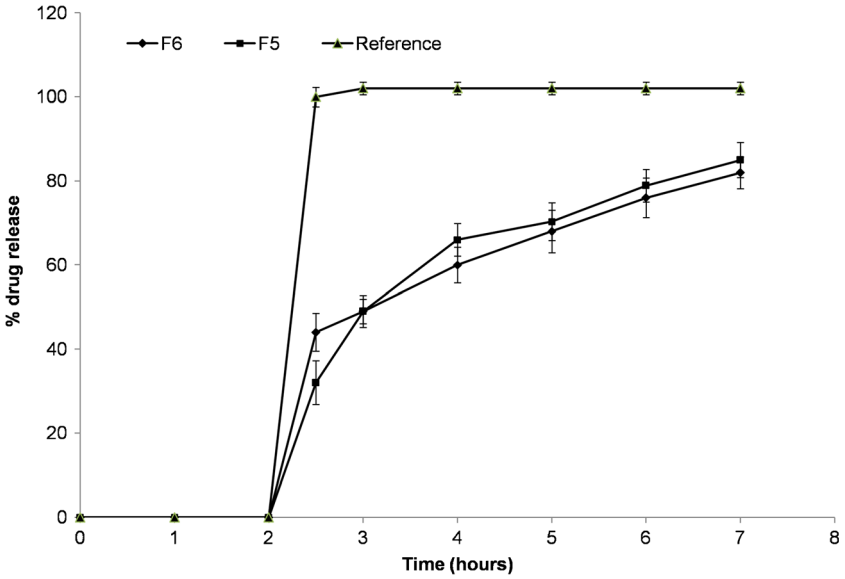

Fig. 7. Dissolution profile of DS tablet F5 and F6 formulations and reference tablet in 0.1 N HCl followed by pH 6.8 buffer

regression coefficient method. On analyzing regression coefficient values, it was found that F6 formulation exhibits first-order kinetics (0.99). The *in vitro* release profiles of drug from this formulations could be best expressed by Higuchi model as the plots showed highest linearity (r^2=0.99). To confirm the diffusion mechanism, the data was further fitted into Korsmeyer–Peppas equation. The formulation showed good linearity (r^2=0.969), and the *n* value (0.22) indicated diffusion-based mechanism of drug release (24).

Pharmacokinetics Studies

The pharmacokinetic profiles of DS polymer-coated tablets (F6) and the reference tablets following oral administration to rabbits are depicted in Fig. 8. From the obtained data, it could be observed that there is a difference between the mean plasma concentrations as a function of time for DS after oral administration of the test formulae at all time intervals compared to the reference tablet. The plasma concentration of DS was detectable in plasma at 2 h for reference tablets and at 4 h for DS-coated tablets indicating delayed drug release nature. The time to achieve C_{max} after oral administration was delayed to 4–6 h for DS-coated tablets. This strongly indicated that the HPMCAS films were able to inhibit the drug release in gastric pH.

The mean pharmacokinetic parameters of DS from test and reference tablets represented by the value of C_{max} (μg/mL), T_{max} (h), and AUC_{0-24} (μg h mL^{-1}) were calculated. The mean plasma concentrations (C_{max}) were 3.25±0.29 μg/mL for test formulation compared to 3.62±0.38 μg/mL for the reference tablets, indicating that the difference was insignificant (p>0.05). From the obtained results, it was evident that the absorption of DS from the reference tablets was delayed and

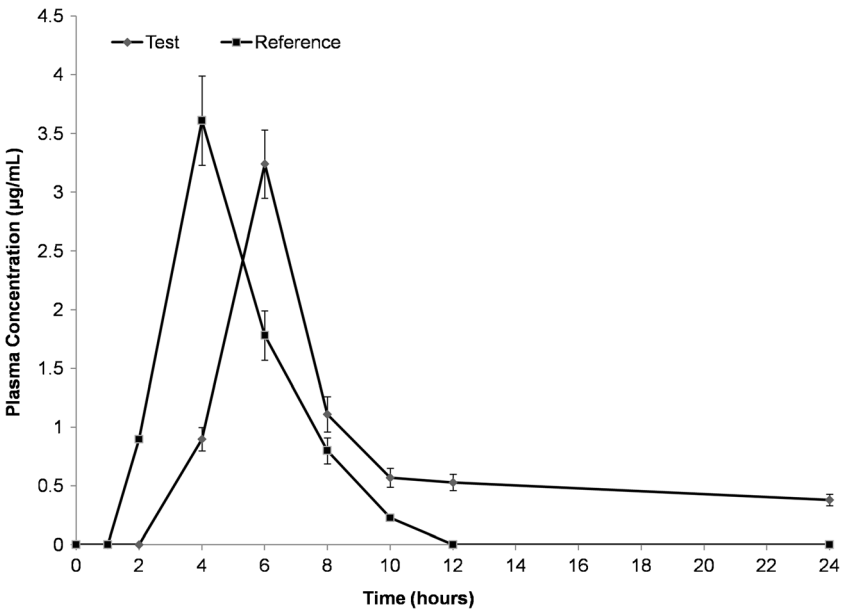

Fig. 8. Comparison of pharmacokinetic profile of reference and DS test (F6) formulation

reached its peak plasma concentration in 4 h, whereas, following oral administration of the test formulae, the T_{max} was attained at 6 h. These results showed that the oral absorption of DS-coated tablets leads to an increase of the mean T_{max} compared to reference tablets and hence indicated the delayed-release behavior of test formulation compared to reference tablets. The mean AUC_{0-24} was found to be 14.99±0.65 μg h mL^{-1} for test formulation compared to 12.9±1.35 μg h mL^{-1} for the reference tablet. It is clear that the test formulation exhibited higher AUC_{0-24} values that were significantly different ($p=0.041$). These findings achieved the goal of delayed-release concept from tablets prepared using HPMCAS-EE-coated tablet which has been estimated in reducing high peak plasma concentration (C_{max}) and prolonging the time required to reach maximum plasma concentration (T_{max}).

CONCLUSION

In this study, pH-dependent and modified release tablets were prepared by LbL adsorption method using anionic HPMCAS polymer and cationic EE polymer for delivery of DS in the lower part of the GI tract. The results of the present study confirmed the formation of PEC between EE and HPMCAS polymer. Tablets coated with polymethacrylate polymer (EE) followed by HPMCAS polymer at the coating level of 2 and 4%, respectively, were able to prevent the drug release in the stomach. Drug release from the polymer coated was found to be pH-dependent, and addition of citric acid was found to be helpful in modifying the microenvironmental pH of the formulation and, thus, controlling the drug release profile from the formulation. Tablets coated by LbL adsorption method using HPMCAS/EE/HPMCAS at the coating level of 2/2/2% *w*/*w* effectively hindered the drug release in stomach environment and showed sustained drug release in pH 6.8 buffer medium. The *in vivo* study of DS polymer-coated tablets using rabbits showed that these tablets were able to ensure delayed and sustained drug release for a longer period than the reference tablets.

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Conflict of Interest The authors report no conflict of interest.

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