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Novel Combination of Anionic and Cationic Polymethacrylate Polymers for Sustained Release Tablet Preparation

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The objectives of this study were to prepare and evaluate a novel sustained release tablet formulation using a binary mixture of polymethacrylate polymers: Eudragit E-100 (EE) and Eudragit L-100 (EL) in their salt forms. Tablets prepared using EE-citrate and EL-Na showed the highest degree of swelling among other combinations of EE and EL. The drug release rates were independent of the pH of the dissolution medium as the release profiles exhibited a continuous release pattern with no burst effect when changing the pH of the medium. These results, along with other test results, indicated the presence of an ionic interaction between both polymers when combined in the salt forms.

Keywords polymethacrylate polymers; wet granulation; swelling; sustained release; pH profile

INTRODUCTION

Most conventional oral tablets are designed to release the drugs immediately after administration resulting in a relatively rapid absorption and high plasma concentration that reaches a maximum and are associated with fast onset of action. However, the initial rise in the plasma drug levels is usually followed by a decline to reach a minimum and the drug looses its therapeutic activity unless another dose is administered to raise the drug plasma levels to the therapeutic range. A substitute for frequent dosing could be the use of a sustained or controlled release tablet that can maintain plasma drug concentrations within therapeutic levels for the desired period of time (Grass & Robinson, 1990). The objective of designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain desired drug blood level. In addition, controlled release dosage forms have been modified to protect drugs from the low pH of the stomach and/or to protect the gastrointestinal tract (GIT) from the irritating effects of drugs (Chien, Cabana, & Mares, 1982).

Modern sustained release dosage forms require reliable excipients to ensure a drug release rate that is reproducible in a narrow range. Eudragit® (polymethacrylates) polymers, which are produced by Pharma Polymers (Darmstadt, Germany), fulfill these requirements to a very high extent and enable the research and development to create tailor-made solutions (Pharma Polymers, 2005). Eudragits are synthetic cationic and anionic copolymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. These copolymers act as polyelectrolytes, which make them suitable for many purposes, from gastric- or intestinal-soluble drug formulations to insoluble but swellable delivery forms, regulated by the number of charged and nonionized groups in the structure of these copolymers. Eudragit polymers have proven to be suitable for a wide variety of pharmaceutical applications and are primarily used in oral capsules and tablets as film-coating agents for protective purposes and to provide sustained release formulations (Ibric et al., 2003; Leopold & Eikeler, 1998; Takka, Rajbhandari, & Sakr, 2001; Vishnubhotla & Himadri, 2000). Depending on the type of polymer used, films of different solubility characteristics can be produced (Rowe, 2005). They are also used as binders in both aqueous and organic wet granulation processes (Pharma Polymers, 2005).

Different types of Eudragits are commercially available and can be obtained as dry powder, granules, aqueous dispersion, or as an organic solution. Some of them are soluble in gastric fluid as well as in weakly acidic buffer solutions up to pH 5 such as Eudragit E (EE), which is a cationic polymer based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters as shown in Figure 1 (Isaac, Russell, & Jean, 1997). Others such as Eudragit L (EL) and Eudragit S (ES) are soluble in neutral to weakly alkaline conditions (pH 6–7) and form salts with alkalis. EL and ES are anionic copolymers based on methacrylic acid and methyl methacrylate (Figure 2). Both EL and

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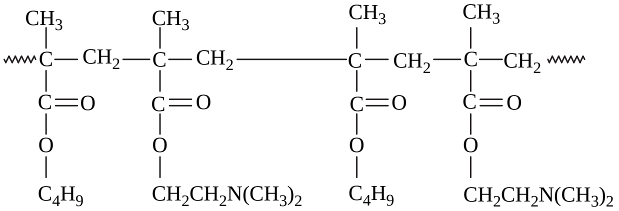

FIGURE 1. Chemical structure of Eudragit E.

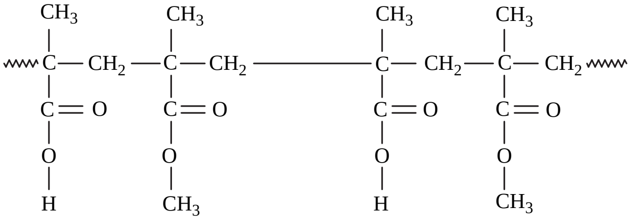

FIGURE 2. Chemical structures of Eudragit L and Eudragit S.

ES enjoy similar physicochemical properties except that the ratio of free carboxyl groups to the ester is approximately 1:1 in EL and approximately 1:2 in ES (Rowe, 2005). They are used as enteric-coating agents because of their resistance to gastric fluid (Di Colo, Falchi, & Zambito, 2002; Fuentes, Arevalo, Gonzalez-Rodriguez, Cirri, & Mura, 2004; Leopold, 1999; Leopold & Eikeler, 1998).

Few papers were devoted to the possibility of involving mixtures of anionic and cationic polymethacrylate polymers in an ionic interaction to prepare new complex (interpolyelectrolyte complex IPEC) that has pH-independent characteristics, which can be used in sustained release solid dosage forms (Kabanova and Mustafin, 2004; Kabanova, Zhdanova, & Moustafine, 2006; Moustafine & Bobyleva, 2006).

In this study, paracetamol was chosen as a model drug. This drug was selected because of its somewhat neutral chemical nature and is expected to possess a minimum, if any, interaction with Eudragit polymers (Omari, Sallam, Abd-Elbary, & El-Samaligy, 2004). The aims of this study were as follows:

1. to prepare a novel controlled release tablet formulation using methacrylic acid copolymers in their salt forms and to evaluate their dissolution properties;
2. to study the release of the drug from matrices formed by EE and EL in their salt form;
3. to study the effect of pH on the release profile of the drug from the controlled release dosage form.

MATERIALS AND METHODS

Materials

The different types of Eudragit polymers of various grades (Eudragit E-PO, Eudragit L-100, and Eudragit S-100) were obtained from Röhm Pharma (Darmstadt, Germany). Methocel® E5, which is a low-viscosity grade of hydroxyl propyl methyl cellulose (HPMC), was obtained from Colorcon (Dartford, Kent, UK). Monobasic potassium phosphate, tribasic sodium phosphate, sodium hydroxide, and glacial acetic acid were provided by Scharlau Chemie (Sentment, Spain). Hydrochloric acid 37% was obtained from Merck (Darmstadt, Germany). Isopropyl alcohol was obtained from Tedia (Fairfield, Ohio, USA). Phosphoric acid 85% was provided by Riedel-de Haen (Seelze, Germany). Lactose monohydrate, citric acid monohydrate, magnesium stearate, and talc were obtained from Hikma Pharmaceutics (Amman, Jordan). Potassium bromide (UVasol®) for Fourier transformed infrared spectroscopy (FTIR) was provided by Merck (Germany). Acetaminophen (Paracetamol) was gifted by Joswe Medicals (Naour, Jordan).

Methods

The Method of Analysis

The analysis for the drug was carried out using the UV/VIS spectrophotometer (Model V-530 Jasco, Tokyo, Japan) at the λ_{max} of the drug, which is 243 nm, using a quartz cuvette cell and against an appropriate blank. All samples were appropriately diluted before reading the absorbance. The absorbance readings were converted to concentration in μg/mL by using an appropriate calibration curve.

Preparation of Matrix Tablets Containing Salt Form of Eudragit Polymers by Wet Granulation Method

The following Eudragit solutions were prepared for the preparation of granules:

- one gram of EE dissolved in 7 g of 0.33 N citric acid solution,
- one gram of EL or ES dissolved in 7 g of 1 N NaOH.

Additional non-salt-forming solutions of Eudragit polymers were prepared for comparative purposes, 1 g of the polymer was dissolved in 7 g of isopropyl alcohol.

The amounts of citric acid or NaOH used were based on the solubility values of EE and EL that were mentioned in the monographs issued by Pharma Polymers (Darmstadt, Germany), which stated that “1 gm of EE dissolves in 7 gm of 1 N HCl, while 1 gm of EL or S dissolves in 7 gm of 1 N NaOH.”

The procedure for granules preparation involved manual blending of the paracetamol with lactose and methocel using a plastic beaker while gradually adding a specified amount of EE, EL, or ES binder solutions until adequate degree of agglomeration was visible. The granules were then dried for 15 min in an oven at 50°C; screened through 3-, 2-, and 1-mm sieves; and each screening was followed by a 15-min drying at 50°C.

For tablet compression, two equal portions of paracetamol/EE granules and paracetamol/EL or paracetamol/ES granules were mixed at a 1:1 ratio. One single portion of the granules was used for formulations containing only one type of Eudragit polymer. The mixture was blended with magnesium stearate and talc for 5 min. The final blend was then compressed into tablets using flat-faced hydraulic single press (Carver®, Wabash, Indiana, USA) at 2,000 kg for 30 s. The diameter of the tablets was 13 mm, the amounts of paracetamol, lactose, and methocel in each tablet were kept constant, and the percentages of magnesium stearate and talc per tablet were kept 0.5% each. The LOD (loss on drying) for all formulas was kept below or close to 1%. Table 1 summarizes the amounts and the percentages of components of the tablets in each formula prepared by wet granulation method. The batch size for the prepared granules was between 30 and 50 g depending on the formula (sufficient to produce 25–40 tablets).

Swelling Studies

The degree of swelling was studied on various formulations in an attempt to explain the mechanism of release of the drug in conditions that simulated the GIT—the first hour in acidic medium (0.1 N HCl, pH 1.2), and then transferred into buffer solution (0.2 N phosphate buffer pH 6.8) (Zaharov, Moustafine, & Kemenova, 2006).

Tablets for swelling study were prepared by compressing 250 mg of polymer carrier (without the drug) using flat-faced manual hydraulic single press at 5,000 kg for 30 s. The polymeric matrix tablet was placed in a tarred basket that was then immersed into the thermostated bath (37°C ± 0.5). The volume of the swelling medium was 40 mL. After every 15 min, the basket was removed from the medium, dried using a filter paper, and accurately weighed. For the determination of equilibrium degree of swelling, a final weighing was performed after 24 h. Three tablets from each formula were used and the mean and standard deviation were calculated. The polymer carrier used for the preparation of tablets were EE/EL powder mixture, EE/ES powder mixture, EE powder, EL powder, ES powder, EE-citrate/EL-Na, EE-citrate/EL, and EE/EL-Na. The polymer combinations were prepared as follows:

- EE-citrate/EL-Na was prepared by thoroughly mixing solutions of EE-citrate with EL-Na and then drying the mixture completely at 50°C. The resulting film was then crushed and grinded to powder and then compressed.
- EE-citrate/EL was prepared by thoroughly mixing solutions of EE-citrate with EL-isopropyl alcohol and then drying the mixture completely at 50°C. The resulting film was then crushed and grinded to powder and then compressed.
- EE/EL-Na was prepared by thoroughly mixing solutions of EE-isopropyl alcohol with EL-Na and then drying the mixture completely at 50°C. The resulting film was then crushed and grinded to powder and then compressed.

The ratio of Eudragit mixtures was 1:1 and the degree of swelling (H%) was calculated as

$$H\% = \frac{m_2 - m_1}{m_1} \times 100,$$

where m_1 is the weight of the dry sample and m_2 is the weight of the swollen samples (Zaharov et al., 2006). Statistical analysis using one-way analysis of variance (ANOVA) test was also carried out to check whether the difference in the degree of swelling for various formulas was significant. The confidence limit was set at 95%.

Drug Release Studies

Dissolution tests were performed using Electrolab USP basket dissolution apparatus (TDT-08L, Mumbai, India) with autosampler accessories (peristaltic pump, temperature controller, and fraction collector) according to the rotating basket method described in USP XXVIII (Apparatus I). The rotating speed was 100 rpm and the temperature was 37 ± 0.5°C. The volume of the dissolution medium was 1,000 mL. The dissolution media used were distilled water pH 6.5, 0.1 N HCl pH 1.2, and 0.2 N phosphate buffer pH 6.8. The effect of pH profile on the release of paracetamol from matrix tablets having mixture of Eudragit polymers was also investigated. The release of the drug was investigated at three different stages—the first stage lasted for 1 h at pH 1.2 and the volume of the dissolution medium was 500 mL. The second stage was conducted at pH 5 for 2 h. The volume of the dissolution medium in the second stage was increased to 740 ± 5 mL by adding about 235 mL of tribasic sodium phosphate (Na_3PO_4), and the pH was adjusted using NaOH or phosphoric acid. The final stage was conducted for 5–24 h, and the pH was adjusted to 6.8 by adding about 80 mL of tribasic sodium phosphate and completing the volume of the dissolution medium to 1,000 mL using distilled water. Tribasic sodium phosphate solution was prepared by dissolving 190 g of Na_3PO_4 powder in 5 L of distilled water.

At appropriate time intervals, 10 mL of samples were withdrawn and replaced with an equal volume of fresh dissolution medium. Samples were filtered, diluted, and analyzed spectrophotometrically at λ_{max} = 243 nm. Three tablets from each formulation were subjected to the dissolution test, and the results were given as the mean values of three determinations, standard deviation, and coefficient of variation (*RSD*). The duration of the study ranged from 8–24 h or until the cumulative drug release reached 90–100%. The percentage of drug released was plotted versus time. Preliminary experiments had shown that Eudragit polymers did not interfere with the quantization of the model drug.

Physical Tests

Crushing Strength (Hardness). Ten tablets from each formula were tested using tablet hardness tester (Model Pharmatron 8M® Tablet Tester, Solothum, Switzerland).

Thickness and Diameter. Thickness and Diameter for all tablets were determined using an electronic digital caliper (Model LTF 327.01 LTF, Bergamo, Italy). Measurements were taken up to two decimal points.

Moisture Content. The moisture content of the freshly prepared powders and granules was calculated using Halogen moisture analyzer (Model HR 85 Halogen Mettler, Toledo,

TABLE 1

Composition of Tablet Formulations Prepared by Wet Granulation Method Using Eudragit Polymers in the Salt Form and the Physical Properties for These Tablets

		Formula No.																	
		1		2		3		4		5		6		7		8		9	
No.	Name	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)	mg/tab	% (wt/wt)
1	Paracetamol	233.92	47.14	233.92	46.32	233.92	46.32	233.92	46.32	233.92	44.79	233.92	44.03	233.92	41.03	233.92	43.86	233.92	44.21
2	Lactose	233.92	47.14	233.92	46.32	233.92	46.32	233.92	46.32	233.92	44.79	233.92	44.03	233.92	41.03	233.92	43.86	233.92	44.21
3	Methocel	23.392	4.71	23.39	4.63	23.39	4.63	23.39	4.63	23.39	4.48	23.39	4.4	23.39	4.1	23.39	4.39	23.39	4.42
4	Mg stearate	2.5	0.5	2.5	0.5	2.5	0.5	2.5	0.5	2.59	0.5	2.63	0.5	2.82	0.5	2.64	0.5	2.62	0.5
5	Talc	2.5	0.5	2.5	0.5	2.5	0.5	2.5	0.5	2.59	0.5	2.63	0.5	2.82	0.5	2.64	0.5	2.62	0.5
6	EE-citrate			4.39[a]	0.87			4.39[a]	0.87	12.94[b]	2.48	18.45[c]	3.47	38.81[d]	6.81	36.86[e]	6.91		
7	EE-isopropyl alcohol					4.39	0.87												
8	EL-isopropyl alcohol			4.39	0.87														
9	EL-Na					4.39[f]	0.87	4.39[g]	0.87	12.94[g]	2.48	16.31[h]	3.07	34.37[i]	6.03			32.61[j]	6.16
10	H_2O	q.s.																	
	Total (mg)	496.23	100	505.01	100	505	100	505	100	522.29	100	531.25	100	570.05	100	533.37	100	529.08	100
	Tablet diameter (mm)	13.07		13.02		13.08		13.08		13.09		13.09		13.05		13.09		13.08	
	Tablet thickness (mm)	3.05		3.02		3.06		3.09		3.17		3.24		3.39		3.23		3.23	
	Tablet hardness (N)	76		70		55		58		90		105		147		93		72	

[a] Equivalent to 3.02 mg of Eudragit E (EE).
[b] Equivalent to 8.20 mg of EE.
[c] Equivalent to 12.94 mg of EE.
[d] Equivalent to 27.26 mg of EE.
[e] Equivalent to 25.87 mg of EE.
[f] Equivalent to 3.46 mg of Eudragit L (EL).
[g] Equivalent to 10.24 mg of EL.
[h] Equivalent to 12.94 mg of EL.
[i] Equivalent to 27.26 mg of EL.
[j] Equivalent to 25.87 mg of EL.
q.s. = L.quantum satis or sufficient quantity.

Switzerland). One gram of the powder or granules was placed on an aluminum pan and the analysis was run automatically at 105°C for 1–2 min or until the weight of the sample is stabilized.

FTIR. The interaction between EE and EL was studied using FTIR. The measurements were performed on EE and EL and on a 1:1 physical mixture of EE and EL in the powder form. The IR absorption spectra of the samples pelletized with KBr were measured using FTIR spectrophotometer (Model 8400S Shimadzu, Japan). Samples were dried at 40°C for 24 h before analysis.

RESULTS AND DISCUSSION

Analytical Method Validation

The UV scanning of paracetamol showed a maximum absorbance at 243 nm as shown in Figure 3. There was no shifting in λ_{max} for the drug at various pH values. The calibration curves of paracetamol was linear in different dissolution media at various pH values, the correlation coefficient (r^2) was higher than .99990. No significant peaks for EE, EL, and ES polymers were observed in the UV range of 200–400 nm.

Swelling Studies

It is well known that the release properties of polymeric carriers can be somehow predicted by determination of their swelling characteristics (Zaharov et al., 2006). A comparative analysis of the swelling characteristics of these polymer carrier matrix systems is shown in Figure 4.

Tablets Containing Either EE, EL, or ES

Tablets containing only EE were already dissolved after 30 min in acidic medium by protonating the dimethylamino groups in its structure as EE is a basic polymer and its pK_a is well above the pH of the medium. Oppositely, tablets prepared from EL or ES swelled in the acidic medium up to 200 and 100%, respectively. However, when they were transferred into phosphate buffer medium pH 6.8, they immediately started dissolution at different rates because of the deprotonation of their carboxylic acid groups as the pH of the environment is greater than the pK_a of the carboxylic acid groups in EL and ES polymers. Because ES has fewer carboxylic acid groups than EL, the pK_a of ES is about which is higher than that of EL, thus, more hydration occurs in case of EL than ES, and EL was more soluble than ES at pH 6.8, and consequently, tablets containing ES were swelled to a slightly smaller extent than EL and disintegrated at longer time.

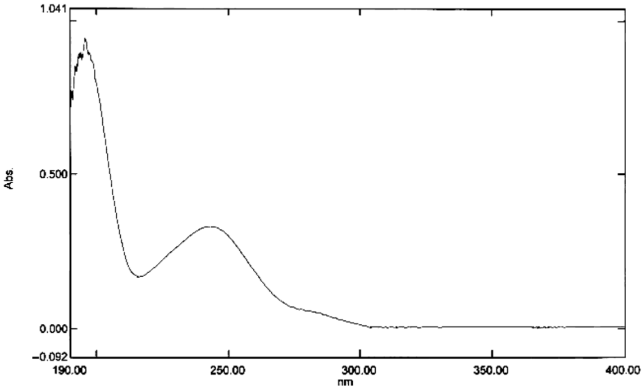

FIGURE 3. The UV scanning of paracetamol solution. The maximum absorbance occurs at 243 nm.

Tablets Containing Either EE/EL or EE/ES

Tablets containing a mixture of EE/EL or EE/ES showed insignificant difference in their swelling behavior ($p > .05$): a slight increase in weight and volume up to 90% after 15 min, but disintegrated rapidly afterward. When tablets were transferred into the buffer medium pH 6.8 after spending 1 h in the acidic medium, only EE/EL tablets showed a second increase in weight to 30%, whereas EE/ES tablets were completely disintegrated. This could be due to the larger degree of ionization of the carboxylic acid groups in EL compared to ES in the buffer medium, thus the possibility of an interaction with the swelled and positively charged EE is high. However, this interaction was kept at minimum level because only one polymer was ionized in one medium at a time and the other was not, thus no significant interpolymer interaction was present.

Tablets Containing EE-Citrate/EL, EE/EL-Na, or EE/ES-Na

Tablets containing one of Eudragit polymers in the salt form (as citrate salt for EE or sodium salt for either EL or ES) exhibited a swelling behavior different from the previous tablets. Unlike EL that is unionized in the acidic medium, the dimethylamino groups of EE were already ionized for tablets containing EE-citrate/EL. The charge density on the polymer increased slightly and the degree of swelling was increased up to 80% because of repulsion of the bulky quaternary groups. During this stage, EE dissolved leaving EL as a major polymer in the matrix. When tablets were transferred into the buffer medium pH 6.8, the carboxylic acid groups of EL were ionized as its pK_a was below the pH of the medium, providing repulsive forces for slight swelling before it was dissolved completely. However, a certain degree of interaction took place between the two polymers resulting in a longer disintegration time up to 3 h. Tablets containing EL as sodium salt (EE/EL-Na) exhibited an initial swelling behavior in acidic medium, where EE became protonated and might have interacted with the salt form of EL. By the end of the acid stage, EE was dissolved leaving EL-Na as a major polymer in the matrix. When tablets were transferred into the buffer medium pH 6.8, EL-Na was already ionized providing repulsive forces for slight swelling before it dissolved completely.

Tablets Containing EE-Citrate/EL-Na

Tablets containing both polymers as salts (EE-citrate/EL-Na) were ionized in all dissolution media, thus possible interaction between the positively and the negatively charged polymers was

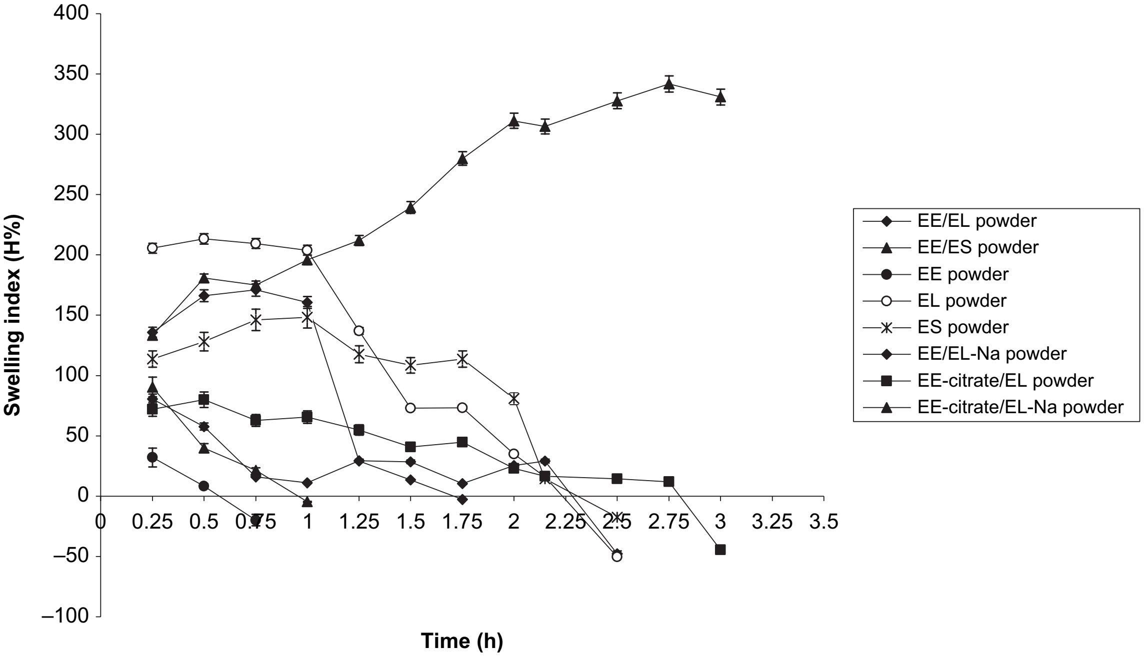

FIGURE 4. The swelling indices (*H*%) plotted against time for various formulations containing different types of Eudragit polymers. The ratio of polymers in mixtures is 1:1.

highly favored. These tablets showed the highest swelling index that was increased linearly throughout the swelling study until they reach an equilibrium value of about 350%. This swelling was probably due to the formation of a cross-linked matrix containing sufficient voids for swelling. In addition, both polymer structures might be changed to a more extended chain form. The continuous rise in swelling for EE-citrate/EL-Na tablets can be further justified as follows: when the tablets come in contact with acidic medium, the free dimethylamino groups were charged by protonation while increasing the charge density on the polymer and cause a change on the polymer structure to a more extended chain form. Later, when the tablets were immersed into buffer medium, the free carboxylic acid groups were ionized while EE retained most of its charge because of salt formation with citrate ions. This will lead to further increase in charge density and polymer chain extension and consequently an increase in the degree of swelling.

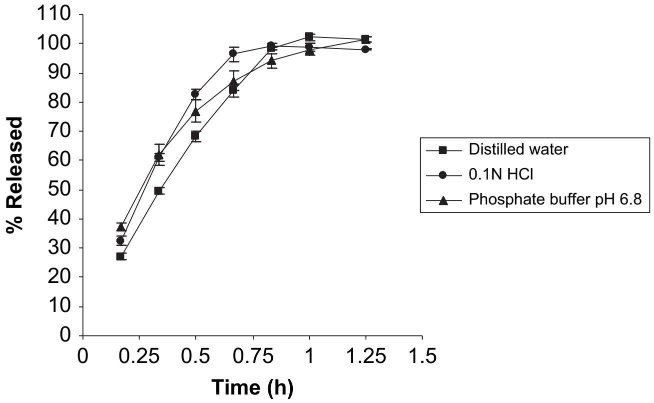

FIGURE 5. Drug release profiles of paracetamol formula 1 in three different media (distilled water pH 6.5, 0.1 N HCl pH 1.2, and phosphate buffer pH 6.8).

Drug Release Studies

A hypothesis of possible interaction between anionic and cationic polymers was suggested to control the release of drugs from matrix systems, mainly by restricting and regulating the diffusion of the drug from such matrices. To study the effect of Eudragit polymers on the release of paracetamol from matrix tablets, paracetamol formulation that is devoid of Eudragit polymers was prepared for comparative purposes (formula 1). The release profile of paracetamol from this tablet formulation is shown in Figure 5. The release behavior of paracetamol did not vary much in the three media because paracetamol is a weak acidic drug with a pK_a 9.51; therefore, it was not ionized in acidic, basic, or neutral media. The solubility of paracetamol in the acidic medium was similar to that in basic medium, but it was slightly lower in distilled water as mentioned in the literature (about 14 mg/mL in distilled water, 20.2 mg/mL in 0.1 N HCl, and 20.5 mg/mL in phosphate buffer pH 6.8) (Shaw, Irwin, Grattan, & Conway, 2005; Siepmann, Streubel, & Peppas, 2002; University of the Sciences in Philadelphia, 2005). Thus, the release of paracetamol from matrix tablet can be considered to be independent of its solubility.

To investigate the validity and the applicability of the aforementioned hypothesis on a cationic polymer EE and an anionic polymer EL, several tablet formulations containing mixtures of the salt forms of these polymers in a 1:1 ratio were prepared by wet granulation method. Other tablet formulations containing either a single polymer or combinations of polymers were also prepared for elucidation of the mechanism of interaction and drug release. The effect of pH and the formulation variables on the drug release profiles were also investigated.

Tablets Containing EE-Citrate/EL

The release rate of paracetamol from matrix tablet containing 1.74% wt/wt of EE-citrate/EL (formula 2) was faster in acidic medium than in buffer or distilled water medium (Figure 6), reaching 100% after 1.5 h. This is because when the tablets were immersed in acidic medium, EE, having dimethylaminoethyl group which is a tertiary amino group as its major functional group, became soluble because of the protonation of the amino groups as EE is a basic polymer and its pK_a is well above the pH of the medium. This would lead to a fast release of the drug from the matrix although EL was acting as film barrier that can—to some extent—control the release of the drug. In phosphate buffer medium pH 6.8, EL became soluble by deprotonation of its carboxylic groups as Eudragit L is an anionic polymer and its pK_a is below the pH of the medium. At the same time, some EE will be precipitated as it was soluble only at a pH lower than 5. However, because EE was prepared as salt having certain degree of ionization, an interaction between the two polymers was more pronounced in buffer than in acidic medium, and consequently, an insoluble complex could be formed. Such a complex would act as a barrier and sustain the release of the drug.

Tablets Containing EE/EL-Na

The release profile of paracetamol from 1.74% wt/wt EE/EL-Na matrix tablet (formula 3) is shown in Figure 7. In this formula, EL was already ionized by salt formation upon granulation during the tableting process. When the tablets came into contact with the acidic medium, EE became ionized by protonation as its pK_a is above the pH of the medium. Yet, a possible ionic interaction between the oppositely charged polymers took place rendering the matrix system more hydrophobic in nature, which might be responsible for regulating drug release at this stage. When the dissolution was carried out in buffer medium pH 6.8, EL dissolved and carried a negative charge while EE precipitated and swelled without being ionized with a minimum interaction was observed and the drug was released by diffusion. The pH release profile was significantly different from that of formula 2, suggesting possible interaction in early stages.

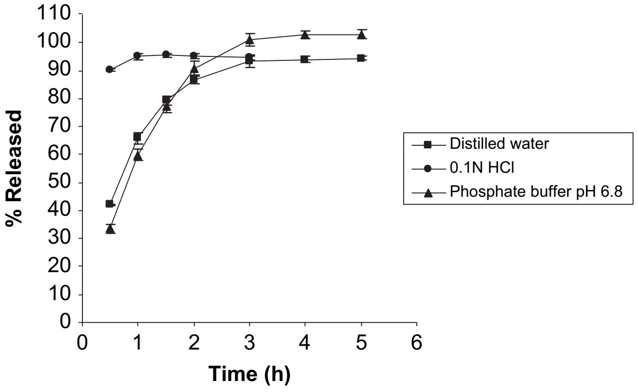

FIGURE 6. Drug release profiles for paracetamol formula 2 [Eudragit E (EE)-citrate/Eudragit L (EL) 1.74% wt/wt] in three different media (distilled water pH 6.5, 0.1 N HCl pH 1.2, and phosphate buffer pH 6.8).

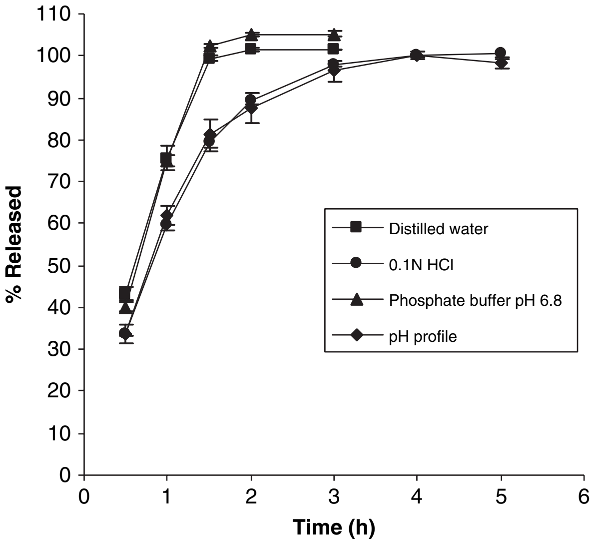

FIGURE 7. Drug release profiles for paracetamol formula 3 [Eudragit E (EE)/Eudragit L (EL)-Na 1.74% wt/wt] in three different media (distilled water pH 6.5, 0.1 N HCl pH 1.2, and phosphate buffer pH 6.8) in addition to pH release profile.

The dissolution profiles of formulas 2 and 3 in distilled water were interesting. The drug release rate was slightly higher for formula 3. This can be attributed to the ability of water to partially deprotonate the carboxylic acid groups in EL in formula 2 and thus favoring its interaction with EE-citrate. This behavior can be further explained as follows: in EE-citrate/EL combination, EE-citrate was dissolved within the matrix system while EL was hydrated and swelled. Yet, the carboxylic groups on EL created a weak interaction on the surface of particles with the amino group on EE in a manner similar to that found in adsorption chromatography causing hindrance of the leaching of EE-citrate from the matrix system to the surrounding environment forming a barrier and slowing the release rate of the drug from tablets. Nevertheless, this interaction seemed to be stronger than the interaction found in EE/EL-Na combination (formula 3) because the results of dissolution profiles in distilled water showed that paracetamol was released faster from EE/EL-Na tablets.

Tablets Containing EE-Citrate/EL-Na

Tablets containing 1.74% wt/wt of EE-citrate/EL-Na (formula 4) showed the best control on the drug release profile among the three previous formulas. This is apparently due to the

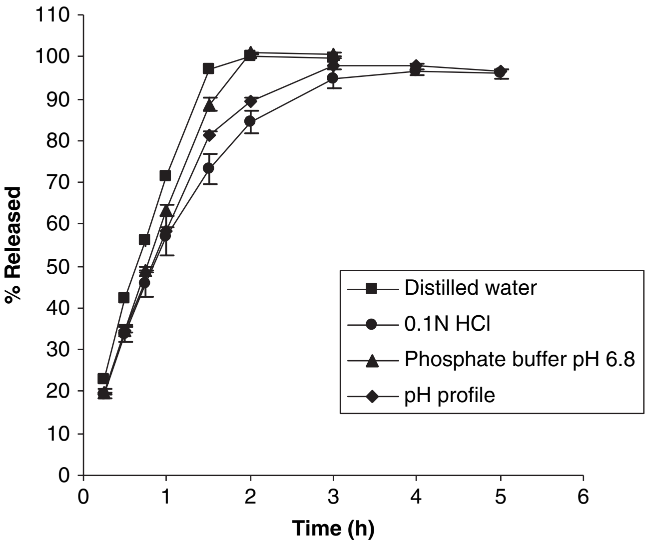

FIGURE 8. Drug release profiles of paracetamol formula 4 [Eudragit E (EE)-citrate/Eudragit L (EL)-Na 1.74% wt/wt] in three different media (distilled water pH 6.5, 0.1 N HCl pH 1.2, and phosphate buffer pH 6.8) in addition to pH release profile.

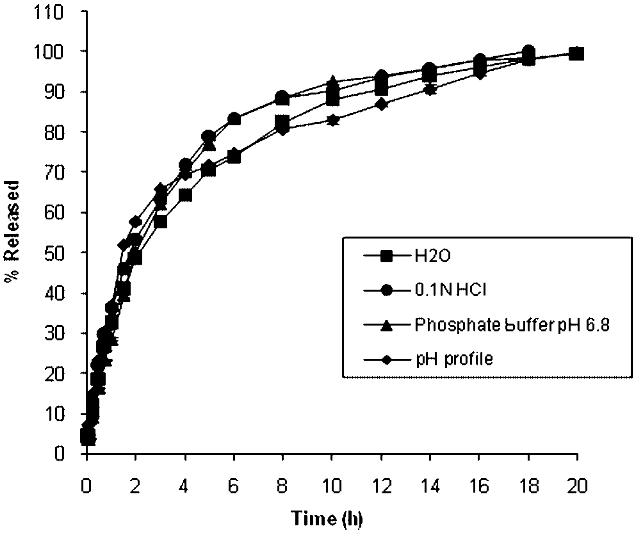

FIGURE 9. Drug release profiles of paracetamol formula 7 [Eudragit E (EE)-citrate/Eudragit L (EL)-Na 12.84% wt/wt] in three different media (distilled water pH 6.5, 0.1 N HCl pH 1.2, and phosphate buffer pH 6.8) in addition to pH release profile.

high degree of interaction that could exist as both polymers were ionized and maximum level charge density was obtained especially in acidic and buffer media (Figure 8). The interaction between the two polymers took place in distilled water because they were present as salts. It was observed that the effect of the acidic stage on EE-citrate/EL-Na tablets was very critical as shown by the two profiles of acid and the pH profile as being slowest and more sustained than in buffer or distilled water media. As the content of EE-citrate/EL-Na mixture per tablet was increased from 1.74 to 12.84% (equivalent to 10% wt/wt of Eudragit polymers in the base form) (formulas 7), the release profile became more linear as shown in Figure 9. It was observed that the variability in the release profiles for the formula 7 in different dissolution media was kept at minimum levels suggesting the formation of ionic compound between EE-citrate and EL-Na that had pH-independent characteristics and provided sustained release effect with highest compressibility.

Figure 10 shows the relationship between the percentage of EE-citrate/EL-Na and the release rate. The release rate was calculated from the slope of Korsemeyer and Peppas equation. As the percentage of EE-citrate/EL-Na increased, the drug release rate decreased. This might be due to the increase of the microviscosity and the hardness of the tablet through the formation of thick film around the granules that made it difficult for drug molecule to penetrate and diffuse. The release profiles for all the formulations were curvilinear except for formula 4 in buffer and distilled water media where the release profile was linear up to about 90%. A sharp drop in the release rate was observed up to about 5% wt/wt of the polymer followed by a less steep decrease from 5 to 13% wt/wt of the polymer. However, the retardation was still prominent at higher concentrations of the polymers.

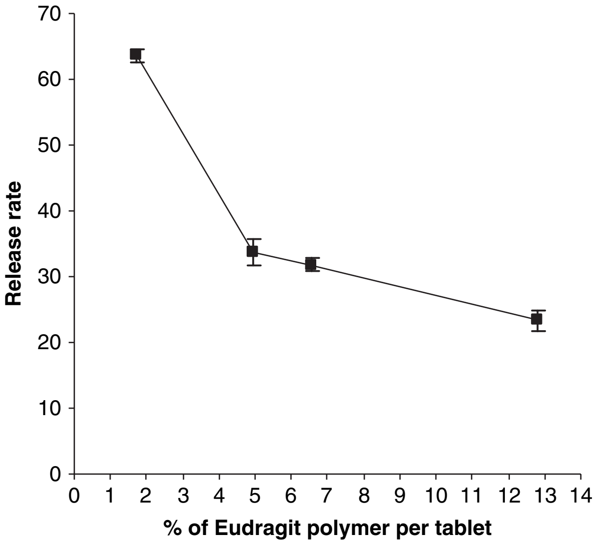

FIGURE 10. Plot of the percentage of Eudragit E (EE)-citrate/Eudragit L (EL)-Na per tablet versus the release rate of drug.

Tablets Containing EE-Citrate/ES-Na

For more investigation of the presence of ionic interaction between EE and EL in salt forms, EL-Na in formulas 4, 5, and 6 was replaced with ES-Na that has fewer number of carboxylic acid groups than EL-Na. The results showed that there were no significant differences in the drug release profiles in acidic medium, and in the acidic stages in pH release profile, both EL and ES salts have very slight solubilities in acidic medium. However, in phosphate buffer pH 6.8 medium, the rate of drug release from tablets containing ES-Na was slower than that containing EL-Na. This might be due to the lower solubility of ES-Na compared to EL-Na due to fewer anionic sites for the interaction with the dissolution medium. Furthermore, it seemed that the high viscosity of ES-Na compensated for the weak ionic interaction with EE-citrate.

Tablets Containing Either EE-Citrate or EL-Na

In a second set of formulations, paracetamol tablets containing only one type of Eudragit polymers as a salt in their matrix system were used; EE-citrate or EL-Na were prepared (formulas 8 and 9, respectively). The amount of Eudragit polymers as base per tablet was 5% wt/wt. Tablets containing only EE-citrate were rapidly dissolved in the acidic medium, as well as in water at neutral pH. Tablets that contain only EL-Na were insoluble in acid medium, that is, resistant to gastric fluid, and soluble only in neutral to weakly alkaline medium. The pH profile showed rapid increase in the release rate when the pH of the dissolution medium was changed from acidic to alkaline medium unlike the pH profiles for tablets containing combination of EE-citrate with either EL-Na or ES-Na.

Comparing the results from formulas 8 and 9 to those of formula 6 (EE-citrate/EL-Na at 5% wt/wt) as shown in Figure 11, strongly supports the hypothesis of the presence of an ionic interaction between EE-citrate and EL-Na.

Based on the acid and alkali values of Eudragit polymers, there are excess citric acid and NaOH in the polymer solutions. Compared to tablets prepared without excess citric acid and NaOH showed that the presence of these salts has insignificant effect on the drug release profiles (data not shown).

Models of the drug release were fitted to the data obtained from the pH release profiles of paracetamol for all formulas. The best-fitted model was Peppas and Korsemeyer model (the power law) (Costa et al., 2001; Korsmeyer, Gurny, Doelker, Buri, & Peppas, 1983):

$$\frac{Q_t}{Q_\infty} = k \cdot t^n,$$

where Q_t and Q_∞ are the amounts of drug released at time t and at the end of dissolution test, respectively, k is a constant incorporating the properties of the macromolecular polymeric systems and the drug, and n is a kinetic constant that is used to characterize the transport mechanism. It was observed from Peppas and Korsemeyer model that the n value was higher than 0.45 in all formulas indicating that the diffusion transport of the drug was not the only factor controlling the drug release, and in this case the release was non-Fickian or anomalous, this suggested that other events occurred during drug diffusion process such as matrix swelling, dissolution, and erosion that might contribute to the overall release mechanism. However, the release rate decreased with time because of the increase in the diffusion path length of the drug. The change in diffusion path length was not only because of the gradual depletion of the drug from the matrix but also because of the moving boundaries such as swelling and erosion.

When formula 4 was subjected to accelerated stability test at 50°C for 5 days, the drug release profiles for these tablets were almost identical to those analyzed at room temperature at all time intervals in all the three dissolution media with similarity factor reaching up to 97.58, indicating that no reaction occurred within the components of the tablets when placed under extreme conditions for 5 days as shown in Figure 12.

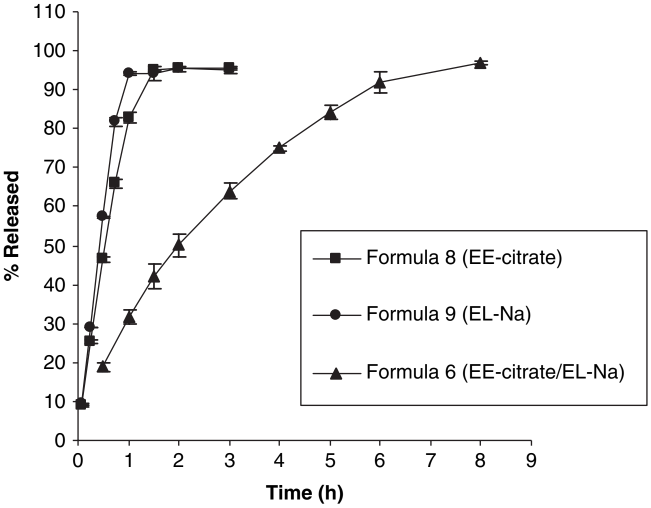

FIGURE 11. Comparison of paracetamol release profiles from formulas 6, 8, and 9 in phosphate buffer pH 6.8.

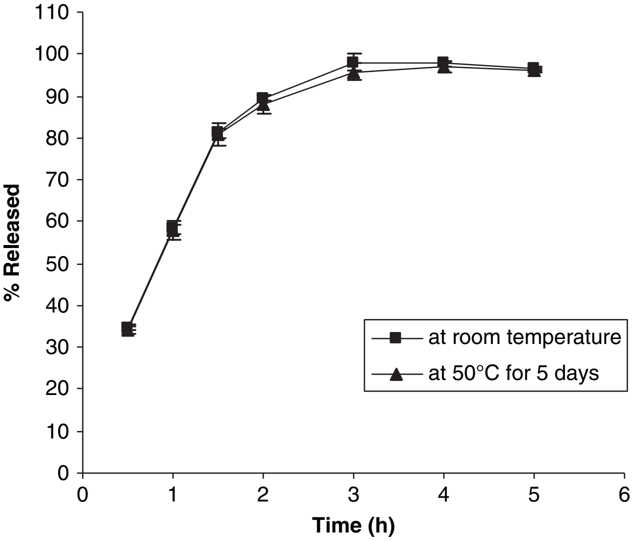

FIGURE 12. Comparison of the pH release profile for paracetamol from formula 4 [Eudragit E (EE)-citrate/Eudragit L (EL)-Na 1.74% wt/wt] analyzed at room temperature and after subjecting the tablets to extreme conditions at 50°C for 5 days.

FTIR Analysis

Figures 13 shows the FTIR spectra of EE powder, EL powder, and EE/EL physical mixture in a 1:1 ratio. As EE and EL belong to the same class—they are derivatives of methacrylic acid copolymers—the FTIR spectra would exhibit many common features. EE showed characteristic band at 1,728 cm^{-1}, which corresponds to absorption of ester groups in addition to two more absorption bands at 2,769 and 2,823 cm^{-1}, which corresponds to the optical absorption because of nonionized dimethylamino groups. On the contrary, the spectrum of EL showed similar but broader absorption band for the nonionized carboxylic acid groups at 1,728 cm^{-1} than that found in EE

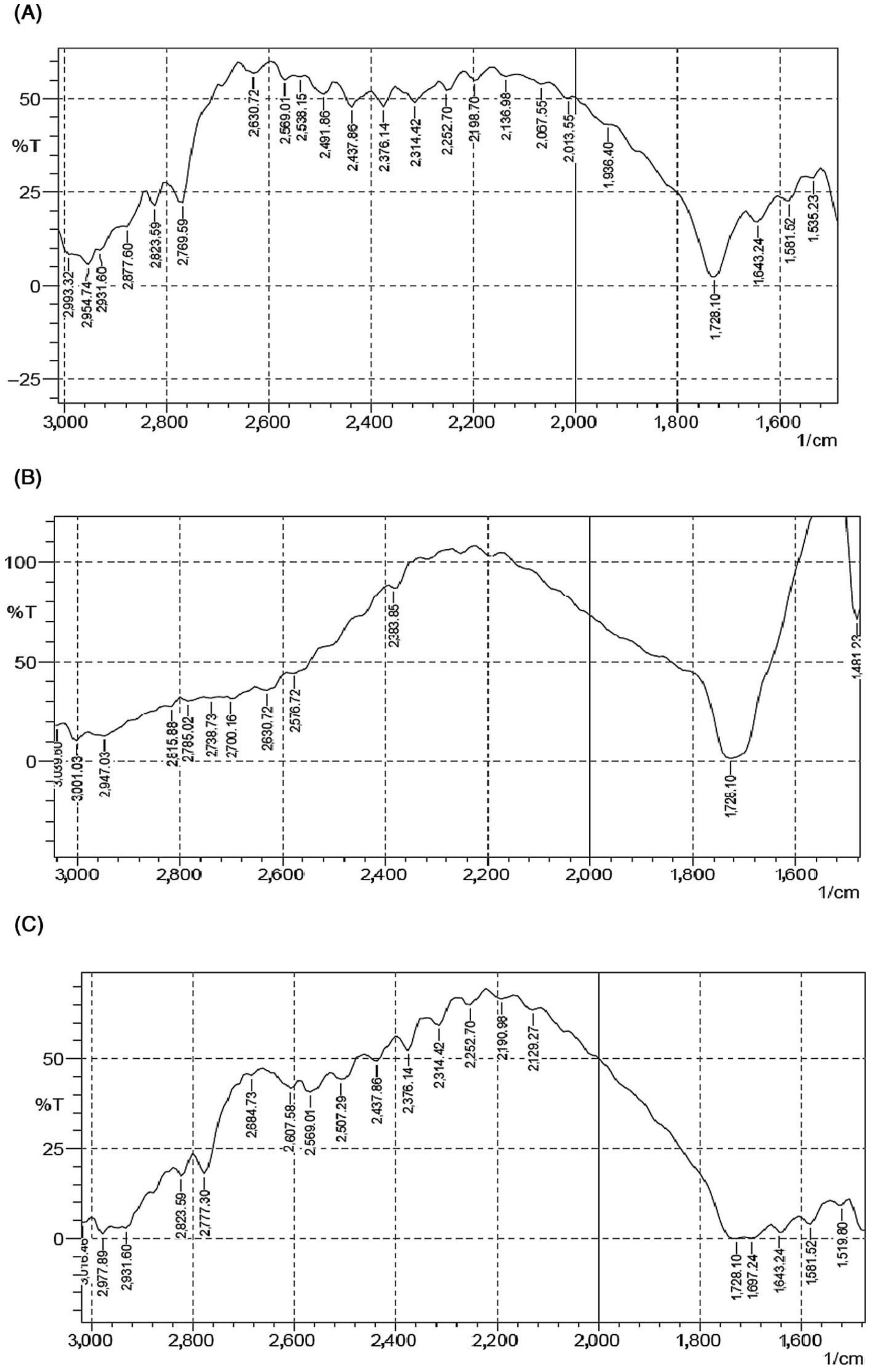

FIGURE 13. FTIR spectra of (A) Eudragit E (EE) powder, (B) Eudragit L (EL) powder, and (C) EE/EL physical mixture in a 1:1 ratio.

because of the intra- and intermolecular hydrogen bonding between the carboxylic acid groups (Coates, 2000). Moreover, EL also showed a wide absorption range of the associated hydroxyl groups between 2,500 and 3,500 cm^{-1}, but this was not clear from the figure, rather several minor peaks has been observed in this range. As can be seen from Figure 13, the FTIR spectrum of the physical mixture EE and EL seemed to be superposition of the spectra of the two polymers, and no new peaks were observed suggesting that only minimum, if any, interaction could be found between EE and EL in their powdered base forms.

CONCLUSIONS

The combination of anionic and cationic polymethacrylate polymers was found to be effective in controlling the release of drug from tablets. The effect of changing the pH of the dissolution medium from pH 1.2 to 5 and then 6.8 seemed to have little influence on the release of paracetamol from matrices containing mixture of Eudragit polymers. There was no sudden burst drug release from such matrices when shifting the pH values from acidic to basic values, suggesting the formation of new ionic compound between EE-citrate and EL-Na, with characteristics different from the individual polymers. The release behavior was almost independent of the pH of surrounding environment especially at higher polymers concentrations (12.84%).

Results from the swelling studies strongly supported the formation of ionic interaction between EE-citrate and EL-Na as seen from the continuous and gradual rise in the degree of swelling for these tablets with much uniform shape and minimum disintegration.

The results of all experimental tests proved that the combination of EE and EL in their salt form is suitable for formulating matrix tablets basically for neutral, unionized drugs. However, large number of possible combinations of Eudragit polymers using the various types of salt can be tailored depending on the properties of drugs to be included within their matrix system. It can also be applied to acidic and basic drugs using one salt form to minimize the interaction between the drug and the polymer and to achieve desired release profiles.

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