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Research Article

Evaluation of Matrix Tablets Based on Eudragit®E100/Carbopol®971P Combinations for Controlled Release and Improved Compaction Properties of Water Soluble Model Drug Paracetamol

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Abstract. The purpose of this work was to investigate the influence of Eudragit®E100 polymer in modifying the release rates and compaction properties of water soluble model drug paracetamol from Carbopol®971P NF polymer matrix tablets prepared by direct compression. The effects of the ratio of the two polymers, the total polymeric content, and the tablets mechanical strength on paracetamol release rates were investigated. Dissolution studies were conducted using USP XX Π rotating paddle apparatus at 50 rpm and 37°C at three different stages (pH 1.2, 4.8, and 6.8). Results showed that the polymers combination improved significantly the compaction properties of paracetamol tablets as evident by the higher crushing strengths (8.3±0.4 Kp) compared to polymer-free tablets (3.4±0.2 Kp) at intermediate compression pressure of 490 MPa. When combined with Carbopol®971P NF, Eudragit®E100 was found to be capable of extending paracetamol release for more than 12 h compared to 1 h for polymers-free tablets. The combined polymers were able to control paracetamol release in a pH independent pattern. The *f2* (similarity factor) analysis showed that the ratio between the polymers and the total polymer concentration exhibited significant impact on drug release rates. In conclusion, Eudragit®E100 when combined with Carbopol®971P NF was capable of improving the compaction and sustained release properties of paracetamol. Korsmeyer–Peppas model was found to be the most suitable for fitting drug release data. The polymer combinations can potentially be used to control the release rates of highly water soluble drugs.

KEY WORDS: Carbopol®971P NF; Eudragit®E100; matrix tablet; pH-independent release; sustained.

INTRODUCTION

The convenience of administration and the versatility sustained release dosage forms have been long recognized in the pharmaceutical art (1,2). Considering the number of formulations and processing variables (3–6), sustained release matrix tablets fabricated by direct compression are the simplest and the most attractive from a formulation and process development perspective; consequently, they are most commonly used technology in controlled release dosage forms. Sustained release dosage forms that release drug in a pH-independent manner are considered to be of specific value in the area of drug delivery. Such dosage forms offer the potential advantage of reduced variability of bioavailability of drugs that can result from the dependence of drug release *in vivo* on the variable pH of the gastrointestinal tract (7–9). Although certain hydrophilic swelling polymers have been explored to be used in matrices to control drug release (10,11), rarely did individual polymers sustain the drug release in a pH-independent fashion (4,5).

Combinations of ionizable polymers with different swelling, gel structure, and characteristics and erosion have gained interest in controlled matrix formulations. Through the optimization of the composition of the polymeric mixture and the total polymeric content of the matrix, a range of release rates of a drug can be obtained by altering the diffusivity of the drug through the gelled matrix structure. For example, a combination of hydroxypropylcellulose with anionic polymers such as sodium alginate (12), or Eudragit®L100-55 (13,14), was proposed to obtain a pH-independent release of basic drugs, while a combination with cationic polymers, such as Eudragit®E100, was proposed to obtain a pH-independent release of acidic drugs (7). Anionic and cationic polymethacrylate polymers combinations were also claimed to be effective in extending paracetamol release with a little effect of changing the pH of the dissolution medium (15). Also, matrix tablets based on Carbopol®971P NF and sodium alginate formed a potentially useful versatile system for pH-independent controlled release of paracetamol, salicylic acid, and verapamil HCl (16).

Carbopol®971P NF is a hydrophilic lightly cross-linked polymer of the Carbomer series. Unlike linear hydrophilic

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polymers, Carbopol® polymers do not dissolve, but only disperse/swell in aqueous environments to forms a three dimensional gel structure (17–19). Due to the anionic nature of Carbopol® polymers, drug release from Carbopol polymers matrices is pH-dependent. At low pH values, the polymers are not fully swollen, and the drug is released faster before complete gel formation occurs. As the pH increases, the ionization of the carboxylic acid groups causes maximum swelling, resulting in fewer and smaller regions of microviscosity; thus, a prolonged drug release is expected (11). Eudragit®E100 is based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters. Being soluble only in gastric fluid and in weakly acidic buffer solutions up to pH 5 (20,21), it has been employed extensively alone or within combinations to mask the bitter taste of drugs (22–24) or to improve the dissolution in acidic medium (25,26). In addition, Eudragit®E100 can act as a pH modifier that alters the microenvironment pH (7) thus affects the solubility and the dissolution rate of loaded drug, and might affect the swelling behavior of the accompanying hydrophilic polymer. Although Eudragit®E100 exhibits high dissolution in the acidic medium, allowing easier drug diffusion and release, it might also influence the pH in the tablet vicinity, and therefore, modify swelling behavior of accompanying polymer. Furthermore, the pK_a of Eudragit®E100 is 7.0–7.3 (27); it is partially protonated at pH close to 5, and an electrostatic interaction with another ionized polymers at this pH could contribute to drug release rate and behavior.

The aim of our work was to investigate the controlled release properties of mixed matrices of Eudragit®E100 and Carbopol®971P NF. Paracetamol was used as a candidate model since it has high aqueous solubility and relatively short biologic half-life of approximately 2 to 3 h in normal adults in the usual dosage range (28). Paracetamol is a white odorless crystalline weakly acidic powder that present in a nonionized form in the physiological pH range since it has a pK_a of 9.51 (29), and therefore, exhibits pH-independent release and as such its drug release would depend on the gelling and erosion properties of the polymeric matrix. Paracetamol is generally classified as a drug with high solubility high intestinal tract permeability, meeting the criteria as a class (I) substance according to the Biopharmaceutics Classification System (30).

MATERIALS AND METHODS

Materials

Paracetamol powder (particle size 52.3±45.5 μm) and Carbopol971P® NF powder (particle size 77.3±38.2 μm) were kindly provided by the Jordan Pharmaceutical Manufacturing (JPM, Amman, Jordan), Eudragit®E100 was obtained from Evonik (Darmstadt, Germany), lactose monohydrate from TQ Pharma (Amman, Jordan), magnesium stearate was obtained from Fizmerk India Chemicals, (Hapur, Uttar Pradesh, India), and talc was obtained from Riedel-De Haen AG (Seelze-Hannover, Germany).

Tablet Formulations, Compression, and Evaluation

The formulations used in this investigation are shown in Table I. The amount and percentage of paracetamol were kept constant in all formulations. Formulations F2 and F4 contained constant percentage of the polymers (Carbopol®971P NF and Eudragit®E100 (sieve cut 150–180 μm) combined at ratios 1:1 and 1:2, respectively. Formulations F2``and F4`` have identical compositions to F2 and F4, respectively, except for the smaller particle size fraction (38–63 μm) of Eudragit®E100. The smaller size fraction of Eudragit®E100 was obtained by milling the material provided in a jet mill. Formulations F7 and F8 were prepared with polymeric content in the tablets, but at constant ratios of the two polymers (1:1). Other formulations contained paracetamol alone and paracetamol with either of the polymers as shown in Table I and were prepared for comparison with the combined polymers tablets formulations.

A 13-mm cylindrical-uniaxial-stainless steel die and flat-faced punches (Carver press, WABASH, Indiana, USA) were used to compress powder formulations into compacts. For the different tablet formulations, the following procedure was followed: paracetamol was mixed with all polymeric excipients and lactose manually using the bottle method for 4 min. Then, Mg stearate and Talc were added and admixed for an additional 1 min. Accurately weighed amounts of the mixtures were manually placed into the die and were directly compressed for 30 s at different pressures (245, 490, and 735 MPa) to evaluate the effect of applied pressure on tablet properties.

The tablets were produced at room temperature between 23 and 26°C with the humidity between 37 and 42% RH. Approximately 30 tablets were prepared at each level of compression and tablets were stored in airtight containers in the same room of production for at least 24 h after compression to allow for consistent stress relaxation and hardening among tablets. For each formula, the average tablet weight was 400±10 mg and the average amount of active ingredient per tablet was 300±5 mg.

Determination of Tablets Weights, Thicknesses, Diameters, True Densities, and Porosities

Three tablets from each formulation were selected randomly and the weight, thickness, and diameter of each individual tablet were measured using digital slide caliber (6 Caliber, China) and the geometric volume of each tablet was calculated. The true density was measured using a gas pycnometer (Ultrapycnometer 1000, Quantachorome Instruments, FL, USA) at 25°C. Samples (sample size was about 1.2 g) were tested in triplicate with each individual run measured 5 times. The tablet porosity was calculated as (1-relative density), where the relative density was calculated as the ratio of apparent density of the compact to its true density.

Determination of Tablet Crushing Strength and Moisture Contents

Tablets crushing strengths in kilopound (Kp) were measured using a hardness tester (Copley, Mod. 2E/205, Switzerland); the test was performed in triplicates. Moisture content values of the prepared tablets were measured while stored at room temperature between 23 and 26°C with the humidity between 37 and 42% RH using volumetric Karl Fischer

Table I. Composition of Tablets Formulations Prepared by Direct Compression Method Using Eudragit® E100 and Carbopol®971P NF Polymers and the Physical Properties of These Tablets

Formulation	PA (mg)	Cp (mg)	EE (mg)	Lactose (mg)	Mg Stearate (mg)	Talc (mg)	Crushing strength (Kp) at 245 MPa	490 MPa	735 MPa	Weight variation (%)	Drug content (%)
FPA	300	–	–	95	2.5	2.5	1.9±0.1	3.4±0.2	3.6±0.1	±1.8	102.7
FCp2	300	13.33	–	75	2.5	2.5	3.3±0.4	3.8±0.5	3.9±0.2	±0.9	99.3
FCp4	300	20	–	81.67	2.5	2.5	2.3±0.4	3.9±0.2	4.3±0.6	±1.4	101.6
FEE2	300	–	20†	75	2.5	2.5	2.2±0.2	3.4±0.2	3.6±0.5	±1.6	98.2
FEE2``	300	–	20*	75	2.5	2.5	2.6±0.3	3.5±0.1	3.7±0.7	±1.8	94.6
FEE4	300	–	26.67†	68.33	2.5	2.5	1.8±0.2	3.3±0.2	3.3±0.1	±1.7	97.2
FEE4``	300	–	26.67*	68.33	2.5	2.5	2.8±0.1	3.3±0.3	3.6±0.2	±0.8	96.6
F2	300	20	20†	55	2.5	2.5	4.7±0.6	5.8±0.5	4.1±0.2	±1.1	98.7
F2``	300	20	20*	55	2.5	2.5	3.1±0.2	8.3±0.4	4.3±0.3	±0.9	103.5
F4	300	13.33	26.67†	55	2.5	2.5	3.3±0.3	6.3±0.4	4.1±0.2	±0.7	95.8
F4``	300	13.33	26.67*	55	2.5	2.5	4.1±0.5	8.2±1.0	6.1±0.8	±1.2	97.5
F7``	300	25	25*	45	2.5	2.5	5.7±0.3	8.2±0.1	9.1±0.6	±1.5	98.0
F8``	300	30	30*	35	2.5	2.5	6.3±0.2	8.1±0.5	9.4±0.4	±1.2	99.2

†Eudragit®E100 (sieve cut 150–180 μm)
*Eudragit®E100 (sieve cut 38–63 μm)

titration method (AF8 KF Titrator, Thermo Fisher Scientific, USA).

Preparation of Eudragit®E100-Carbopol®971P NF Interpolyelectrolyte Complex (IPEC)

Eudragit®E100 solution was prepared by dissolving Eudragit®E100 ground powder in phosphate buffer solution (pH 5±0.2). To this solution, a weighed amount of paracetamol was gradually added until completely dissolved. Then the above solution was gradually titrated with a phosphate buffer solution (pH 5±0.2) containing dissolved Carbopol®971P NF of equal concentration to Eudragit®E100 solution. The mixture was mixed well using magnetic stirrer for 24 h at room temperature to allow for complete formation of the complex. The final precipitate was then dried for 48 h at 40°C, ground, and sieved via a 1-mm sieve to minimize variation in granule size. The granules were stored in a glass bottle and kept away from sunlight.

Differential Scanning Calorimetry Analysis

Differential scanning calorimetry (DSC) traces of individual components: paracetamol powder, polymers, physical mixture of paracetamol with the polymers, interpolyelectrolyte, and paracetamol-containing interpolyelectrolyte were recorded using (DSC-50 Shimadzu, Japan). Samples of approximately 4–7 mg were heated from 25 to 250°C at 10°C/min. Pierced aluminum pans were used for all samples. Pure indium was used to calibrate the DSC.

Fourier Transform Infrared Analysis (FT-IR)

FT-IR spectra of moisture-free individual components: paracetamol powder, polymers, physical mixture of paracetamol with the polymers, interpolyelectrolyte, and paracetamol-containing interpolyelectrolyte were obtained using (IRAffinity-1, Shimadzu, Japan) with KBr as a reference. The scanning range was 450–4,000 cm^{-1}.

Dissolution Testing

All dissolution tests were conducted using USP XX Π rotating paddle apparatus (Copley Scientific, NE4-COP, UK) with the dissolution media temperature maintained at 37°C while being stirred at a rate of 50 rpm.

The release of the drug from each formulation was investigated at three different stages that mimic the different pH values of the gastrointestinal environment. The first stage lasted for 1 h at pH 1.2±0.2 and the volume of the dissolution medium was 500 ml. This was followed by 2 h dissolution at second stage where the pH of the dissolution medium was 4.8±0.2. The volume of the dissolution medium was increased to 740±5 ml by adding about 235 ml of sodium tribasic phosphate (Na_3PO_4) and the pH was adjusted using NaOH or phosphoric acid. The final stage was conducted for 5 to 12 h, and the pH was adjusted to 6.8±0.2 by adding a sufficient volume of sodium tribasic phosphate (Na_3PO_4) and completing the volume of the dissolution medium to 1,000 ml using distilled water. Samples were taken at predetermined intervals then filtered through 0.45 μm Millipore filters and the concentration of paracetamol was determined by measuring the absorbance of the samples 243 nm and using properly constructed calibration curves. Samples taken were replaced by the same volume of fresh medium. The percentage released was calculated and the average values were plotted against time to obtain the release profiles of the different tablet formulations.

To investigate the similarities among the dissolution profiles generated in the pH-gradient method, data were compared by *f*2 calculation (31; Eq. 1), using dissolution time points at 60, 75, 90, 120, 240, and 480 min. These time points correspond to FDA criteria, i.e., not more than one

measurement after 85% dissolution of the product was considered (32).

$$f_2 = 50 \bullet \log\left\{\left[1 + \left(1/n\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \bullet 100\right\} \quad (1)$$

RESULTS

Analytical Method Validation and Drug-Polymers Compatibility

The UV scanning of paracetamol showed a maximum absorbance at 243 nm without shifting at various pH values. The calibration curves of paracetamol were linear in different dissolution media in various pH media with a correlation coefficient of 0.9998. The UV scan showed an absence of significant peaks for Carbopol971P® NF and Eudragit®E100 polymers in the UV range of 200–400 nm. Therefore, no apparent drug–polymer interactions have been observed at the concentrations employed in this study, and the UV analytical method was considered specific.

Physical Characterization of Prepared Tablets

The compaction properties of paracetamol were found to be improved by incorporation of binary polymer mixture of Carbopol971P® NF and Eudragit®E100 in the tablet formulations compared to tablets containing paracetamol and lactose without the polymers combination or tablets containing paracetamol and lactose with either of the two polymers as shown in Table I. This improvement was more evident in tablets compressed at an intermediate compression pressure (490 MPa) in comparison to those compressed at the low (245 MPa) or high (735 MPa) pressures. For example, at a compression pressure of 490 MPa, the crushing strength of paracetamol tablets improved from 3.4±0.2 Kp in polymer-free paracetamol tablets to 5.8±0.5 and 6.3±0.4 Kp in F2 and F4 formulations which contained polymeric combinations at 10% total content and at two different ratios (1:1 in F2, and 1:2 in F4). The crushing strength was further increased to 8.3±0.4 Kp in F2`` and to 8.2±1.0 Kp in F4`` which contained a smaller sieve cut of Eudragit®E100 (38–63 μm) in addition to Carbopol971P® NF at similar ratios and total polymeric content as in F2 and F4, respectively. The higher crushing strengths of F2`` and F4`` tablets were associated also with lower tablets porosities, as shown in Table II. An increase in the compression pressure to 735 MPa resulted in reduction in tablets crushing strengths that were associated with an increase in tablets porosities compared to tablets compressed at intermediate pressure of 490 Mpa, as shown in Table II. However, when the total polymers concentration was increased to 12.5% (F7`` tablets) and 15% (F8`` tablets) at the same ratio of the two polymers (1:1 ratio), the tablets crushing strengths increased when the compression pressure increased from 245 to 735 MPa.

Drug Release from Tablets Containing Either No Polymer or A Single Polymer

Figure 1 shows paracetamol release from FPA formulation (devoid of any polymer) in acidic (pH 1.2±0.2) and in buffered (pH 6.8±0.2) media. It was observed that FPA tablets exhibited nearly a pH-independent and rapid release in both media

Table II. Crushing Strengths (Kp) and the Calculated Porosities of the Different Tablet Formulations Prepared by Direct Compression Method Using Eudragit® E100 and Carbopol®971P NF Polymers

Formulation	Crushing strengths (Kp) at 490 MPa	Porosity (%) at 490 MPa	Crushing strengths (Kp) at 735 MPa	Porosity (%) at 735 MPa
FEE2	3.4±0.2	10.33	3.6±0.5	9.50
FEE2``	3.5±0.1	7.45	3.7±0.7	6.55
FEE4	3.3±0.2	9.44	3.3±0.1	8.41
FEE4``	3.3±0.3	7.25	3.6±0.2	7.10
F2	5.8±0.5	8.45	4.1±0.2	8.66
F2``	8.3±0.4	6.65	4.3±0.3	6.89
F4	6.3±0.4	9.40	4.1±0.2	9.88
F4``	8.2±1.0	8.02	6.1±0.8	8.90
F7``	8.2±0.1	7.33	9.1±0.6	6.62
F8``	8.1±0.5	7.77	9.4±0.4	5.56

The pH dissolution profiles of paracetamol tablet formulations containing 5 and 7.5% of Eudragit®E100 of small sieve cut of 38–63 μm (formulations FEE2``and FEE4``) or larger sieve cut of 150–180 μm (formulations FEE2 and FEE4) are shown in Fig. 2. The pH dissolution profiles for FCp2 and FCp4 tablet formulations that contain 5 and 3.33% of Carbopol971P® NF, respectively, are shown in Fig. 3. These two tablet formulations had similar crushing strengths at all compression pressures employed. Both formulations exhibited similar and relatively rapid drug release during the first (pH 1.2±0.2) and the second stages (pH 4.8±0.2) of dissolution process. During the third stage (pH 6.8±0.2), both formulations experienced reductions in release rates, with FCp2 that containing a larger amount of Carbopol971P® NF, showing slower release rates compared to FCp4.

Drug Release from Tablets Containing Binary Mixtures of Eudragit®E100 and Carbopol971P® NF

The dissolution behaviors of F2, F2``, F4, and F4`` tablets compressed at 490 MPa are shown in Fig. 4. In these

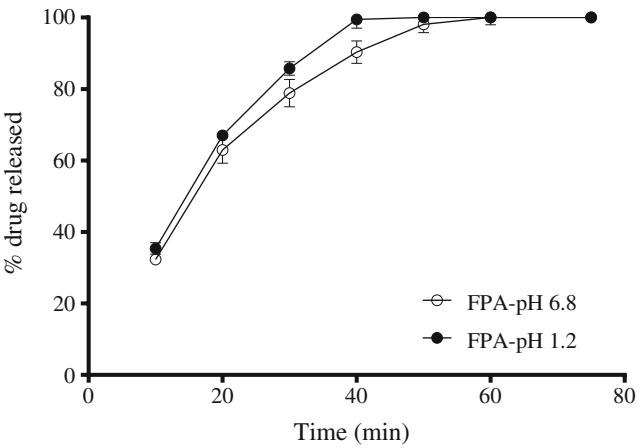

Fig. 1. Dissolution profiles of paracetamol in acidic (pH 1.2) and buffered (pH 6.8) media at 37°C

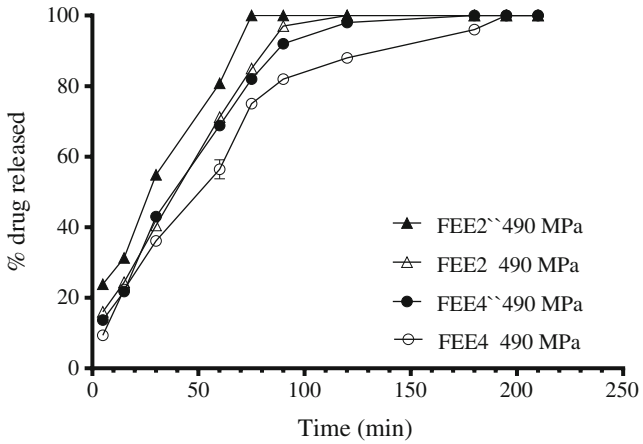

Fig. 2. 2The pH dissolution profile for paracetamol tablets formulations FEE2, FEE2``, FEE4, and FEE4`` compressed at 490 MPa at 37°C

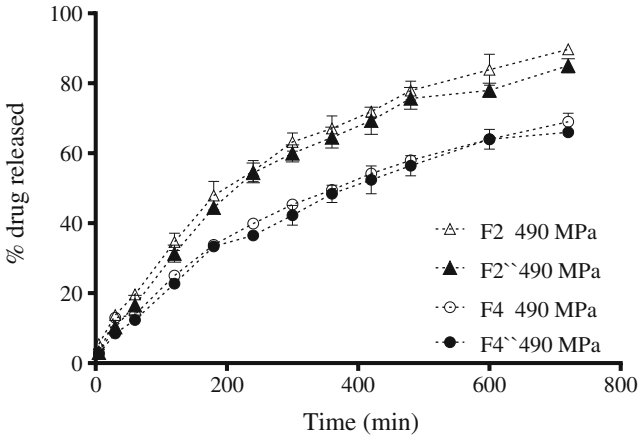

Fig. 4. The pH dissolution profile for paracetamol tablets formulations F2, F2``, F4, and F4`` compressed at 490 MPa at 37°C

formulations, Eudragit®E100 polymer was incorporated along with Carbopol971P® NF in different ratios; 1:1 in F2 and F2``, and 2:1 in F4 and F4``, at a total polymers concentration of 10%. Tablet formulations F2`` and F4`` contained smaller sieve cut Eudragit®E100 (38–63 μm), while formulations F2 and F4 contained Eudragit®E100 of large sieve cut (150–180 μm). It was apparent from the analysis of three-stage dissolution data that the addition of Eudragit®E100 to Carbopol971P® NF slowed down the overall drug release rate compared without a polymer or those containing Carbopol971P® NF alone. The retardation of drug release was more prominent during the second (pH 4.8±0.2) and the third dissolution stages (pH 6.8±0.2). The retardation behavior was more prominent at higher Eudragit®E100 content within the binary polymers mixtures, as deduced from similarity factor (*f*2) calculations. The small particle size of Eudragit®E100 employed in formulations F2``and F4`` resulted in similar dissolution profiles to F2 and F4 tablet formulations that contain larger size Eudragit®E100. The incorporation of Eudragit®E100 with Carbopol971P® NF at different total polymers contents of 10%, 12.5% and 15% significantly improved the tablets crushing strengths especially at a compression pressure of 490 MPa for F2, F2``, F4, and F4``formulations, and at 490 and 735 MPa for F7`` and F8`` tablet formulations compared to Carbopol971P® NF tablet formulations as shown in Table I.

Effect of Total Polymeric Contents and Compression Pressure on Drug Release

Tablets formulations containing Eudragit®E100 and Carbopol971P® NF polymers at 1:1 ratio and higher total polymeric content of 12.5% (formulation F7``) and 15% (formulations F8``) were prepared using Eudragit®E100 of the small sieve cut. The use of the small sieve cut was based on our earlier findings that it produced compacts with higher crushing strengths. The mechanical properties of these tablets compressed at 490 and 735 MPa are reported in Table I. Unlike F2`` tablets, the F7``and F8`` tablets exhibited higher crushing strengths at higher compression pressures. The pH-dissolution profiles of F7`` and F8`` tablets are shown in Fig. 5, along with dissolution profile of F2`` which contained 10% total polymers concentration, all at 1:1 ratio. It was apparent that F7`` had a slightly slower release rates than F2``, while F8`` tablets exhibited significantly slower drug release. The calculated similarity factor, *f*2 indicated the similarity of F2`` and F7`` tablets, and

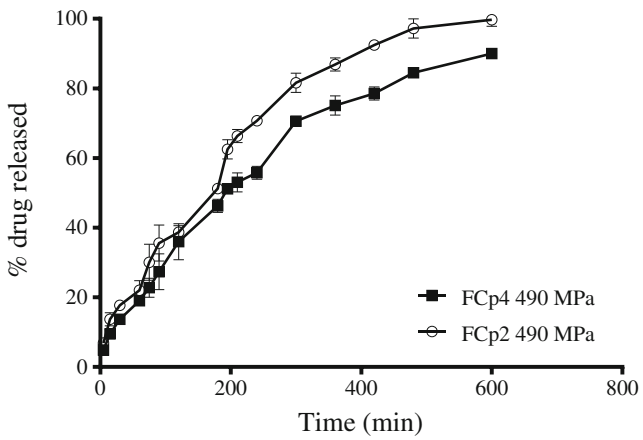

Fig. 3. The pH dissolution profile for paracetamol tablets formulations FCp2 and FCp4 compressed at 490 MPa at 37°C

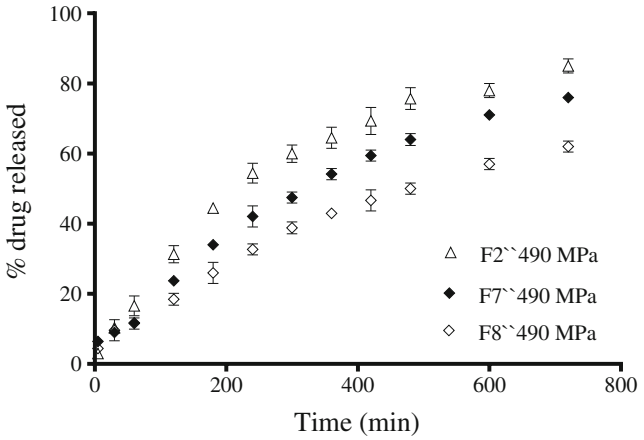

Fig. 5. The pH dissolution profile for paracetamol tablets formulations F2``, F7``, and F8`` compressed at 490 MPa at 37°C

the dissimilarities between F2`` and F8`` tablets, as shown in Table III.

Despite the statistically significant different crushing strengths ($p<0.05$) at the different compression pressures employed for each tablet formulations containing combined polymers at a fixed total content (Table I), the calculated similarity factor *f2* (shown in Table III) indicated that the drug release profiles were not significantly affected by the compression pressure as shown also in Fig. 6.

Mechanism of Drug Release from Tablets Made of Carbopol971P® NF and Eudragit®E100 Polymeric Combinations

Several kinetic models (zero order, first order, square root, Korsmeyer–Peppas, and Hixson–Crowell) were used to fit the drug release data; regression analysis results are shown in Table IV. Korsmeyer–Peppas (the power law) model was found to have the best fit to the drug release data (the power law, Eq. 2; 33,34):

$$\frac{Q_t}{Q_\infty} = K.t^n \tag{2}$$

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. Using Korsmeyer–Peppas model, the n values were found to be higher than 0.45 in all formulas as shown in Table IV.

FT-IR Spectroscopic Analysis and Differential Scanning Calorimetry

The Fourier-transform infrared spectroscopy (FT-IR) spectra for the individual components: paracetamol, Carbopol971P® NF, Eudragit®E100, as well as their physical mixture (PM), the interpolyelectrolyte complex (IPEC) of Carbopol971P® NF and Eudragit®E100, and for the IPEC containing paracetamol (IPEC PA) are shown in Fig. 7. Generally, the FT-IR spectra of tablet formulations (PM) containing combinations of the polymers with paracetamol did not show significant changes with respect to the FT-IR spectra of the individual components; hence, all characteristic bands of paracetamol and the polymers were preserved indicating the absence of any interaction of the drug and the polymers after mixing. For IPEC PA, all characteristic peaks of paracetamol were also preserved. However, for Eudragit® E100, the peak at 2,820 cm^{-1} was greatly minimized, and the peak at 1,730 cm^{-1} completely disappeared, while for Carbopol971P® NF, the peak at 1,720 cm^{-1} was completely disappeared. On the other hand, all characteristic peaks of the polymers were preserved in IPEC without paracetamol. Figure 8 depicts the differential scanning calorimetry (DSC) traces of individual components (paracetamol, Carbopol971P® NF and Eudragit®E100) as well as their PM, the IPEC of Carbopol971P® NF and Eudragit®E100 and the IPEC PA. Paracetamol powder exhibited a single sharp endothermic peak at 168.7°C. The PM showed a single endothermic peak characteristic for paracetamol melting at 168.8°C indicating again the absence of any interaction of the drug and the polymers after mixing. Similarly, paracetamol contained in the IPEC showed a sharp endothermic peak corresponding to its melting point at 168.3°C. In addition, IPEC and IPEC-containing paracetamol formulation exhibited another transition at about 205°C which could be attributed to the complex.

DISCUSSION

During compression, paracetamol particles are known to fragment markedly into new, smaller particles that then deform elastically (35,36). Higher compression pressures result in more elastic particles; therefore, tablets containing paracetamol without appropriate binders tend to cap at higher pressures (37). In addition, these tablets were found in this study to have low strengths when compressed under intermediate pressures (490 MPa). The crushing strengths of paracetamol tablets were found to be improved by incorporation of the binary polymeric mixture (Carbopol971P® NF and Eudragit®E100) in the tablet formulations. At intermediate pressure of 490 MPa, 10% total polymers content was found to improve the binding between the tablets ingredients. An increase in the compression pressure to 735 MPa at the same total polymers content (10%) resulted in reduction in tablets crushing strengths associated with an increase in tablets porosities as shown in Table II. This might indicate that while the polymers may act as binders to the newly created paracetamol particles formed at low compression pressure, their amounts seemed to be insufficient to counteract the elastic behavior of the new smaller paracetamol particles formed at higher pressures. Hence, when the total polymers concentration increased to 12.5% (F7`` tablets) and to 15% (F8`` tablets) at the same ratio of the two polymers (1:1 ratio), the tablets crushing strengths increased with the increase of the compression pressure from 245 to 735 MPa. Given that the moisture contents of all tablets formulations were found to be 1.87–2.66% as determined by Karl Fischer titration method, this improvement in tablets strengths with the increase in compression pressure can be related to the ability of higher total polymers content to provide better binding of the tablets components that prevented to great extent the elastic relaxation of paracetamol particles.

The increase in crushing strengths was more pronounced when the small sieve cut of Eudragit®E100 was employed which is in agreement with reported relationships between particles sizes and tablet mechanical strengths (38–43). In addition, the small sieve cut of Eudragit®E100 (38–63 μm) was very close to the average particle size of the most abundant component in the tablet formulation; paracetamol, which would reduce drug particles segregation (44), and facilitate tabletting by direct compression (45).

The dissolution behavior of paracetamol tablets shown in Fig. 1 indicated that paracetamol dissolved fairly rapidly in acidic and basic media; where the entire drug amount was released in less than an hour in both media in a pH-independent fashion. The incorporation of Eudragit®E100 in FEE and FEE`` formulations resulted in rapid drug release as shown in Fig. 2 due to the dissolution of Eudragit®E100. However, the release was not complete during the dissolution

in acid stage in the first hour; about 60–80% of the drug was released depending on Eudragit®E100 concentration. This lowering of paracetamol release rates from such formulations in the acid stage can be attributed to the improved mechanical strength of the tablets and to resistance to diffusion of paracetamol through the undissolved Eudragit®E100 polymer throughout the tablet matrix. Such pH-dependent behavior was reported for granules containing Eudragit®E100 and paracetamol (46). Throughout the pH-gradient dissolution profile, Eudragit®E100 containing formulations (FEE formulations) exhibited an almost similar dissolution behavior as indicated by the similarity factor, *f*2, shown in Table III. When Carbopol971P® NF was employed solely to control the release rate of paracetamol (Fig. 3), approximately 18–20% of the drug was released during the acidic stage, and the rate was almost similar during the second stage and became slower in the third one. This behavior is attributed to pH-dependent nature of Carbopol971P® NF. In the acidic environment, Carbopol971P® NF was not fully ionized and, therefore not swollen, and the drug is released faster. While at pH 4.8 and in the neutral stage (pH 6.8), Carbopol971P® NF became ionized to various extents depending on the pH of the medium, and therefore gelled to various extents, leading to drug entrapment and slower release.

According to the pH-gradient dissolution profiles shown in Fig. 4, the addition of Eudragit®E100 to Carbopol971P® NF modified the dissolution profile of paracetamol tablets compared to tablets containing Carbopol971P® NF alone. The change in the release profile was not observed (Fig. 3) during the acid stage, while release rates during the second (pH 4.8) and third stages (pH 6.8) were lowered to various degrees, depending on the formulation. For example, during the third stage, the release rates were reduced by 20–35%, which was increasing as the proportion of Eudragit®E100 was increased.

According to the FDA guidelines for industry (47), generally, the *f*2 values greater than 50 (i.e., 50–100) indicated sameness or equivalence of two curves. The calculated similarity factor (*f*2) according to Eq. 1 indicated that F2 *vs* F4 and F2`` *vs* F4`` dissolution profiles were dissimilar. The dissolution behavior of F2``and F4`` tablets that contain small sieve cuts of Eudragit®E100, showed similar behavior to the corresponding tablet formulations (F2 and F4) containing the larger sieve cuts of Eudragit®E100, but with slightly retardation in drug release.

The dissolution behavior of tablets containing combination of polymers (F2, F2``, F4, and F4``) can be explained as follows: during the first stage (pH 1.2), Carbopol 971P® NF was expected to provide low resistance to drug diffusion since it was not sufficiently swollen or gelled. On the other hand, Eudragit®E100 in the acidic environment gets protonated and eventually dissolves, thus, facilitating drug release. However, it is known that drug release is also related to the compression pressure used to prepare the tablets and the crushing strengths and porosities of the produced tablets. The incorporation of Eudragit® E100 with Carbopol 971P® NF improved the crushing strengths of the tablets significantly, especially those compressed at a compression pressure of 490 MPa for F2, F2``, F4, and F4``formulations compared to tablets containing Carbopol 971P® NF alone (FCp formulations) which exhibited poor mechanical properties. However, despite the higher crushing strength, the incorporation of Eudragit®E100 has led to drug release rates that were comparable to the FCp tablet formulations. Also, since Eudragit®E100 is a basic excipient, when dissolved during the acid stage, it can change the microenvronmental pH in the matrix causing a certain degree of ionization in Cabopol 971P® NF polymers which are anionic in nature, resulting in some swelling of Carbopol 971P® NF particles. Na_3PO_4 was reported to result in a similar enhancing effect of Carbopol 971P® NF swelling in different dissolution media (48).

This behavior was more prominent when higher Eudragit®E100 concentration within the binary polymers mixtures was employed (F4 and F4`` formulations). In summary, despite the increase in the crushing strengths of these tablets formulations, and despite the minimal enhancement of early Carbopol971P® NF swelling, Eudragit®E100 was able to release paracetamol in a rate that was comparable to tablets containing Carbopol971P® NF alone during the acid stage (1 h).

At the end of the acid stage, an undissolved amount of Eudragit®E100 was confirmed by the FTIR to exist (data not shown); therefore, during the second stage of dissolution run (pH 4.8), both Eudragit®E100 and Carbopol 971P® NF are believed to be ionized to a certain extent (pK_a of Carbopol=6 ±0.5 (11), and that of Eudragit®E=7.0–7.3 (27), and the possibility of an electrostatic interaction exist when the polyme,s are in close proximities. The low rate of paracetamol release could be attributed to such interaction during this stage. Similar behaviors of reducing the release rates were reported for

Table III. The Calculated Similarity Factor, *f*2, for the pH Dissolution Profiles of the Different Tablets Formulations Prepared by Direct Compression Method Using Eudragit® E100 and Carbopol®971P NF Polymers

Formulation	*f*2 similarity factor	Formulation	*f*2 similarity factor
F2 and FCp2 at 490.3 MPa	39.21	F4 and F4`` at 735.5 MPa	61.45
F2 and FCp2 at 735.5 MPa	37.66	F2 and F4 at 490.3 MPa	41.07
F4 and FCp4 at 490.3 MPa	36.55	F2 and F4 at 735.5 MPa	43.77
F4 and FCp4 at 735.5 MPa	34.71	F2 and F7`` at 490.3 MPa	67.06
FEE2 and FEE2`` at 490.3 MPa	56.76	F2 and F7`` at 735.5 MPa	64.30
FEE4 and FEE4`` at 490.3 MPa	65.75	F2 and F8`` at 490.3 MPa	37.56
FEE2 and FEE4 at 490.3 MPa	61.99	F2 and F8`` at 735.5 MPa	41.55
F2 and F2`` at 490.3 MPa	59.33	F7 and F8`` at 490.3 MPa	49.61
F2 and F2`` at 735.5 MPa	60.21	F7 and F8`` at 735.5 MPa	48.23
F4 and F4`` at 490.3 MPa	64.58	F2 at 490.3 and 735.5 MPa	55.22
F4 at 490.3 and 735.5 MPa	54.56		

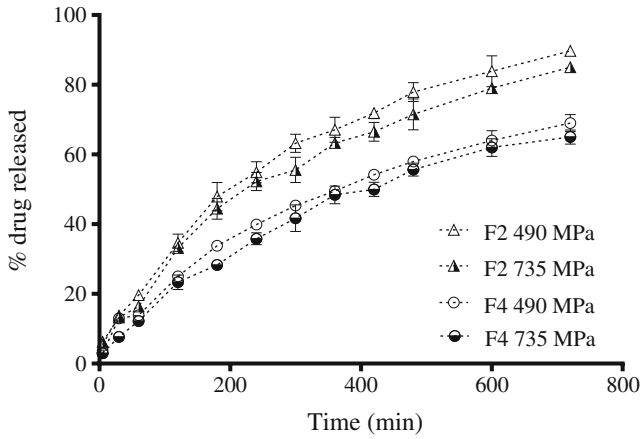

Fig. 6. The pH dissolution profile for paracetamol tablets formulations F2 and F4 compressed at 490 and 735 MPa at 37°C

paracetamol using salt forms of Eudragit®E100 and Eudragit®L100 (15), where the combination was able to extend paracetamol release times, and for diltiazem HCl using interpolyelectrolyte complex of Eudragit®E and Carbopol®934 (49).

During the third stage dissolution (pH 6.8), another reduction in paracetamol release rate was observed. This was more noticeable at high total polymers contents (formulations F7`` and F8``). The reduction in drug release rates in this stage can be attributed to the coexistence of two contributing factors. First, Carbopol971P® NF became ionized to a great extent (pK_a of Carbopol=6±0.5), and therefore, experienced high degree of swelling and gel formation. The formed gel increased the matrix microviscosity, which in turn restricted drug diffusion and sustained the release of the highly soluble drug from the polymeric matrices (2). During this stage, Eudragit®E100 became unionized, and therefore, precipitated within the matrix structure (27). The existence of Eudragit®E100 at the end of dissolution profile was confirmed by FTIR spectroscopy (data not shown). Therefore, as an insoluble polymer during this stage, Eudragit®E100 contributed to further diffusion resistance, which along with gelled Carbopol971P® NF, provided significant reduction in drug release rates in comparison to those obtained from tablets containing only Carbopol971P® NF.

The effect of total polymers concentrations at 1:1 ratio of the two polymers was studied by preparing tablets with a polymeric content of 12.5% (F7`` formulation) and 15% (F8`` formulation), in addition to the previously prepared 10% tablets. Higher tablets strengths were observed as the total polymeric content increased as shown in Table I. This could be explained by the presence of higher percentage of the polymers, since Carbopol971P® NF (11,48) and Eudragit®E100 (50) polymers were reported to act as efficient tablet binders. The higher strengths of F7`` and F8`` tablets, in addition to the higher resistance offered by the higher polymers contents, could also explain the dissolution behavior shown in Fig. 5. In addition, the decrease in lactose concentration as soluble excipient from 23.75% (*w*/*w*) in FPA to 13.75% (*w*/*w*) in F2 and 8.75% (*w*/*w*) in F8" could have an influence also in drug release rates.

The effect of compression pressure on tablets crushing strengths has been reported frequently in literature (51,52). An increase in the compression pressure usually resulted in an increase in the crushing strength and the apparent density of matrix tablet, thereby reducing the matrix porosity (42). The incorporation of combinations of the polymers, Carbopol971P® NF and Eudragit®E100, at different total polymers concentrations of 10, 12.5, and 15% improved significantly the crushing strengths of paracetamol tablets. However, despite that tablets containing any given total polymers concentration exhibited a statistically different crushing strengths ($p<0.05$) at the different compression pressures employed, the calculated similarity factor *f*2 (shown in Table III) indicated that the drug release rates during the pH dissolution testing were not significantly affected by the compression pressure as shown in Fig. 6. This can be attributed to the nature of the polymers involved and the pH of the dissolution medium. Since most of the dissolution time was in pH 4.8 and 6.8; therefore, Carbopol971P® NF exhibited various degrees of hydration and swelling. Therefore, as porosity of the hydrated matrix was independent of the initial porosity and the compression pressure, the differences in tablet porosities at different compression pressures seemed to have little influence on drug release (53,54). The hydration and swelling

Table IV. Rate Constants Obtained from the pH Dissolution Profiles of the Different Tablets Formulations Prepared by Direct Compression Method Using Eudragit® E100 and Carbopol®971P NF Polymers, Using Various Kinetic Models

	Zero order model		First order model		Square root model		Korsmeyer–Peppas model		Hixon–Crowel model	
Formulation	R^2	K_0	R^2	K_1	R^2	K_H	R^2	n	R^2	K_{HC}
F2 5,000 kg	0.9515	0.1409	0.8342	0.0035	0.9934	4.0148	0.9934	0.6965	0.8807	0.0039
F2 7,500 kg	0.9533	0.1400	0.8356	0.0033	0.9944	4.0121	0.9951	0.6876	0.8777	0.0037
F2`` 5,000 kg	0.9670	0.1357	0.8357	0.0040	0.9947	3.8386	0.9968	0.7828	0.8889	0.0042
F2`` 7,500 kg	0.9530	0.1217	0.8337	0.0037	0.9956	3.7356	0.9661	0.8228	0.8663	0.0037
F4 5,000 kg	0.9741	0.1021	0.8498	0.0039	0.9978	2.8803	0.9971	0.7483	0.9032	0.0038
F4 7,500 kg	0.9633	0.1125	0.8584	0.0042	0.9998	2.6030	0.9999	0.7553	0.9137	0.0041
F4``5,000 kg	0.9782	0.0956	0.8634	0.0037	0.9970	2.6904	0.9982	0.6862	0.9125	0.0035
F4``7,500 kg	0.9886	0.0899	0.8355	0.0031	0.9990	2.6604	0.9995	0.6763	0.9033	0.0039
F7``5,000 kg	0.9780	0.0910	0.8619	0.0036	0.9987	2.5640	0.9992	0.6846	0.9120	0.0035
F7``7,500 kg	0.9885	0.0966	0.8789	0.0042	0.9998	2.4673	0.9998	0.6657	0.9222	0.0031
F8``5,000 kg	0.9861	0.0824	0.8994	0.0039	0.9889	2.3010	0.9917	0.6479	0.9396	0.0035
F8``7,500 kg	0.9667	0.0854	0.9004	0.0036	0.9977	2.4323	0.9996	0.6557	0.9444	0.0041

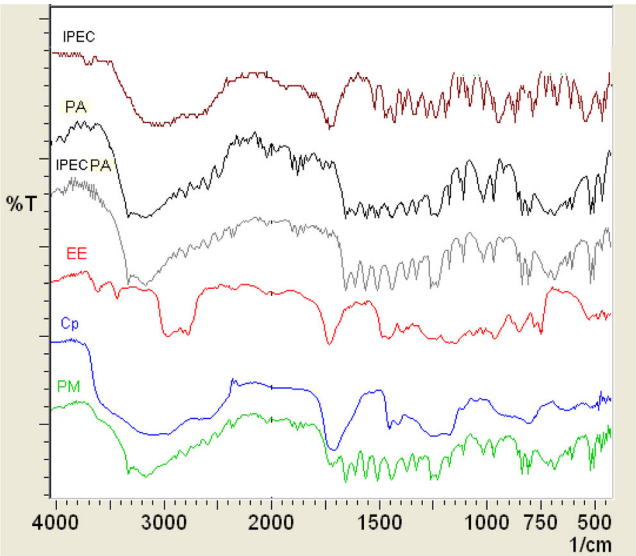

Fig. 7. FT-IR spectra of paracetamol (PA), Eudragit® E100 polymer (EE), Carbopol 971P® NF polymer (Cp), the physical mixture of the two polymers and paracetamol (PM), the interpolyelectrolyte complex (IPEC) of the two polymers, and the IPEC containing paracetamol (IPEC PA)

behavior throughout most of the dissolution time (>90%) seemed also to affect the whole mechanism of dug release. Hence, the dissolution data throughout the pH profile were fitted best to the Korsmeyer–Peppas model, the *n* values were found to be $0.45<n<0.85$ in all formulas indicating that the diffusion mechanism was not the only factor controlling the drug release, and in this case, the release was non-Fickian or anomalous. However, although to a lesser extent, a good fit was also found also to the square root model which could be due to the fact that at early times (3 h) the release had very much occurred by diffusion or leaching though water filled pores since Carbopol 971P® NF was not gelled, while Eudragit®E100 was soluble to some extent. The good fit to Korsmeyer–Peppas model suggested that other events occurred during drug diffusion process such as polymer relaxation and swelling, and matrix erosion that might contribute to the overall release mechanism. The drug release rate decreased with time because of the increase in the diffusion path length which could be attributed to the appearance of moving boundaries due to polymer relaxation and swelling, accompanied with less gradual depletion rate of the swollen matrix.

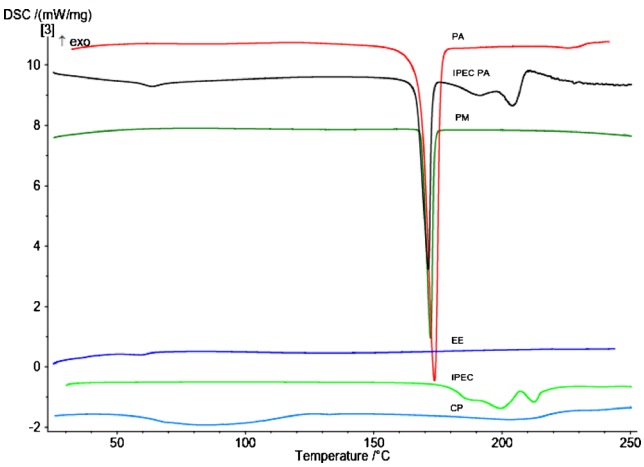

Fig. 8. DSC thermogramsof paracetamol (PA), Eudragit® E100 polymer (EE), Carbopol 971P® NF polymer (Cp), the physical mixture of the two polymers and paracetamol (PM), the interpolyelectrolyte complex (IPEC) of the two polymers, and the IPEC containing paracetamol (IPEC PA)

The Fourier-transform infrared spectroscopy (FT-IR) spectrum of paracetamol is characterized by absorbance bands for hydroxyl groups at 3,324 and 3,162 cm^{-1}, unsaturation (1,653 and 1,610 cm^{-1}), and aromatic ring (1,562, 1,505, and 836 cm^{-1}). Eudragit®E100 showed a characteristic band at 1,730 cm^{-1} which corresponds to absorbance of ester groups. The absorbance bands at 2,770 and 2,820 cm^{-1} can be assigned to non-ionized dimethylamino groups. The IR spectrum of Carbopol971P® NF is characterized by principal absorption peaks at 3,110 (O–H stretching) and 1,720 cm^{-1} (carboxyl group). The FT-IR spectra in Fig. 7 indicated that drug bands were preserved within the tablets (mixed powders) and within the IPEC without paracetamol. However, for the polymers, Eudragit®E100 peak at 2,820 cm^{-1} was greatly minimized, and the peak at 1,730 cm^{-1} disappeared, and for Carbopol971P® NF, the peak at 1,720 cm^{-1} disappeared in IPEC containing paracetamol. This can be attributed to the existence of paracetamol as the major constituent in this composition. These results were also confirmed by the DSC thermograms as shown in Fig. 8, which indicated that the drug was preserved in a crystalline state in all formulations. The transition that appeared at temperature at 205°C in IPEC PA could be attributed to the IPEC itself. This was confirmed by the existence of the same transition for in the DSC trace of IPEC alone (without paracetamol) as shown in Fig. 8.

CONCLUSION

A controlled/sustained release matrix tablet containing paracetamol was developed using Eudragit®E100 polymer along with Carbopol971P® polymer at minimal total polymers concentrations. The combined polymers were found to significantly improve the tablet mechanical properties especially at higher polymeric contents. It is believed that the partial dissolution of Eudragit®E100, polymers electrostatic interactions, and swelling of Carbopol971P® polymer play roles in extending the dissolution behavior of paracetamol tablets. Results indicated that it may be possible to control the release rate of water soluble drugs by modifying the proportion of Eudragit®E100 and Carbopol971P® and their total concentrations.

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