

Blend of cellulose ester and enteric polymers for delayed and enteric coating of core tablets of hydrophilic and hydrophobic drugs

Sogra F. Barakh Ali^a, Hamideh Afroz^a, Rachel Hampel^b, Eman M. Mohamed^{a,c}, Raktima Bhattacharya^a, Phillip Cook^d, Mansoor A. Khan^a, Ziyaur Rahman^{a,*}

^a Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Texas A&M University, College Station, TX 77843, USA

^b Artie McFerrin Department of Chemical Engineering, College of Engineering, Texas A&M University, College Station, TX 77843, USA

^c Department of Pharmaceutics, Faculty of Pharmacy, Beni-Suef University, Egypt

^d Eastman Chemical Company, Kingsport, TN 37664, USA



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ABSTRACT

The focus of this work was to explore feasibility of using blends of cellulose esters (CA 320S, CA 3980-10 or CAB 171-15) and enteric polymers (C-A-P, Eudragit® L100 or HPMCP HP-55) for delayed and enteric coating of tablets containing either diclofenac sodium (DFS, high dose) or prednisone (PDS, low dose) drug. The core tablets of DFS or PDS were coated with polymer blends to achieve approximate weight gain of 5% and 10%. The coated tablets were characterized for dissolution (0.1 N HCl and phosphate buffer pH 6.8) and surface morphology. The surface morphology of CA 398-10 or CAB 171-15 based polymer blends was rough and fibrous. Less than 0.5% drug was dissolved in 120 min from 5% w/w coated tablets in acid-phase dissolution testing. The dissolution in phosphate buffer pH 6.8 medium varied from 16.2 ± 0.2 to $98 \pm 2.1\%$, and $30.1 \pm 0.5\%$ to $101.7 \pm 3.4\%$ in 120 min from DFS and PDS coated tablets, respectively. Dissolution was less in CA 320S based blends compared to CA 398-10 or CAB 171-15 blends in phosphate buffer medium. Furthermore, there were no significant differences observed in dissolution profiles of coated tablets of DFS or PDS. This can be explained by dose of the drugs. Additionally, dissolution was higher in tablets coated with enteric polymer alone compared with the blends. In conclusion, core tablets can be coated with cellulose ester and enteric polymers blend to impart both delayed and enteric release feature to the tablets containing hydrophilic or hydrophobic drug.

1. Introduction

Tablets are the most widely used solid dosage form (Helliwell and Taylor, 1993). Oftentimes, tablets are coated with polymer(s), which could be functional or non-functional. One purpose of a functional coating is to impart delayed release properties. A delayed release dosage form is defined as one that releases a drug(s) at a time other than promptly after administration (Shibata et al., 2016). A delayed release dosage form utilizes an enteric protective film coating that is resistant to dissolution in gastric acidic environment but dissolves in a more alkaline environment such as the intestine. Delayed release of drugs is desired for following reasons; 1) to protect drugs from acidic environment of stomach and thus improving stability and bioavailability of the drug (Bampalidis and Grypouli, 2018); 2) to protect gastric mucosa from irritating effects of some drugs (Altman et al., 2015); 3) to deliver drugs to local region of intestine for site-specific delivery e.g. colon-specific delivery of mesalamine to treat localized inflammation

(Abinusawa and Tenjarla, 2015). Various polymers are used for delayed coating of tablets or other solid dosage forms e.g. cellulose acetate phthalate (C-A-P), hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), and methacrylic acid copolymers etc (Missaghi et al., 2010). These polymers have acidic ionizable carboxylic acid groups on their structure, which impart pH dependent solubility i.e. insoluble at low gastric pH but soluble at higher pH of the intestine. The performance of delayed release formulations are affected by polymer type, pH solubility threshold, coating composition (plasticizer type and level, other components), core tablet characteristics, and coating level etc (Missaghi et al., 2010).

Cellulose ester polymers such as cellulose acetate (CA), cellulose acetate butyrate (CAB) and cellulose acetate phthalate (C-A-P) are widely reported in the literature for various pharmaceutical applications. CA alone or blended with other polymers (ethyl cellulose) have also been reported for use in osmotic coating applications. (Arjun et al.,

* Corresponding author at: 310 Reynolds Medical Sciences Building, College Station, TX 77843-1114, USA.

E-mail address: rahman@pharmacy.tamhsc.edu (Z. Rahman).

2016; Patel et al., 2016; Derakhshandeh and Berenji, 2014; Li et al., 2014). It has also been reported for use in various drug delivery systems such as gastro retentive (Ammar et al., 2016), colon targeted drug delivery (Nour et al., 2015) and nanofibers (Khoshnevisan et al., 2018) etc. Mixtures of cellulose acetate propionate and CAB have been reported as matrix formers for sustained release of the drug (Obeidat and Alzoubi, 2014). Similarly, blends of CAB, Eudragit® RL and triethyl citrate have been investigated for use in osmotic coating applications (Ali et al., 2018). The objective of the present research was to investigate the feasibility of using CA or CAB polymer in combination with an enteric polymer such as C-A-P, Eudragit® L100 or HPMCP HP-55 for delayed and enteric coating applications. These blends have not been investigated for delayed and enteric release application to the best of our knowledge. The polymer blend may be useful in modulating the dissolution of the drug instead of using enteric polymer alone. We selected two model drugs for use in the study namely, diclofenac sodium (DFS) and prednisone (PDS) as examples of hydrophilic and hydrophobic, and high and low dose drugs, respectively (Liu et al., 2014). BCS class of DFS is II (Chuasawan et al., 2009) while it is BCS I for PDS for dose 1–5 mg (Australian Public Assessment Report for Prednisone, 2013; Vogt et al., 2013). Furthermore, DFS is a commonly used non-steroidal anti-inflammatory drug (NSAIDs). Gastric irritation is the most common adverse effect of NSAIDs (Altman et al., 2015). Delayed release formulations of DFS are commercially available to improve therapeutic efficacy and compliance in patients (Arthrotec® FDA label, 2018; Voltaren® FDA label, 2018). Similarly, PDS is used for the treatment of various allergic and inflammatory conditions. FDA has approved delayed release formulation of PDS for chemotherapy of various pathologic inflammatory conditions (Rayos FDA label, 2018; Krasselt and Baerwald, 2016). The core tablets of DFS or PDS were coated with blends of cellulose ester and enteric polymers, and evaluated for surface morphology and dissolution (0.1 N HCl and 0.2 M phosphate buffer pH 6.8).

2. Materials and methods

2.1. Materials

DFS and PDS were obtained from Leap Chem, Hangzhou, China. CA 320, CA 398-10, CAB 171-15, C-A-P polymers were provided by Eastman Chemical Company, Kingsport, TN. Eudragit® L100 and HPMCP HP-55 were purchased from Evonik Industries, AG and Shin-Etsu, Dallas, TX, respectively. Acetone, acetonitrile (ACN), monobasic potassium phosphate, croscarmellose sodium (CCS), magnesium stearate (MGS), polyethylene glycol 400 were purchased from Fisher Scientific, Asheville, NC. Hydroxypropyl cellulose (HPC, MW 100,000) was purchased from Sigma-Aldrich, St Louis, MO. Lactose monohydrate (LMH, Supertab 145D) and microcrystalline cellulose (MCC, Vivapur® 102) were obtained from Mutchler Inc, Harrington Park, NJ and JRS Pharma, Patterson, NY, respectively. In-house water (18 MΩ.cm, Millipore Milli-Q Gradient A-10 water purification system) was used in

the study.

3. Methods

3.1. Compatibility studies

DFS, PDS and excipients were sieved through a #60 screen. The drug was mixed with individual excipients in 1:1 ratio. The samples were stored for 4 weeks at 40 °C/75%RH and two weeks at 60 °C in open scintillation vials. Samples were analyzed by Fourier transform infrared spectroscopy (FTIR), X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) methods.

3.2. Fourier transform infrared spectroscopy

Modular Nicolet™ iS™ 50 system (Thermo Fisher Scientific, Austin, TX) was used for collecting FTIR spectra of compatibility studies samples. The spectra collection parameters were: absorbance mode, wavelength range 400–4000 cm⁻¹, data resolution 8 cm⁻¹ and 100 scans. Spectra were collected using OMNIC software version 9.0 (Thermo Fisher Scientific, Austin, TX). The spectra were collected in duplicate.

3.3. Differential scanning calorimetry

Differential scanning calorimetry (DSC) of the samples were collected using Q2000 instruments (TA Instruments Co., New Castle, DE, USA). The temperature-scanning rate was 10 °C/min for DSC measurement and scanned up to 300 °C to cover the melting point of the drug and excipients. Nitrogen gas was purged at a pressure of 20 psi and 50 ml/min flow rate to provide inert atmosphere during the measurement. The thermograms were collected in duplicate.

3.4. X-ray powder diffraction

XRPD patterns of the samples were collected using Bruker D2 Phaser SSD 160 Diffractometer (Bruker AXS, Madison, WI) equipped with the LYNXEYE scintillation detector and Cu K α radiation ($\lambda = 1.54184 \text{ \AA}$) at a voltage of 30 KV and a current of 10 mA. The samples were prepared by evenly spreading the appropriate amount of powder on the sample holder. The mounted samples were scanned over 20 range of 5–30° at 1 s per step with an increment of 0.0202° and rotated at 15 rpm to get the average diffractogram. The collected data was evaluated using Difrac.EVA Suite version V4.2.1 and further processed using File Exchange 5.0 (Bruker AXS, Madison, WI). The diffractogram were collected in duplicate.

3.5. Preparation of core tablets

Core tablet formulations of DFS and PDS were prepared as per Table 1, and batch size was 1 kg. DFS or PDS, LM, MCC and HPC were sieved through a #18 screen. Powder components were blended (V-

Table 1
Composition of core tablet formulations.

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9
Quantity (mg/tablet)									
Diclofenac sodium	50	50	50	50	50	50	50	–	–
Prednisone	–	–	–	–	–	–	–	5	5
Lactose monohydrate	85	95	105	110	104.5	99.5	94.5	127	122
Microcrystalline Cellulose	28	28	28	28	28	28	28	50.5	50.5
Hydroxypropyl Cellulose	30	20	10	5	2.5	2.5	2.5	2.5	2.5
Croscarmellose sodium	2	2	2	2	10	15	20	10	15
Magnesium stearate	5	5	5	5	5	5	5	5	5
Hardness (kP)	7.2–8.9	7.1–9.2	6.9–9.1	7.2–8.9	7.1–9.3	7.2–8.4	6.0–7.1	8.1–8.7	8.2–8.9
Disintegration time (min)	30.0–36.4	24.2–26.5	19.3–20.2	13.1–15.4	6.0–6.2	6.5–7.2	4.5–5.0	3.2–4.0	2.73–3.50

blender, Model VH-2) and granulated with water (25% w/w, water resistivity 18 MΩ.cm) in a high shear granulator (KG5, KEY International Inc. NJ, USA). The granules were oven dried at 50 °C (Binder, USA) to a target loss on drying of ≤2% w/w. The dried granules were milled in a Quadro Comil® (Model-193, Quadro Engineering Inc, Waterloo, Canada), and sieved through a #18 screen. CCS was added to dried granules and lubricated with MGS for 2 min in a V-blender. The final blend was compressed into tablets using Mini Press-1 (Globe Pharma, New Brunswick, NJ, USA) 10-station tabletting machine with 8 mm flat die and punches (Natoli Engineering Company, Saint Charles, MO, USA). The tablets were characterized for hardness (VK 200, Varian Inc, Cary, NC), friability (USP friability tester, Varian Inc, Cary, NC), disintegration (USP disintegration tester in 900 ml water at 37 °C, VK 100, Agilent Technologies, Santa Clara, CA) and dissolution tests (Model 708-DS with 850-DS autosampler, Agilent Technologies, CA, USA).

3.6. Coating

Core tablets of DFS (formulation C7) and PDS (formulation C9) were coated at 5 and 10% w/w weight gain using an 8" Vector Hi-Coater (Model HCT Mini, Freund Vector, Marion, IA). The coating formulations (8.5–10%) were prepared according to Table 2. The coating parameters were: inlet temperature 60–80 °C; core tablets bed temperature 55–70 °C; pan rotation speed 35–40 rpm; atomization pressure 1.5–2.0 bar; spray rate 10–15 gm/min and tablet bed to spray gun distance 10 cm. About 400 gm core tablets were charged into the pan and prewarmed before coating. Weight gain was monitored during the coating process. The final coated tablets were dried for 30 min at 60 °C. Only one batch is coated per coating composition (Table 2). The coated tablets were characterized for surface morphology before and after dissolution, disintegration (USP disintegration tester in 900 ml 0.1 N HCl for 2 h at 37 °C, VK 100, Agilent Technologies, Santa Clara, CA) and dissolution (0.1 N HCl and 0.2 M phosphate buffer pH 6.8, Model 708-DS with 850-DS autosampler, Agilent Technologies, CA, USA).

3.7. Surface morphology

Surface morphology of coated tablets before and after dissolution was determined by scanning electron microscopy (SEM, JSM-7500F, JEOL, Tokyo, Japan). Samples were coated approximately to 5 nm thickness with carbon using sputter coater (Cressington, 208 HR with MTM-20 High Resolution Thickness Controller) under high vacuum (argon gas pressure 0.01 mbar) and high voltage of 40 mV. Morphology was captured at a working distance of 15 mm, an accelerated voltage of

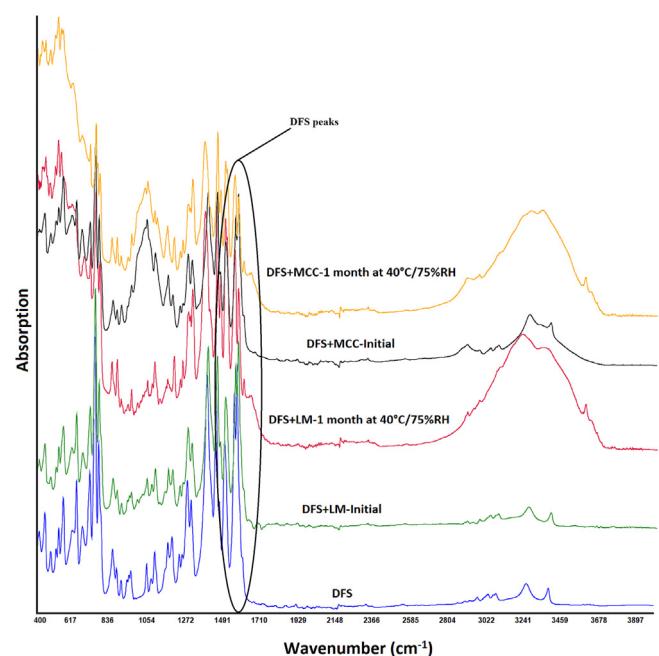


Fig. 1. FTIR spectra of diclofenac sodium and binary mixtures.

5 KV and an emission current of 20 μA. Two samples of coated tablets were used for collecting SEM images.

3.8. Dissolution of core and coated tablets

Dissolution of core and coated tablets was performed using USP apparatus 2 (Model 708-DS with 850-DS autosampler, Agilent Technologies, CA, USA). The dissolution of DFS core tablets was performed in 900 ml 0.2 M phosphate buffer pH 6.8 at 50 rpm and 37 °C. Samples (1 ml) were collected at 5, 15, 30, 45 min intervals and 20 μL of sample was injected into HPLC system to determine amount of dissolved drug. Dissolution of core tablets of PDS was performed in 500 ml water and samples were collected at 5, 15 and 30 min.

Dissolution of coated tablets was performed in 0.1 N HCl and 0.2 M phosphate buffer pH 6.8 mediums employing USP apparatus 2 (Model 708-DS with 850-DS autosampler, Agilent Technologies, CA, USA). In acid condition, dissolution was performed in 500 ml 0.1 N HCl at 50 rpm and 37 °C for 2 h. Samples (1 ml) were collected and analyzed by HPLC for amount of drug dissolved. Dissolution of DFS coated tablets

Table 2
Coating formulations composition.

Coating formulation	Cellulose ester	Enteric polymer	Polymers blend (cellulose ester: enteric polymer)	Polyethylene glycol 400 (%)	Solvents (acetone: Water)
F1	CA 320S	C-A-P	9:1	20	80:20
F2	CA 320S	C-A-P	1:1	20	80:20
F3	CA 398-10	C-A-P	9:1	20	100:0
F4	CA 398-10	C-A-P	1:1	20	100:0
F5	CAB 171-15	C-A-P	9:1	20	100:0
F6	CAB 171-15	C-A-P	1:1	20	100:0
F7	CA 320S	HPMCP HP-55	9:1	20	80:20
F8	CA 320S	HPMCP HP-55	1:1	20	80:20
F9	CA 398-10	HPMCP HP-55	9:1	20	100:0
F10	CA 398-10	HPMCP HP-55	1:1	20	100:0
F11	CAB 171-15	HPMCP HP-55	9:1	20	100:0
F12	CAB 171-15	HPMCP HP-55	1:1	20	100:0
F13	CA 320S	Eudragit® L100	9:1	20	80:20
F14	CA 320S	Eudragit® L100	1:1	20	80:20
F15	CA 398-10	Eudragit® L100	9:1	20	98:02
F16	CA 398-10	Eudragit® L100	1:1	20	98:02
F17	CAB 171-15	Eudragit® L100	9:1	20	98:02
F18	CAB 171-15	Eudragit® L100	1:1	20	98:02

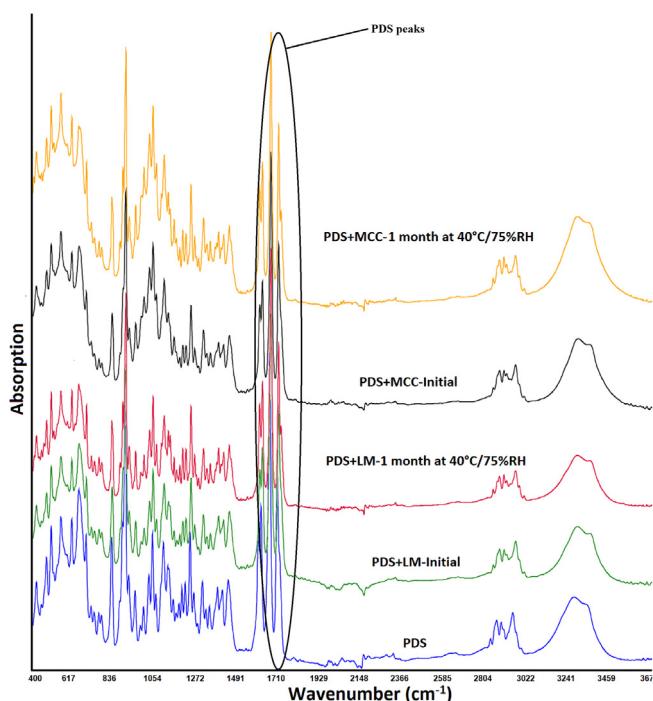


Fig. 2. FTIR spectra of prednisone and binary mixtures.

were performed in 900 ml 0.2 M phosphate buffer 6.8 and samples were collected at 15, 30, 45, 60, 90 and 120 min interval and filtered through 70 μm filter. A 20 μL sample was injected into HPLC system to quantitate the amount of drug dissolved. Dissolution method for PDS coated tablets was the same except 500 ml dissolution medium was used instead of 900 ml. Dissolution of core and coated tablets were performed in triplicate.

3.9. HPLC method

HPLC methods for PDS and DFS were developed and validated as per ICH guidelines (ICH, 2005). The HPLC equipment consisted of Agilent 1260 series (Agilent Technologies, Wilmington, DE, US) equipped with a quaternary pump, online degasser, column heater, autosampler and UV/Vis detector. Data collection and analysis were performed using Openlab software (Agilent Technologies, Wilmington, DE, US). Separation of the drugs was achieved on a 4.6 \times 150 mm, 5 μm Luna C18 (Phenomenex, Torrance, CA, USA) column and a C18, 4.6 \times 2.5 mm (5 μm packing) Luna C18 guard column (Phenomenex, Torrance, CA, USA). The mobile phase for PDS and DFS was ACN: water (35:65, v/v) and ACN: 20 mM phosphate buffer pH 7.0 (30:70, v/v), respectively, flowing at 1.0 ml/min. Detection wavelength for DFS and PDS was 280 and 254 nm, respectively. The column and auto-sampler were maintained at 30 °C and 25 °C, respectively. Sample volume of 20 μL was injected into the system. Two injection per samples were analyzed by HPLC to demonstrate reproducibility of the data.

4. Results and discussion

4.1. Compatibility studies

FTIR spectra of DFS showed asymmetrical and symmetrical stretching vibration bands at 1572 and 1450 cm^{-1} due to carboxylate group, respectively (Fig. 1). NH vibration band was exhibited at 3386 cm^{-1} (Shivakumar et al., 2008). Initial binary mixtures of DFS with LM, MCC, HPC, MGS and CCS exhibited characteristics bands of DFS. No changes in FTIR spectra were observed in the samples stored at 60 °C for two weeks. Similar results were obtained for the samples exposed to 40 °C/75% RH for one month except samples did not show a well-defined NH vibration band at 3386 cm^{-1} . Possibly, this was due to interference of water absorption bands that appeared as a hump between 2900 and 3650 cm^{-1} . Diclofenac can undergoes disproportionation during stability. This would be reflected change in position of carboxylate and amide groups stretching bands. For

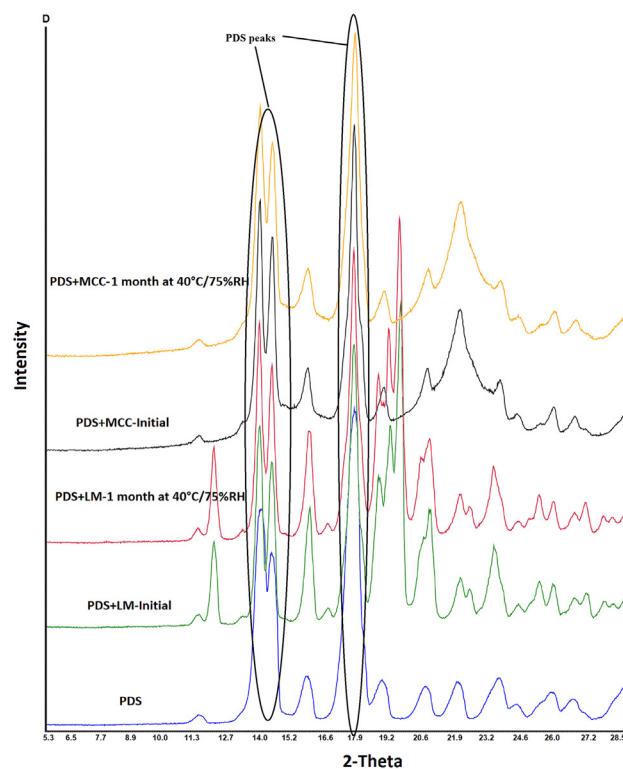
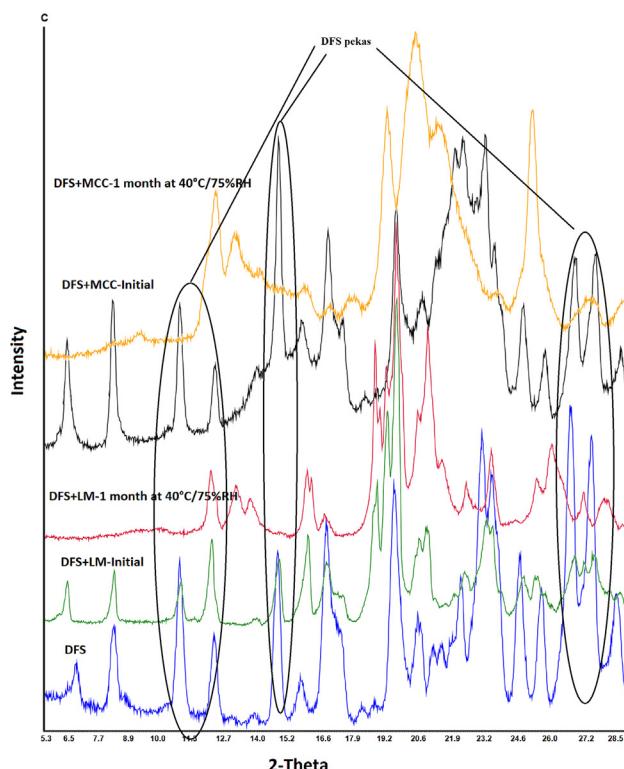


Fig. 3. XRD spectra of A) diclofenac sodium and binary mixtures, and C) prednisone and binary mixtures.

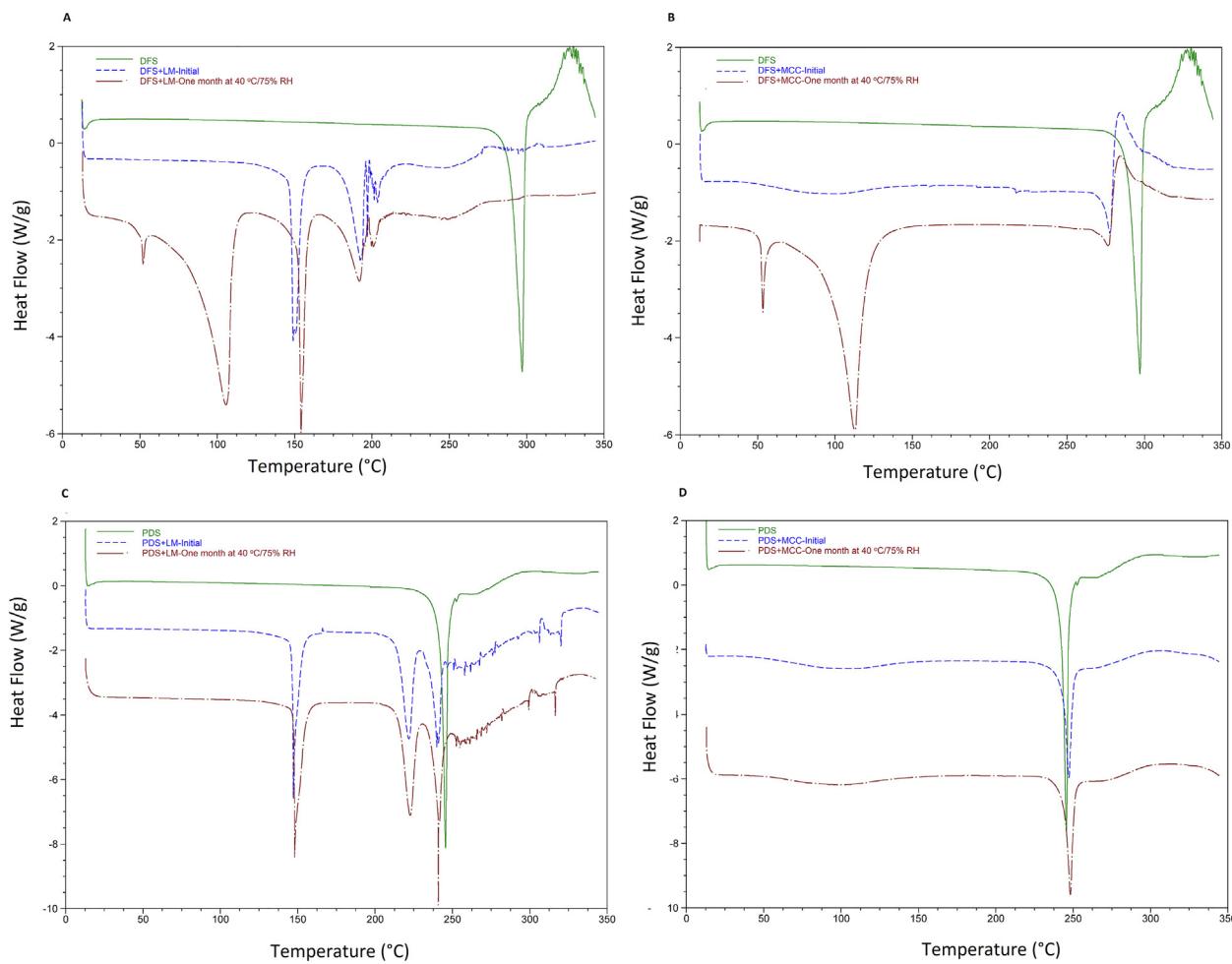


Fig. 4. DSC thermograms of A) DFS, DFS + LM initial and 40 °C/75% exposed samples, B) DFS, DFS + MCC initial and 40 °C/75%, C) PDS, PDS + LM initial and 40 °C/75% exposed samples and D) PDS, PDS + MCC initial and 40 °C/75% exposed samples.

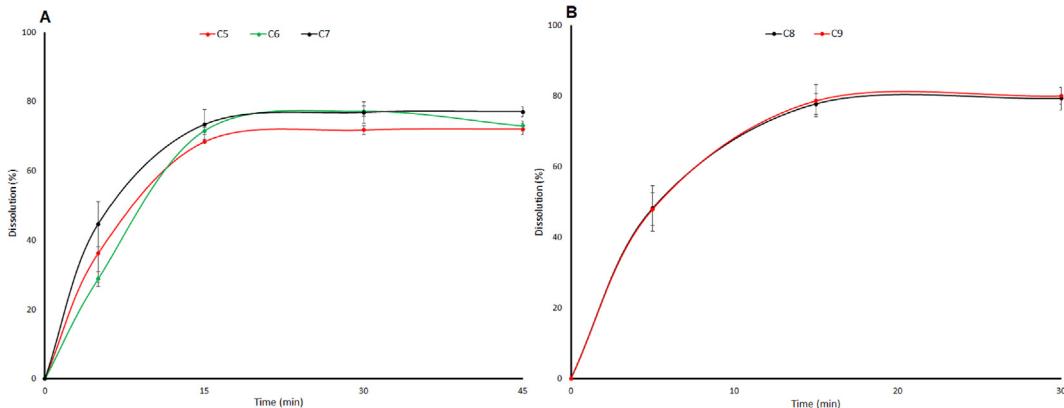


Fig. 5. Dissolution profiles of A) diclofenac core tablet formulations and B) prednisone core tablets formulations in 0.2 M phosphate buffer. Data is presented as mean \pm SD, n = 3.

example, carbonyl and amide stretching vibration bands shift from 1572 to 1576 cm^{-1} and 3386 to 3325 cm^{-1} , respectively. if diclofenac sodium changes to diclofenac acid (Ramachandran and Ramukutty, 2014). Furthermore, peak at 1604 cm^{-1} appeared that was shoulder in the initial samples, which indicated hydrate form formation of the drug (Fig. 1) (Bartolomei et al., 2007). Furthermore, these changes in spectra indicated physical changes in the samples such as hydrate formation or polymorphic changes in the drug and excipients rather than chemical interactions between the components of the samples, which was further

confirmed by XRPD and DSC data. Similarly, PDS exhibited characteristic bands due to carbonyl (α,β -unsaturated) group at 1706 cm^{-1} and C=C due to olefinic group at 1666 cm^{-1} (Fig. 2) (Li et al., 2009). A band due to the hydroxyl group was exhibited in the region 3170–3400 cm^{-1} . Initial and stability samples exhibited characteristics peaks of PDS (Fig. 2), which indicated no physical or chemical change in the drug on exposure to high temperature and humidity. These observations were corroborated by XRPD and DSC data.

DFS exhibited characteristic reflection peaks at 8.25, 10.90, 12.25,

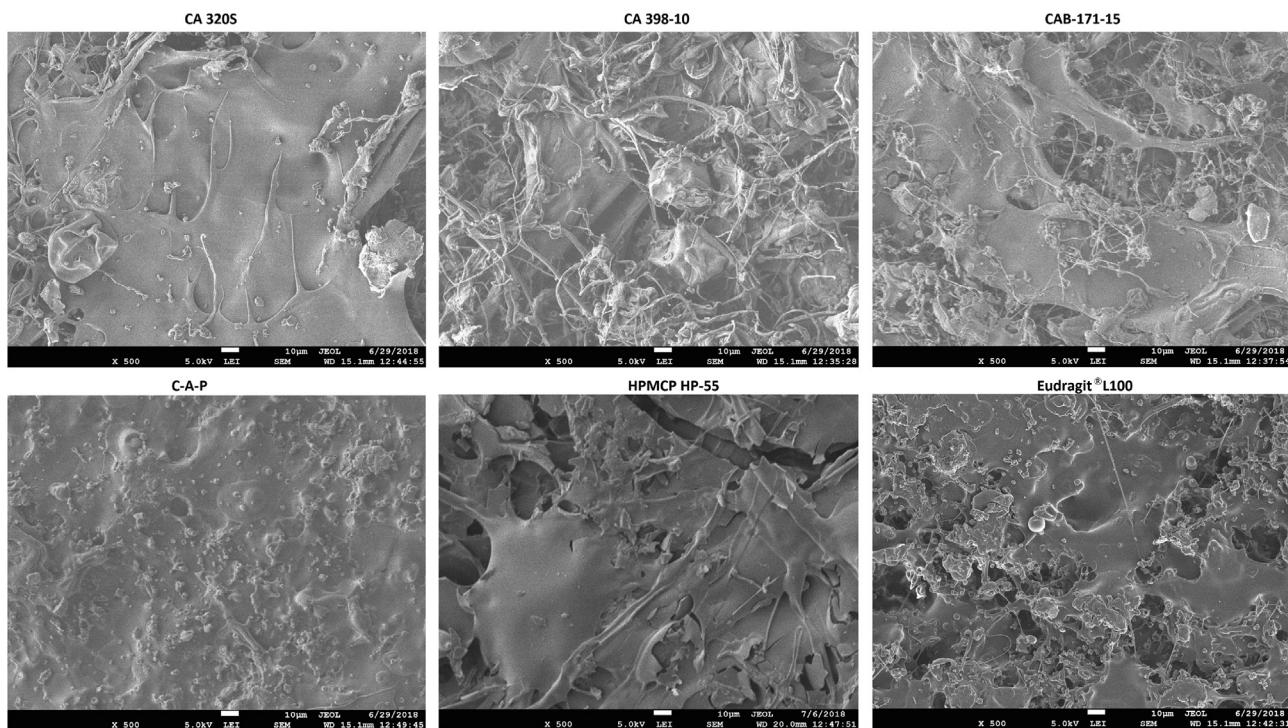


Fig. 6. SEM micrographs of coated tablets with CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP HP-55 or Eudragit® L100 coating formulations.

14.85, 16.82, 19.55, 23.10, 23.55, 26.70 and 27.50° that indicated crystalline nature of the drug (Fig. 3A). All binary mixtures showed characteristic DFS reflection peaks at 8.25, 10.90 and 14.85°. Samples exposed at 60 °C for two weeks showed no change in characteristic reflection peaks of DFS. However, binary samples exposed to 40 °C/75% RH for one month showed no characteristic peaks of DFS. Moreover, new reflection peaks appeared in all the samples except binary mixture of DFS and HPC, which indicated formation of hydrated forms of the drug (Fig. 3A). Monohydrate, trihydrate and pentahydrate forms of diclofenac are reported in literature, which are formed under various temperature and humidity conditions (Muangsin et al., 2004; Bartolomei et al., 2007; Llinàs et al., 2007). It is likely that exposure of the binary mixtures to 40 °C/75% RH cause dissolution of anhydrous forms of DFS and subsequent crystallization into mixtures of hydrated forms. In the case of binary mixture of DFS and HPC, a halo diffractogram was obtained indicating dissolution of DFS on exposure to high humidity and subsequent entrapment of DFS in HPC polymer, which prevented recrystallization of the drug. Similarly, characteristic major reflection peaks at 14.15, 14.60 and 17.90° and many minor peaks confirmed the crystalline nature of PDS. Initial and stability samples of binary mixtures of PDS exposed to 60 °C for two weeks and 40 °C/75% RH for one month showed no changes in diffractograms (Fig. 3B), indicating no changes in physical form of the drug.

DSC thermograms of DFS showed a single melting endothermic peak at 290.1 °C (Fig. 4A and B), which indicated crystalline nature of the drug. Furthermore, there was no peak below or above 100 °C which indicated DFS was anhydrous form. LM showed characteristic peaks at 149.20 (dehydration) and 221.90 °C (decomposition) (α -Monohydrate phase in lactose by DSC, TA Instruments) (Applications Notes Library, 2018). MCC showed broad peak at 100 °C and MGS showed sharp melting endotherm at 127.80 °C. Binary mixtures of the drug with MCC, LM, HPC, MGS or CCS did not show characteristic melting peak of DFS. This might be due to formation of amorphous solid dispersion with excipient on heating. Stability samples stored at 60 °C for two weeks showed no change in the thermograms when compared with initial samples (not shown). On the other hand, samples stored at 40 °C/75%

RH for a month showed two additional peaks at 52.02–53.84 °C and 98.05–112.76 °C. These peaks indicated formation of trihydrate form of the DFS. On heating, trihydrate form loss water of crystallization from the crystal lattice of the drug (Bartolomei et al., 2007). Similarly, the thermogram of PDS showed melting peak at 245.6 °C (Fig. 4C and D). Initial binary mixtures showed melting endotherm of PDS with reduced peak intensity possibly due to dilution of the drug with the excipient in all the samples except with MGS. Binary mixture of MGS and drug did not show melting endothermic peak of PDS possibly due to melting of MGS, which subsequently, dissolved PDS in the melt. Binary mixtures of PDS with excipients showed no changes in the thermograms of the samples stored at 60 °C for two weeks and 40 °C/75% RH for a month when compared with initial samples. These observations indicated no physical and chemical interactions between components of the formulations.

4.2. Characterization of core tablets

The friability of core tablets were less than 1% w/w. The hardness of both DFS and PDS core tablets were 6.0–9.3 and 8.1–8.9 kP, respectively. Disintegration time decreased with a decrease and an increase in HPC and CCS amount in the DFS core tablets, respectively. Disintegration time varied from 36.4 to 5 min in formulations C1 and C7 (Table 1). These DFS core tablet formulations contained 15 and 1.25% HPC. Similarly, formulations of PDS core tablets containing 1.25% HPC were prepared (C8 and C9). Dissolution varied from 72.1 ± 1.6 to $77.1 \pm 1.4\%$ in 45 min in DFS formulations (Fig. 5A), and 79.3 ± 3.2 to $80.1 \pm 2.3\%$ in 30 min in PDS formulations (Fig. 5B). Formulations C7 and C9 were selected as the core tablet formulations. Both formulations released more than 75% drug in 45 and 30 min, respectively.

4.3. Surface morphology

Surface morphology of individual polymer coated tablets varied widely. The tablet surface has smooth surface morphology in C-A-P

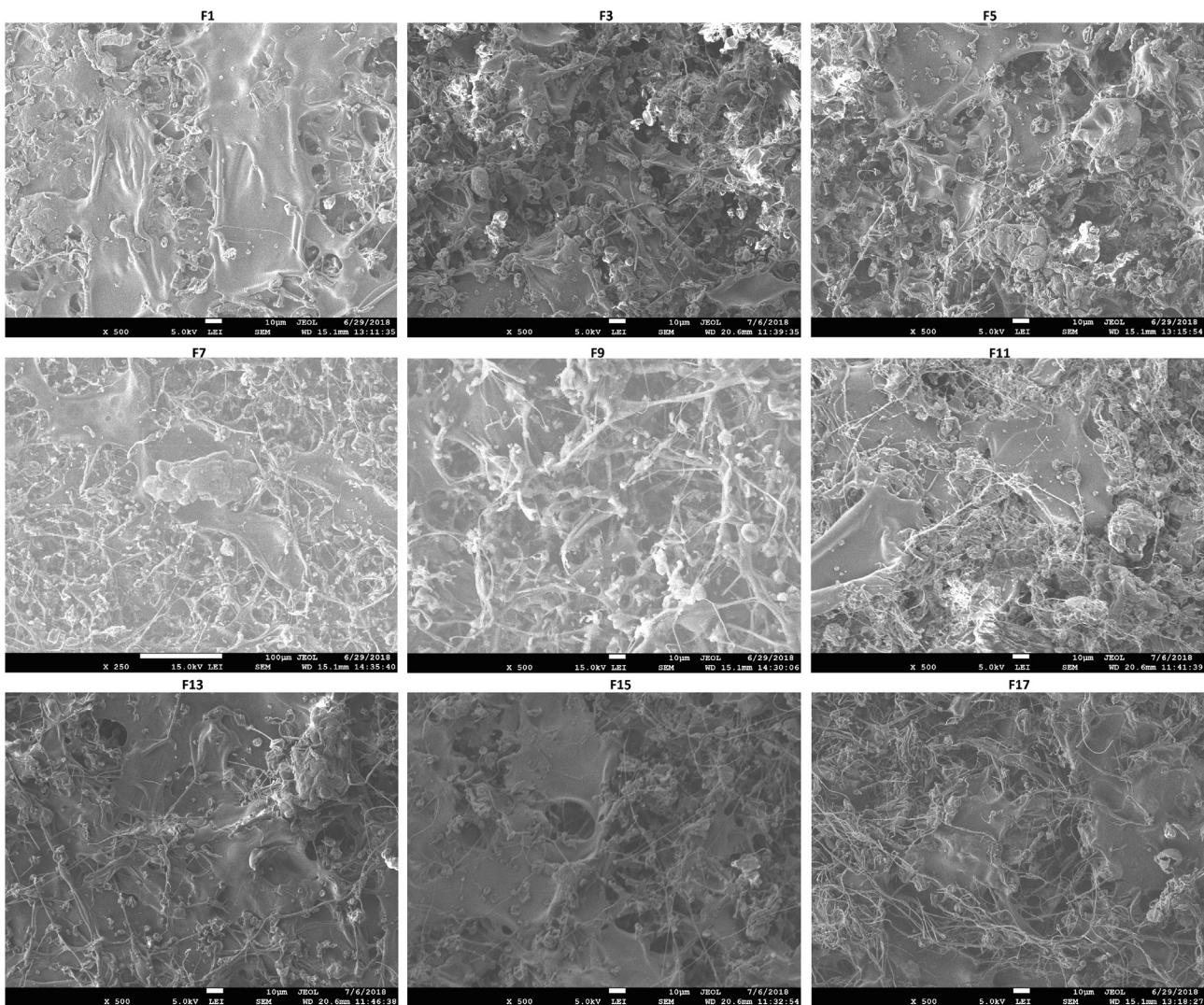


Fig. 7. SEM micrographs of coated tablets with 9:1 cellulose ester and enteric polymers coating formulations.

coated tablets. However, tablet surface has small semi-spherical protrusion with little hole structures, which were possibly formed during solvent evaporation step of coating process. HPMCP HP-55 polymer coated tablets showed smooth and cracked surface while Eudragit® L100 coated tablets showed smooth surface with holes and craters. Tablet surface coated with CA 320S polymer showed smooth surface with few strands of the polymer, and holes and craters. The tablets coated with CA 398-10 or CAB 171-15 showed increased number of fibrous strands compared with tablets coated with CA 320S polymer (Fig. 6). Coating with 9:1 blend of CA 398-10 and C-A-P, HPMCP HP-55 or Eudragit® L100 resulted in improvement in surface morphology. However, no improvement in surface morphology was observed in 9:1 blend of CAB 171-15 and enteric polymer. No significant change in surface morphology was observed in 9:1 CA 320S and enteric polymers blend compared to CA 398-10 based coating blend (Fig. 7). Furthermore, significant improvement in surface morphology was observed in the core tablets coated with 1:1 CA 398-10 or CAB 171-10 and enteric polymers blend. The improvement in surface morphology in CA 398-10 or CAB 171-10 based coating blends with an increased in enteric polymer proportion was due to filling of CA 398-10 or CAB 171-10 polymer strands with enteric polymer. Moreover, no significant changes in surface morphology of core tablets coated with CA 320S based polymer blends were observed (Fig. 8). Unlike CA 398-10 and CAB 171-15, CA 320S polymer produced fewer fibrous strands on the core

tablets. It was possible that fibrous strands, craters or holes on the surface of coated tablets might be produced due to film shrinkage during evaporation, poor flow of the tablets/poor spread of coating solution during coating process due to flat surface or non-optimized amount/type of plasticizer in the formulation and/or process.

4.4. Dissolution of diclofenac sodium coated tablets

Coated tablets were intact during disintegration testing in acid medium, and less than 0.5% drug was released in 0.1 N HCl dissolution medium. Dissolution rates were higher in tablets coated with enteric polymer (C-A-P, Eudragit® L100 or HPMCP HP-55) than those coated with cellulose ester polymer (CA 320S, CA 398-10 or CAB 171-15) (Fig. 9A). Among the enteric polymer coated tablets, drug release was higher in Eudragit® L100 and HPMCP HP-55 than C-A-P coated tablets. These differences in dissolution of enteric polymer coated tablets can probably be explained by pH and solubility of enteric polymer. HPMCP HP-55 dissolves at pH \geq 5.5 (HPMCP, Shin Etsu, 2018). On the other hand, Eudragit® L100 (Eudragit®, Evonik Industries, 2018) and C-A-P (Eastman C-A-P enteric coating material) dissolve above pH 6.0 and > 6.2, respectively. At these pH values, enteric polymer starts to dissolve. We determined approximate solubility of enteric polymers in 20 ml 0.2 M phosphate buffer pH 6.8 by sonicating for 2 min and visually observed the samples for clarity and adding more polymer if

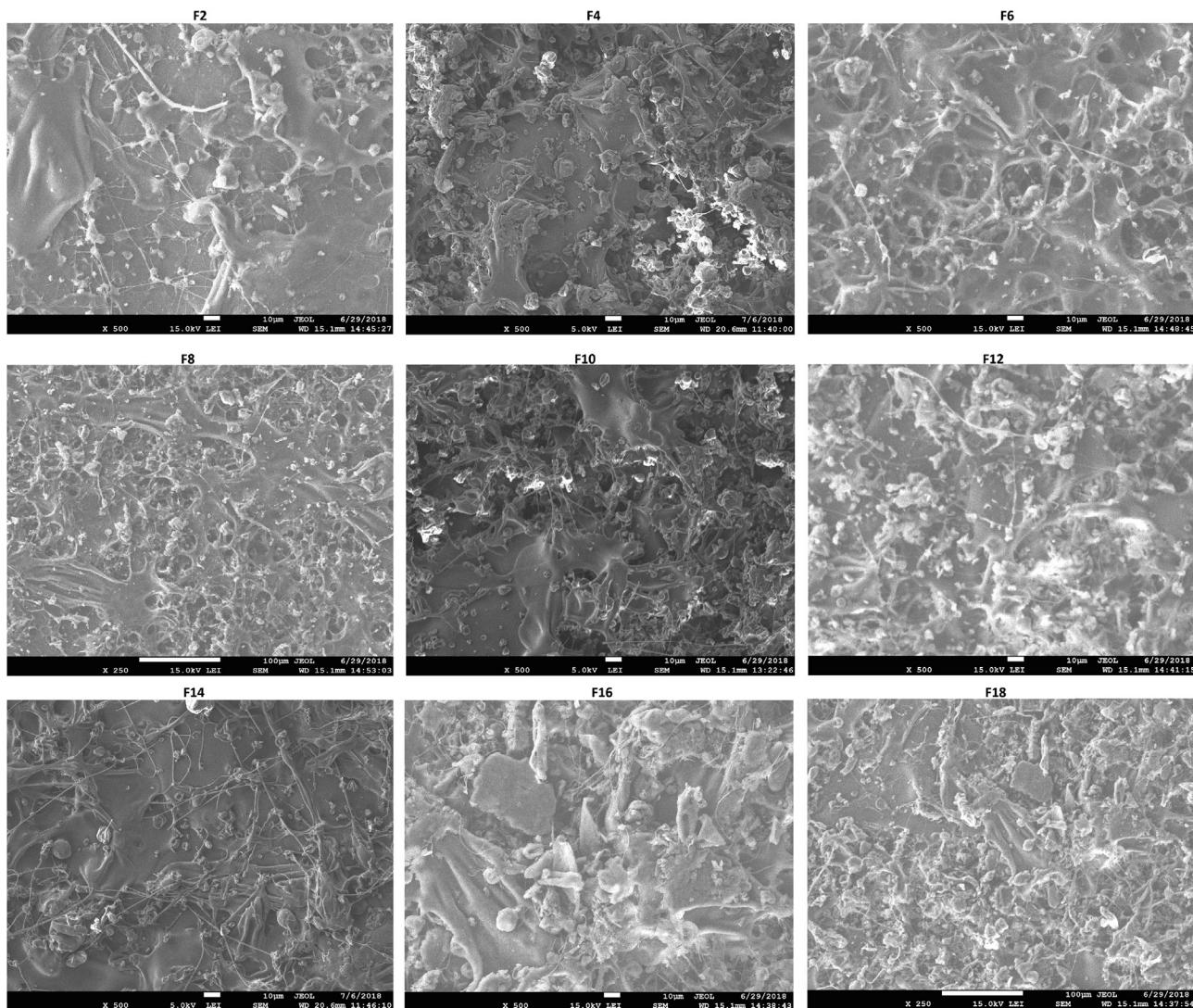


Fig. 8. SEM micrographs of coated tablets with 1:1 cellulose ester and enteric polymers coating formulation.

needed. Eudragit® L100, HPMCP HP-55 and C-A-P solubilities in phosphate buffer pH 6.8 were > 5 mg/mL, < 2.5 mg/mL and < 0.5 mg/mL, respectively. Dissolution profiles of coated tablets correlated well with solubility of enteric polymer. On the other hand, CA 320S, CA 398-10 and CAB 171-15 have pH independent solubility and these form a water-permeable layer. CA 320S and CA 398-10 are chemically cellulose acetate but differ in terms of viscosity, acetyl and hydroxyl contents, and other characteristics such as refractive index, melting point, specific gravity, dielectric strength and Tukon strength etc. CA 398-10 has a high molecular weight with higher acetate (39.8%) and low hydroxyl (3.5%) content that accounts for higher hydrophobicity and viscosity of 38 Poise (Eastman™ CA 398-10) while CA 320S (acetyl and hydroxyl content 32% and 8.7%, respectively) has viscosity of 2.1 Poise (Eastman™ CA 320S). Due to higher hydrophobicity and viscosity of CA 398-10, the rate and extent of dissolution should be lower in tablets coated with CA 398-10 compared to those coated with CA 320S. However, reverse trend was observed. This might be linked to surface morphology of the coated tablets. The tablet surface coated with CA 398-10 had a high number of fibrous strand and holes that explained less intact coating compared to tablets coated with CA 320S (Fig. 6). This allowed deeper and faster penetration of dissolution medium, and subsequently, resulted in higher dissolution in CA 398-10 coated tablets. On the other hand, CAB 171-15 polymer is even more hydrophobic (acetyl, butyl and hydroxyl content are 28-31, 16.5-19 and 0.8-

14%, respectively) and more viscous (57 Poise) (Eastman™ CAB 171-10) than CA 398-10 that suggest a lower dissolution than CA 320S and CA 398-10. However, higher dissolution was observed from CAB 171-15 than CA polymers. This may be due to formation of fibrous strands on the tablets surface that leads to uneven coating and holes on the tablets surface as indicated by SEM data (Fig. 6). These findings also suggest that formulation (shape of tablets, plasticizer type and concentration, and solvent system) and processing parameters need to be optimized for CAB 171-15 and CA 398-10 coating formulations. Core tablets coated with CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP 55 or Eudragit® L100 at 5% w/w weight gain dissolved 33.6 ± 1.0 , 61.9 ± 1.1 , 73.0 ± 1.7 , 76.3 ± 2.1 , 101.0 ± 2.9 and $99.5 \pm 3.4\%$ drug in 120 min, respectively. Coating of core tablets with CA 320S, CA 398-10, CAB 171-15 or C-A-P sustained the drug dissolution compared to core tablets coated with HPMCP HP-55 or Eudragit® L100. As the polymer coating level increased from 5 to 10% of core tablet weight, the amount of dissolved drug decreased (Fig. 10A). It is very well-known phenomenon in coated tablets. As coating amount increases, dissolution decreases due to an increase in time taken to dissolve coating layer if polymer is water-soluble. On the other hands, if polymer is water insoluble, it increases time taken by medium to traverse through coated layer due to increased thickness of coating layer (Spencer et al., 2008; Piao et al., 2010).

Dissolution from cellulose ester and enteric polymer blends

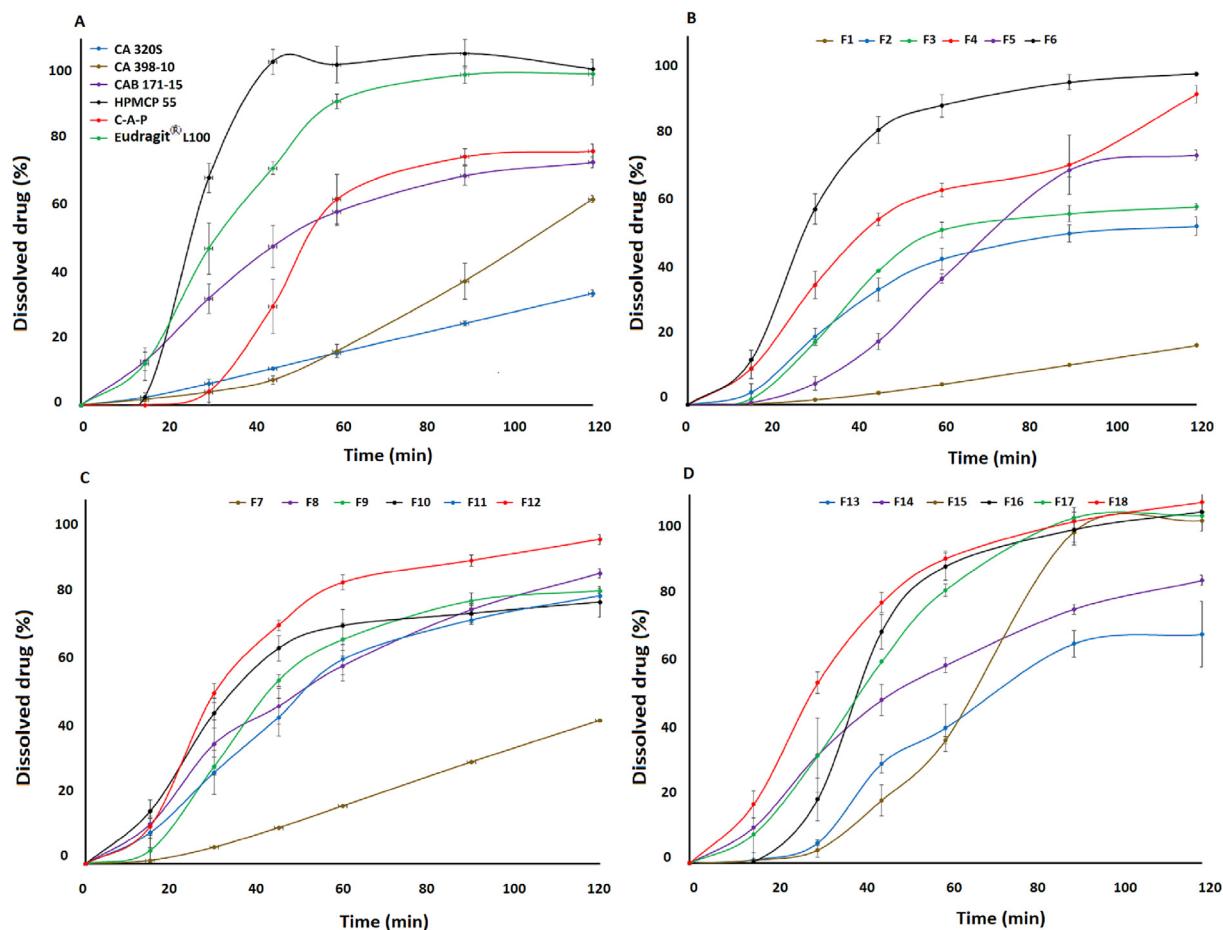


Fig. 9. Dissolution profiles of diclofenac sodium tablets coated at 5% w/w with A) CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP HP-55 or Eudragit® L100, B) cellulose ester and enteric polymers blend F1-F6, C) cellulose ester and enteric polymers blend F7-F12 and D) cellulose ester and enteric polymers blend F13-F18 in 0.2 M phosphate buffer pH 6.8. Data is presented as mean \pm SD, n = 3.

exhibited varied dissolution profiles depending on composition and coating level (Fig. 9B, C and D). Coating formulations based on 9:1 polymers blend of CA 320S and C-A-P, CA 320S and HPMCP HP-55, and CA 320S and Eudragit® L100 released 16.2 ± 2.5 , 39.3 ± 0.3 and $62.2 \pm 8.9\%$ drug in 120 min coated at 5 %w/w weight gain, respectively (Fig. 9B). Dissolution was highest in formulation coated with 9:1 ratio of CA 320S and Eudragit® L100 and lowest in 9:1 ratio of CA 320S and C-A-P, respectively. This can be explained by solubility differences of C-A-P, HPMCP HP-55 and Eudragit® L100 in phosphate buffer pH 6.8. Eudragit® L100 has a higher solubility than C-A-P and HPMCP HP-55 that resulted in faster and increased number of pore formations on the surface of the coated tablet. This increased the access of the dissolution medium to core tablets and thus resulted in higher dissolution than HPMCP HP-55 or C-A-P based blends. SEM micrograph pictures of F1, F3 and F5 (Fig. 11) supported these observations. Formulations F1, F3 and F5 were coated with blend of CA 320S and C-A-P, CA 320S and HPMCP HP-55, and CA 320S and Eudragit® L100, respectively. Dissolution increased as proportion of CA 320S decreased by changing ratio from 9:1 to 1:1 with respect to enteric polymer. Enteric polymer dissolves on the coated film and thus, leaves behind pores on the surface of coated tablets. High proportion of enteric polymer in the coating formulations increased the number of pores on the coated tablets. This was confirmed by SEM pictures of F7 and F8 coated tablets after dissolution (Fig. 11). These formulations represent 9:1 and 1:1 ratio of CA 320S and HPMCP HP-55 blends. Tablets coated at 5% weight gain with 9:1 ratio of CA 398-10 and C-A-P, CA 398-10 and HPMCP HP-55, and CA 398-10 and Eudragit® L100 polymers blends released 53.7 ± 0.9 , 74.9 ± 0.7 and $92.9 \pm 2.9\%$ drug, respectively (Fig. 9C). As

proportion of CA 398-10 decreased from 9:1 to 1:1 with respect to enteric polymer, there were an increase in rate and extent of dissolution in C-A-P based blend, and significant change in rate of dissolution in HPMCP HP-55 and Eudragit® L100 based blend formulations. However, no change in extent of dissolution occurred. Furthermore, percentage of drug released from formulations coated with CA 398-10 and enteric polymer blends was higher when compared with CA-320S and enteric polymer blends. This was probably due to fibrous strands and non-intact film formation. Coating of tablets at 5% weight gain with 9:1 ratio polymers blend of CAB 171-15 and C-A-P, CAB 171-15 and HPMCP 55, and CAB 171-15 and Eudragit® L100 dissolved 67.8 ± 1.5 , 73.6 ± 0.5 and $94.3 \pm 1.4\%$ drug, respectively (Fig. 9D). As the enteric polymer proportion increased while proportion of CAB polymer decreased by changing ratio from 9:1 to 1:1, rate and extent of dissolution increased in C-A-P and HPMCP HP-55 based formulations while only rate changed significantly in Eudragit® L100 blend as the dissolution was almost 95% in 1:1 CAB and enteric polymer blends. Additionally, amount of drug dissolved was higher in CAB and enteric polymer blends compared with CAs and enteric polymer blends. This was possibly due to fibrous nature of CAB that might not have completely covered the tablets matrix, non-uniform coating and/or non-optimized formulation and process parameters. However, powdery/fibrous nature of CAB based coating formulations decreased as the concentration of enteric polymer increased. In all the formulations, dissolution decreased as the coating level increased from 5 to 10% w/w of core tablet weight as observed in tablets coated with cellulose ester or enteric polymer (Fig. 10).

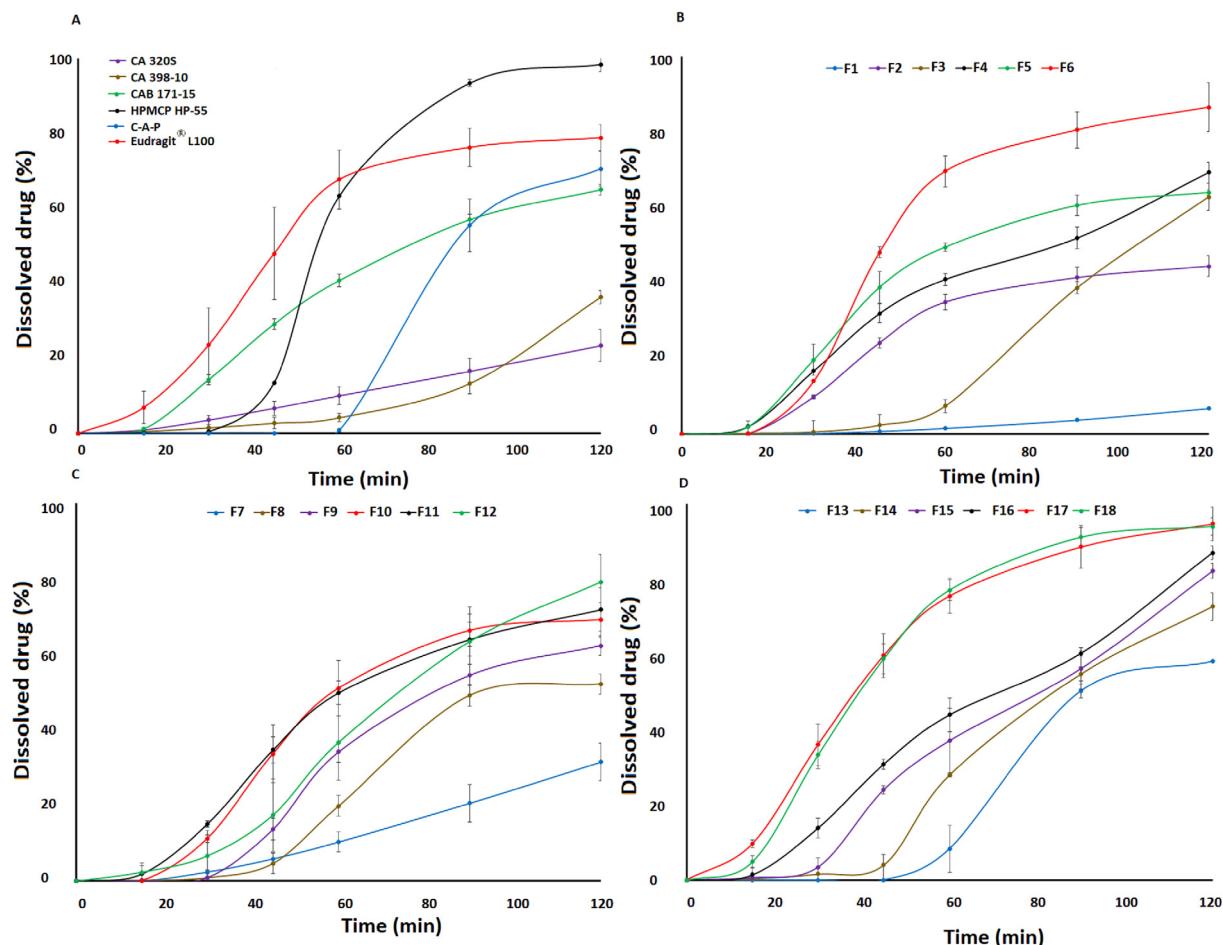


Fig. 10. Dissolution profiles of diclofenac tablets coated at 10% w/w with A) CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP HP-55 or Eudragit® L100, B) cellulose ester and enteric polymers blend F1-F6, C) cellulose ester and enteric polymers blend F7-F12 and D) cellulose ester and enteric polymers blend F13-F18 in 0.2 M phosphate buffer pH 6.8. Data is presented as mean \pm SD, n = 3.

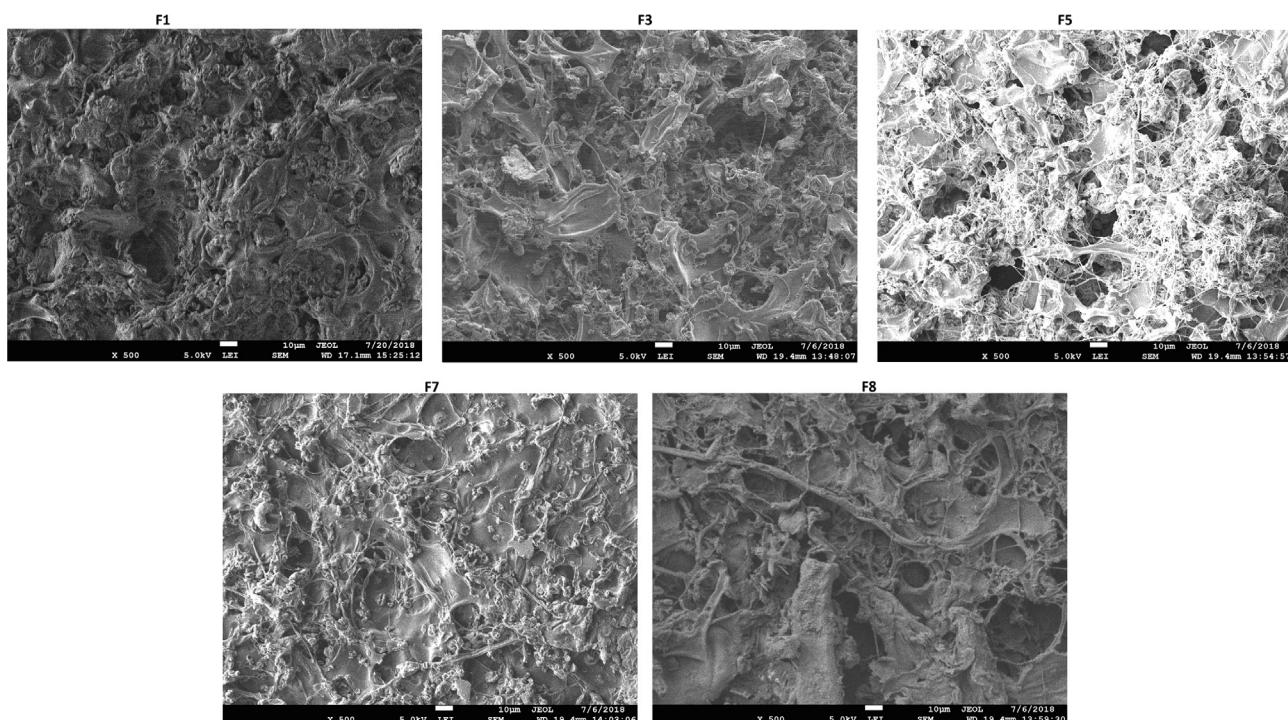


Fig. 11. SEM micrographs of coated tablets after dissolution test in 0.2 M phosphate buffer pH 6.8.

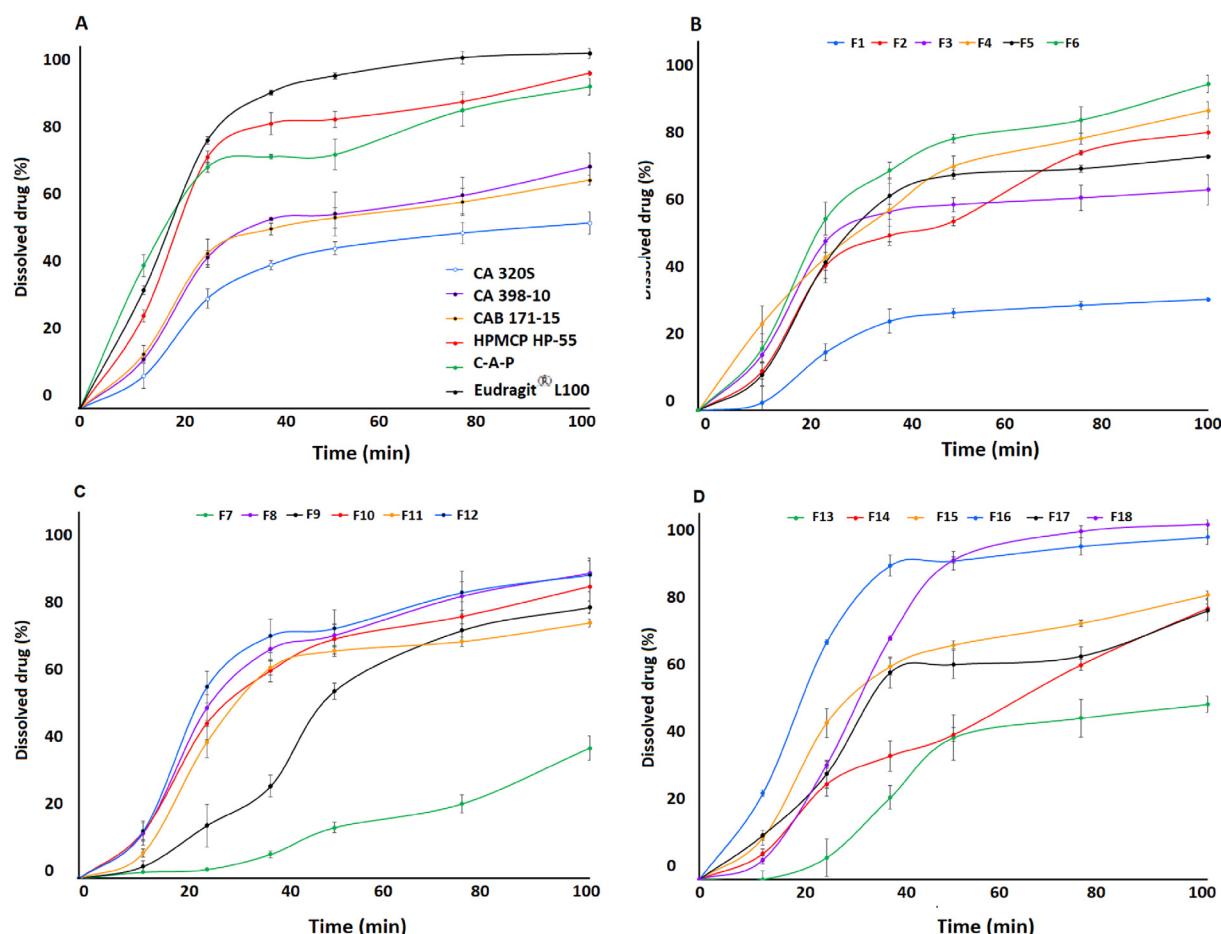


Fig. 12. Dissolution profiles of prednisone tablets coated at 5% w/w with A) CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP HP-55 or Eudragit® L100, B) cellulose ester and enteric polymers blend F1-F6, C) cellulose ester and enteric polymers blend F7-F12 and D) cellulose ester and enteric polymers blend F13-F18 in 0.2 M phosphate buffer pH 6.8. Data is presented as mean \pm SD, n = 3.

4.5. Dissolution of prednisone coated tablets

Similar dissolution trends were observed in PDS core tablets coated with cellulose ester or enteric polymer at approximately 5% (4.4–6.3%) weight gain (Fig. 12). Dissolution was higher in tablets coated with C-A-P, Eudragit® L100 or HPMCP HP-55 compared with CA 320S, CA 398-10 or CAB 171-15. Drug dissolution was at least 22.1% higher in C-A-P, Eudragit® L100 or HPMCP HP-55 coated tablets compared to those coated with CA 320S, CA 398-10 or CAB 171-15 (Fig. 12A). Therefore, dissolution was controlled by solubility of enteric polymer in dissolution medium beside other factors. Enteric polymers are soluble in dissolution medium (phosphate buffer pH 6.8) compared to non-enteric polymers and thus produced higher dissolution. PDS core tablets coated with CA 320S, CA 398-10, CAB 171-15, C-A-P, HPMCP HP-55 or Eudragit® L100 at 5% w/w weight gain dissolved 51.2 \pm 3.1, 66.8 \pm 3.8, 63.1 \pm 1.4, 88.8 \pm 2.3, 92.5 \pm 0.6 and 98.0 \pm 1.4% drug in 120 min, respectively. Higher drug dissolution were observed in CA 398-10 and CAB 171-15 coated tablets even though these polymers have higher viscosity (viscosity for CA 320S is only 2.1 P versus 38 P for CA 398-10, and 57 P for CAB 171-15) and are more hydrophobic than CA 320S. Tablets coated with CA 320S has fuller film coverage of core tablets and less number of holes than CA 398-10 or CAB 171-15 coated tablets (Fig. 6).

PDS core tablets coated with blends of cellulose ester and enteric polymers at 5% w/w weight gain showed dissolution profiles similar to DFS coated tablets. Dissolution was higher in core tablets coated with blend of cellulose ester and Eudragit® L100 (formulations F13-F18) (Fig. 12D) than blend of cellulose ester and C-A-P (formulations F1-F6)

(Fig. 12B) or HPMCP HP-55 (formulations F7-F12) (Fig. 12C). This was due to higher solubility of Eudragit® L100 compared to C-A-P or HPMCP HP-55. Dissolution was 30.1 \pm 0.5, 35.5 \pm 3.3 and 50.2 \pm 2.3% in 120 min in F1, F7 and F13 formulations, respectively. These formulations were coated with blends of CA 320S and C-A-P, CA 320S and HPMCP HP-55, and CA 320S and Eudragit® L100. Furthermore, dissolution increased as cellulose ester to enteric polymer ratio increased from 9:1 to 1:1 in the blends. For examples, dissolution was 30.1 \pm 0.5% in F1 and 75.3 \pm 1.7% in F2. F1 and F2 formulations were coated with blends of CA 320S and C-A-P polymers, and ratio of CA 320S and C-A-P polymers was 9:1 and 1:1, respectively.

5. Conclusion

Core tablets were successfully coated with cellulose esters (CA 320S, CA 398-10 or CAB 171-15) or enteric polymers (C-A-P, Eudragit® L100 and HPMCP HP-55) or their blends. Tablet surface was smooth with few holes and craters coated with CA 320S and enteric polymer blends compared with CAB 171-15 and enteric polymer or CA 398-10 and enteric polymer blend. Dissolution was higher in CAB 171-15 and enteric polymer blends or CA 398-10 and enteric polymer blends compared with CA 320S and enteric polymer blends. Among the enteric polymers used, dissolution was higher in the tablets coated with Eudragit® L100, HMP55 or blends with cellulose esters. Dissolution was fast and slow in the tablets coated with enteric polymer and cellulose polymer alone, respectively. The dissolution of drug from the tablets coated with cellulose ester polymer alone can be increased by incorporating enteric polymer (C-A-P, Eudragit® L100 and HPMCP HP-

55) in cellulose ester polymer (CA 320S, CA 398-10 or CAB 171-15). Conversely, dissolution of drug from enteric polymer alone coated tablets can be prolonged by incorporating cellulose ester polymer. Thus, the blend of cellulose ester and enteric polymers as a coating material provide means to modulate the dissolution profile, which can be used to match a specific dissolution profile. Additionally, modulation of dissolution profile also depend upon cellulose ester, enteric polymer and plasticizer type and ratio and process parameters. Furthermore, it is possible to produce a delayed as well as an enteric coated tablets using polymers blend.

Declaration of Competing Interest

None.

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