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Novel Salted Anionic-Cationic Polymethacrylate Polymer Blends for Sustained Release of Acidic and Basic Drugs

Wasfy M. Obeidat^{1*}; Duaa Qasim¹; Ali Nokhodchi²; Ahmad Al-jabery³; AL-Sayed Sallam⁴

¹Department of Pharmaceutical Technology, Jordan University of Science and Technology, Irbid, P.O. Box 3030, Jordan. E-mail:obeidatw@just.edu.jo. * To whom correspondence should be addressed.

²School of Life Sciences, University of Sussex, Falmer Brighton, United Kingdom

³Faculty of Pharmacy, Amman Applied University, Amman, Jordan

⁴Executive manager, TQ Pharma, Amman, Jordan

Abstract: Since a unique matrix tablet formulation that independently controls the release of various drug types is in a great demand, the objective of this research was to develop a sustained release matrix tablet as a universal dosage form using a binary mixture of the salt forms of Eudragit polymers rather than their interpolyelectrolyte complexes. Tablets were prepared by wet granulation and compressed at different compression forces, depending on drug type. Dissolution tests were conducted using USP XXII rotating paddle apparatus at 50 rpm at 37°C in consecutive pH stages. Tablets containing Ibuprofen (IB) as a model acidic drug and Metronidazole (MD) as a model basic drug showed controlled/sustained release behavior. For IB tablets containing 80% Ibuprofen and 5% (w/w) polymeric combination; the time for 50% of the drug release was about 24 hours compared to 8.5 hours for plain tablets containing 80% IB. In case of MD, the drug release extended to about 7 hours for tablets containing 80% MD and 5% (w/w) polymeric combination, compared to about 1 hour for plain tablets containing 80% MD. In terms of extending the release of medications, the dissolution profiles of the tablets containing polymeric salts forms were found to be statistically superior to tablets prepared by direct compression of the polymers in their powdered base forms, and superior to tablets containing the same polymers granulated using isopropyl alcohol. The findings indicated the significance of combining the polymers in their salt forms in controlling the release of various drug types from matrices.

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Keywords: Polymethacrylates, Granules, Controlled/Sustained-Release, Ibuprofen, Metronidazole, pH Profile.

1. INTRODUCTION

1.1. Eudragit[®] polymers proved to be suitable for wide variety of pharmaceutical applications such as film-coating agents for protective purposes and to provide sustained-release formulations [1-6], and as binders in both aqueous and organic wet granulation processes [7]. Eudragit E (EE); is a cationic polymer based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters that is soluble in gastric fluid as well as in weakly acidic buffer solutions up to pH 5 [1].

With a pK of 7.0–7.3 [8], EE would be partially protonated at pH close to 5; therefore an electrostatic interaction with another ionized polymers/drugs at this pH could contribute to extend drug release and impact its behavior [9, 10]. Eudragit L (EL) and Eudragit S (ES) are resistant to gastric fluids [11-13], but soluble in neutral to weakly alkaline conditions (pH 6-7) and form salts with alkalis. EL and ES

*Address correspondence to this author at the Department of Pharmaceutical Technology, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box: 3030, Irbid, Jordan; Tel: +96227201000, E-mails: Obeidatw@just.edu.jo.

are anionic copolymers based on methacrylic acid and methyl methacrylate. Both EL and 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 [3].

The polyelectrolytic nature of Eudragit[®] polymers was utilized by some researchers in the formation of interpolyelectrolyte complexes (IPECs) to control the release of certain drugs [9, 10, 14-17]. Interpolymer complexes are generally obtained by noncovalent interaction between oppositely charged polymers [18-26], and the drug plays mainly a passive role [27].

On the other hand, the use of mixtures of anionic and cationic polymethacrylate polymers rather than the use of their interpolyelectrolytic complex (IPEC) has been recently employed in our laboratory in order to control the release of neutral model drug Paracetamol. Tablets containing a combination of EE-citrate and EL-Na at 1:1 ratio and at 5-12% w/w total polymeric contents were found effective in controlling the release of Paracetamol in sustained manner, which suggested the presence of certain specific interaction between EE-citrate and EL-Na with characteristics different from those of the individual polymers in their base forms

[28] and different from their interpolyelectrolytic complex (IPEC) [29]. However, since it was claimed in that earlier work that such combinations of polymers in their salt forms [individual granules] could have the potential to be employed as a universal carrier to control/sustain the release of drugs with different physicochemical properties, it was the aim of the current study to evaluate the behavior of acidic Ibuprofen (IB), and basic Metronidazole (MD) model drugs when incorporated in the same carrier system. Therefore, the release behavior of these model drugs from matrices containing mixtures of anionic and cationic polymethacrylate polymers (in their salt forms) are investigated and compared to matrices containing similar polymers in their base forms. IB is a non-steroidal anti-inflammatory drug available in doses ranging from 200 to 800 mg, and exhibits a pH solubility dependence due to its weakly acidic properties (pka 4.91) [30], while MD is an anti-infective agent available in doses ranging from 250 to 750 mg and exhibits a pH solubility dependence due to its weakly basic properties (pka 2.62) [30]. For convenience, the chemical structures of model drugs and polymers employed in this study are shown in **Figure 1**.

Insert Figure 1 here

2. MATERIALS AND METHOD

2.1. Materials

The different types of Eudragit® polymers of various grades (Eudragit® E100, Eudragit® L100, and Eudragit® S100) were obtained from Evonik Industries AG Germany. Methocel® E5, which is a low-viscosity grade of hydroxyl-propyl methyl-cellulose (HPMC), was obtained from Colorcon-USA. Monobasic potassium phosphate, tri-basic sodium phosphate, sodium hydroxide were obtained from Scharlau-Spain. Hydrochloric acid 37% and potassium bromide (UVasol®) for FTIR spectroscopy were provided by Merck-Germany. Isopropyl alcohol (IPA) was obtained from Tedia-USA. Phosphoric acid 85% was provided by Riedel-de Haen-Germany. Lactose monohydrate, magnesium stearate, and talc were obtained from Hikma Pharmaceuticals-Jordan. Ibuprofen and Metronidazole were kindly provided by Jordan Pharmaceutical Manufacturing (JPM, Amman, Jordan).

2.2. Methods

2.2.1. Preparation of tablets

Plain IB formulations were prepared by blending IB with lactose for four minutes, then magnesium stearate and talc were added and blended for one minute and the final blend was then compressed into tablets. Plain MD formulation were prepared similarly except for an additional component (Methocel E5) added in the first four minutes of mixing. Methocel E5 was added to aid producing MD tablets at a relatively lower compression force. Similar procedure was followed for preparation of tablets containing single, or binary (1:1 ratio) Eudragit® polymers in their powdered base forms.

Tablets containing polymeric granules were prepared by manual blending of the individual model drugs (IB or MD) with lactose using a mortar and a pestle followed by gradual addition of a specified amounts (3-5 g, depending on formulation) of binder solutions while mixing until an adequate degree of agglomeration was visible in the dumpy mass. The following Eudragit® solutions were prepared for preparation of granules: for binder solutions containing polymeric salts, a specific amount of EE was dissolved in 1 N hydrochloric solution, and specific amounts of EL or ES were dissolved in 1 N NaOH. Additionally, tablets containing polymeric granules in their non-salt forms were prepared by granulation using isopropyl alcohol (IPA) as a binder solution. Once a dumpy mass was produced, it was directly sieved into wet granules. The granules were then dried for 30 minutes in an oven at 50 °C followed by sifting the granules through different sieves (3, 2 and 1 mm aperture size). The moisture content of the dried granules was calculated using Halogen moisture analyzer (Model HR 85 Halogen Mettler, USA) and was about 1.246- 1.862%.

Tablets containing single, or binary (1:1 ratio) polymeric salt were prepared. In case of MD, Methocel E5 was added along with magnesium stearate and talc and blended with the granules for one minute and the final mixture was then compressed into tablets. All tablets were compressed using flat-faced, 13 mm diameter punches and die on a hydraulic single press (Carver®, USA). IB containing tablets were compressed at 500 kg for 30 seconds, while MD containing tablets were compressed at 5000 kg for 30 seconds to yield compacts of sufficient strength. The amounts of the model drug, lactose, and Methocel (in case of Metronidazole tablets) for each tablet were kept constant. Magnesium stearate and talc were used for lubrication at 0.25% w/w each. The tablets were produced at room temperature between 23 and 27 °C with the relative humidity between 37 and 42%. Approximately 30 tablets were manufactured at each level of compression force and tablets were stored in airtight containers for at least 24 hours at room temperature to allow for consistent stress relaxation and hardening of the tablets. For each formula, mostly the aimed average tablet weight was 500 ±10 mg (except in certain formulations) and the average amount of active ingredient per tablet was 400 mg ±5 mg.

Tables 1a and 1b show the composition of the tablets containing IB prepared by direct compression of powders or by wet granulation, respectively. The composition of tablet formulations containing MD prepared by direct compression of powders or by wet granulation methods are shown in **Tables 2a and 2b**, respectively. The polymers concentrations in wet granulation method were determined by adding the specified amounts of polymeric solutions (in grams) to the drug and diluent.

Insert Tables 1a, 1b, 2a, and 2b here.

2.2.2. Dissolution studies

Dissolution tests were performed using Copley USP paddle dissolution apparatus II (Copley 10000, UK)

described in USP XX II (Apparatus II). The rotating speed was 50 rpm and the temperature was 37 ± 0.5 °C. The release of the drug was investigated at 3 different stages that mimic the different pH values of the gastrointestinal environment; the first stage lasted for one hour at pH 1.2 ± 0.2 and the volume of the dissolution medium was 500 ml. The second stage was conducted at pH 4.8 ± 0.2 for 2 hours. The volume of the dissolution medium in the second stage was increased to 740 ± 5 ml by adding tribasic sodium phosphate (0.2 M Na_3PO_4) solution. The final stage was conducted from 5 to 24 hours and the pH was adjusted to 6.8 ± 0.2 by adding (0.2 M Na_3PO_4) and completing the volume of the dissolution medium to 1000 ml. In addition, dissolutions of certain tablets formulations were conducted in media of constant pH values 1.2 ± 0.2 and 6.8 ± 0.2 . In all cases, samples of 5 milliliters were withdrawn at appropriate time intervals, and replaced with an equal volume of fresh dissolution medium. Samples were filtered, diluted, and analyzed spectrophotometrically at the suitable λ_{max} for each drug. Three tablets from each formulation were subjected to the dissolution test and the results were presented as the mean values of three determinations, standard deviation. The duration of the study ranged from 8-24 hours or until the cumulative drug release reached 90-100%. The percentage of drug released was plotted versus time.

2.2.3. Physical tests

2.2.3.1. Crushing strengths, thicknesses and diameters

Three tablets from each formula were tested for their crushing strengths using tablet hardness tester (Copley, 2E/205/ Switzerland) in kilopond (Kp). The diameters and thicknesses for all tablets were determined using an electronic digital caliper (Digital Caliper 6'', Toolsnow, China) and the measurements were taken up to two decimal points.

2.2.3.2. Stability study

The stability in terms of drug release behavior of matrices containing model drugs and a combination polymeric salts was performed for short term (3 months) at room temperature. In addition, an accelerated stability test at 50°C was performed for 5 days.

2.2.3.3. Differential Scanning Calorimetry Analysis

Differential scanning calorimetry (DSC) traces of plain Ibuprofen as well as plain Metronidazole powders, plain polymers, and physical mixture of Ibuprofen with the polymers, were recorded using a Shimadzu DSC-50 (Japan). Samples of approximately 5-8 mg were heated from 25 to 250°C at 10°C/min. Pierced Aluminium pans were used for all samples. Pure indium was used to calibrate the DSC.

2.2.3.4. Fourier transform infrared analysis (FT-IR)

The interaction between EE and EL was studied using FT-IR spectroscopy. FT-IR spectra of pure EE and EL polymers, physical mix of EE and EL, and physical mixture of EE and EL granules were obtained using an FT-IR spectrophotometer (Model 8400S Shimadzu, Japan) using

KBr as a reference. The scanning range was 450-4000 cm^{-1} . Samples were dried at 40 °C for 24 hours before analysis.

2.2.4 Area under the dissolution curves and statistical analysis

For each of the two formulations being compared, the areas under the dissolution curves for three tablets were calculated using the trapezoidal rule, and the mean area under the curve and its standard deviation were estimated. The ratio of the mean area under the curve of the test formulation to that of the reference (plain) formulation was calculated (i.e., mean of test to mean of reference). Student T-test was employed to compare the mean of the area under the curve of the test formulation to the mean area under the curve of the reference (plain) formulation, at level of significance of 0.05. The threshold for a difference was considered significant when p value ≤ 0.05 .

3. RESULTS AND DISCUSSION

3.1. Analytical method and Physical characterization of tablets

Throughout this study, the UV analysis for the drugs was carried out at the appropriate λ_{max} after dilution of the samples when needed. The UV/VIS spectrophotometric scanning of Ibuprofen showed an appropriate absorbance at 264 nm without shifting at various pH values. The appropriate absorbance value was also reported by the European Pharmacopoeia (Ph. Eur.) [31]. On the other hand, Metronidazole showed maximum absorbance at 275 nm in acidic medium (pH 1.2), and at 320 nm in the buffered medium (pH 6.8). The calibration curves for both IB and MD were linear in different dissolution media in various pH values with a correlation coefficient close to 0.9998. No significant UV/VIS interaction between the drugs and the polymers employed in tablets preparation at the adopted wavelengths.

Tablets crushing strengths in terms of kilopond (Kp) were reported in Table 3 for all IB and MD tablets formulations. Apparently, IB was found to produce compacts of sufficient strengths under lower compression forces (500 Kg) compared to MD (5000 Kg). All tablets formulations were also evaluated for their thicknesses and diameters in terms of millimeters, and the results were reported in Table 3. Tablet formulations (IB and MD formulations) showed similar diameters, but slightly higher thicknesses compared to the plain tablets (IB#1) or (MD#1), respectively.

3.2. Tablet dissolution and drug release studies

Both model drugs suffer pH dependent solubility profiles. Preliminary results during pH dissolution profiles (from pH 1.2 to 6.8 through 4.8) revealed that plain IB tablets (IB#1) exhibited negligible drug release in the acidic medium (pH 1.2), low release at pH 4.8, and an increased release at pH 6.8. Inversely, MD tablets (MD#1) exhibited rapid dissolution in the acidic stage (pH 1.2), and slower dissolution at pH 4.8 and 6.8 (data not shown).

An interaction in the form of plasticization or liquefaction was visually noticed within a week upon storage at room temperature when EE in its base form was mixed with IB powders to form tablets. This can be due to an acid-base or an anion-cation interaction. Similar phenomena was reported for the interaction of EE with Enalapril Maleate [34], and with different anionic drugs [35, 36], and for the interaction of anionic drugs with cationic polymers containing amino groups [37-39]. However, when the salt form of EE was employed via granulation, no such interaction was observed and tablets were found stable upon storage. Freshly prepared tablets containing EE base (IB#2) or EEHCl (IB#10) exhibited approximately similar release rates of IB at pH values of 1.2 and 4.8 due to the low solubility of IB in these media. Nevertheless, EEHCl provided significant retardation of IB release from IB#10 compared to EE base tablets IB#2 in the buffered dissolution stage at pH 6.8. This was evident when the areas under the dissolution profiles of both formulations were compared as shown in **Table 4**. This can be attributed to the influence of wet granulation using EEHCl as a binder solution where it forms a film layer around each substrate particle within the granule [40] or completely envelope the particles [41]; resulting in a barrier to drug release during dissolution. In addition, the aforementioned plasticization effect exhibited by IB#2 tablets due to the presence of EE base might have accelerated IB dissolution and release.

Insert Table 4 here

Unlike IB, MD was found to be compatible with EE in both forms (EE base or EEHCl). When MD was directly compressed with 5% EE base (MD#2), or when MD was granulated using 5% EEHCl solution (MD#10), the release rates were modified to different extents, but insignificantly ($p > 0.05$) compared to plain MD tablets devoid of EE (**Table 4**). Despite that both EEHCl and MD are positively charged with possible electrostatic repulsion existed during the acid dissolution stage, the observed reduction in drug release rate could be attributed to the effect of granulation and probably to the film barrier effect [40, 41].

Generally, IB tablets prepared using 5% EE granules (EEHCl) (IB#10) were found to result in a significant decrease in drug release rates compared to plain tablets, or compared to tablets containing EE base form (IB#2) during the buffer stage (pH 6.8) dissolution ($p \leq 0.05$). Similar behavior was noticed for the dissolution profile MD tablets prepared using 5% EE granules (EEHCl) (MD#10) when compared to MD#2 tablets containing similar concentration of EE base instead (data not shown).

Generally, both EL and ES in their powdered base forms induced faster IB release from the respective formulations to various degrees depending on the polymer type and concentration within the tablet as shown in **Figure 1**. This increase in drug release can be attributed to the fact that IB, EL or ES became ionized at pH 6.8; therefore, owing to possible electrostatic repulsion, faster diffusion of IB was obtained. Higher concentrations (10%) of EL powder (IB#4)

or ES powder (IB#6) produced significant increase in drug release rates compared to lower concentrations (5%); (IB#3) or (IB#5), respectively. Also, the drug release enhancement effect due to ES powder was significantly more than the effects due to EL powder at similar concentrations as shown in **Table 4**.

The behavior of the salt forms of these polymers (ELNa and ESNa) was different. While, 5% of ELNa (IB#11) produced marked retardation in IB release rates, similar concentration (5%) of ESNa (IB#12) enhanced the release rates of IB compared to those from plain IB tablets (IB#1), as shown in **Figure 2**. However, tablets containing the polymers in their salt forms (IB#11 and IB#12) exhibited marked retardation in IB release compared to tablets with polymers in their base forms (IB#3 and IB#5). This can be attributed to the impact of granulation process on distributing and enveloping the polymeric binders around the drug and excipients [40, 41]. The behavior can also be attributed to the significantly lower crushing strengths of tablets containing powdered polymers (IB#3, 4, 5, and IB#6) compared to those formulated via granulation (IB#11 and IB#12) as shown in **Table 3**.

Insert Table 4 here

In general, it can be observed from **Figures 2 and 3** that the use of EL in its base or salt forms resulted in more resistance to drug release from matrices compared to the use of ES in its base or salt forms. Tablets containing ES powder exhibited higher crushing strengths than those containing EL powder, while tablets containing the salt forms of EL or ES were nearly comparable (**Table 3**). Since ES is less ionized than EL in the buffered medium at pH 6.8 due to the lower number of free carboxylic acid groups in its structure, it was expected to be more capable of retaining the already dissociated form of IB in this medium. Therefore, it logical to anticipate that other factors such as the nature and degree of polymer swelling and/or the magnitude of tablet porosity might have influenced such rapid release from ES-containing tablets.

Insert Figures 2 and 3 here

For the basic model drug Metronidazole, the same release profile as the MD plain tablets was obtained upon incorporation of up to 10% EL or ES powders in the formulations as presented in **Figure 4**.

Insert Figure 4 here

However, when MD was granulated using 5 or 10% ELNa (MD#11 or MD#12), or using 5 or 10% ESNa (MD#13 or MD#14), significant retardations in MD release in all dissolution media were observed ($p \leq 0.05$). An interaction between a cationic drug containing an amino group and a polymer with anionic pending groups, that is, carboxylic group, electrostatically [42-46] or by hydrogen bonding [47-51] has been reported frequently. However, it seemed that

such interaction was insignificant in case of MD with EL or with ES since drug release retardation was experienced in tablets containing the salt forms of the polymers. Since the crushing strengths of tablets containing ELNa or ESNa at 5 or 10% were comparable to those of tablets containing 5 or 10% EL or ES powders, respectively, then the retardation induced by granulation using ELNa or ESNa polymers could be attributed to the effects of granulation and film formation [40, 41], rather than to a specific drug-polymer interaction. It was noteworthy that both polymers (ELNa or ESNa) behaved similarly in terms of regulating the release of MD from their compressed granules.

When polymeric combination was used at 5% total polymeric salts concentration (w/w) instead of individual polymers, a more sustained release of IB was observed compared to plain IB tablets as it is evident in **Figure 5**.

Insert Figure 5 here

However, IB tablets prepared by granulation using the salt forms of the polymers, i.e. EEHCl : ELNa (IB#13) or EEHCl:ESNa (IB#14) at 1:1 ratio, exhibited a significantly more sustained release compared to tablets containing a binary combination of the free polymers in their powdered base forms of similar ratios and concentrations, ($p \leq 0.05$). This trend was apparent regardless the tablets were prepared by direct compression (IB#7) or granulation (IB#9) using the free polymers combination.

During dissolution in the buffered medium at pH 6.8, IB will be ionized carrying a negative charge. It is also anticipated that certain amount of EEHCl would become deprotonated and precipitated, while ELNa or ESNa remain as such; negatively charged. It was demonstrated earlier that tablets containing EEHCl alone (IB#10) exhibited more retardation of IB release compared to tablets containing EE base alone (IB#2). It was also shown in **Figure 3** that tablets containing ELNa salt alone (IB#11) produced a significant retardation in IB release rates. However, tablets containing the polymeric salts combination (IB#13 and IB#14) resulted in a significantly more retardation effects on IB release compared to tablets containing EEHCl alone (IB#10) or ELNa salt alone (IB#11). The behavior seemed to be additive at the first glimpse. However, this is not the case considering the retardation of IB release from tablets containing ESNa salt with EEHCl salt (IB#14) compared to the enhancement of IB release from those containing ES salt alone (IB#12). This peculiar behavior may provide more evidence of polymeric interactions rather than a simple additive effect. Therefore, the behavior of tablets containing a combination of the salt forms is attributed to a possible synergism due to certain interactions between the two polymeric salts upon dissolution. Moreover, it is this interaction between the two polymeric salts rather than the effect of granulation per se is believed to be responsible for the retardation in drug release as discussed earlier and illustrated in **Figure 5**.

Generally, similar behavior was noticed with regard to MD tablet formulations as shown in part in **Figure 6**. The

polymeric salt combinations used in preparing MD#15 and MD#17 tablets resulted in significant lowering in MD release compared to MD#7 and 10% MD#8 tablets containing polymeric combinations in their free forms. It was observed from **Figure 6** that the drug release rates have been significantly reduced in all consecutive dissolution stages.

Insert Figure 6 here

In the acidic medium at pH 1.2, MD and EEHCl are protonated with positive charges and thus, the possibility of electrostatic repulsion exists. Upon using polymeric salts combinations, the drug release rates during the acidic stage were significantly lower compared to those from MD#10 containing EEHCl alone. This can only be attributed to the presence of the second polymer which is ELNa or ESNa and a possible polymeric interaction that is responsible for extending the MD release in this medium. During dissolution in buffered medium at pH 4.8, MD and the two polymers existed in two states; protonated and unprotonated ones to various extents. However, unlike in MD#7 containing the binary polymers in their base forms, the drug release rates were significantly reduced for MD#15 and MD#17 where the polymers existed originally in their salt forms (MD#15 and MD#17). In the buffered medium at pH 6.8, MD and certain amount of EEHCl might become deprotonated and precipitated, while ELNa or ESNa remained ionized and thus negatively charged. It was observed in **Figure 5** that tablets containing ELNa alone or ESNa alone resulted in a retardation of MD release from MD#11 and MD#13 (at 5% concentration). However, this retardation was significantly lower than that brought up by the synergistic action of polymeric salts combinations of similar total polymers concentrations (5%) during dissolution in this stage (pH 6.8). Again, this indicated the presence of certain interaction that might have taken place upon dissolution between polymeric salts combination that lead to such significant drug release retardation.

The dissolution behaviors of Ibuprofen (IB#13) and Metronidazole (MD#15) tablets made of polymeric salts combination in acidic (pH 1.2) as well as in buffered media (pH 6.8) shown in **Figures 7 and 8** were in agreement with those shown in **Figures 5 and 6**; indicating the influence of such combination on drugs release patterns. In addition, tablets subjected to short term stability (3 months) at room temperature and to an accelerated stability test at 50°C for 5 days, yielded statistically similar drug release behavior to those analyzed at room temperature at all times intervals in all the three dissolution media ($p > 0.05$).

Insert Figures 7 and 8 here

Therefore, the results were in support of a possible interaction upon dissolution that was suggested earlier to control the release of neutral model drug Paracetamol from matrix systems [28, 29]. This was apparently due to the high degree of interactions that could be existed between the

ionized polymers where maximum level charge density was obtained. In addition, hydrogen bonding which implies a weaker interaction than electrostatic bond, might have taken place. For example, a complex between Naltrexone hydrochloride and Eudragit L was successfully obtained by hydrogen bond occurring among polar group of both molecules [48]. Also, hydrogen bond was used to prepare interpolymer complexes for pharmaceutical applications [49, 51, 52].

3.3. Drug release mechanism

Data curve fitting and simulation were analyzed using SigmaPlot software, version SPW 11 (Systat Software, Inc., Ca, USA). Models of the drug release were fitted to the drug release data obtained from the dissolution of certain polymeric combination tablets selected for convenience; IB#13 and MD#15 in both acidic (pH 1.2) and buffered (pH 6.8) media. Korsmeyer–Peppas (the power law) model was found to have the best fit to the drug release data limited to 60% release. [32, 33]:

$$\frac{Q_t}{Q_\infty} = K \cdot t^n \quad [1]$$

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. In the case of a cylindrical matrices such as tablets, $n=0.45$ suggests that the release mechanism follows Fickian diffusion where $n = 0.89$ indicates a case II transport mechanism. A hybrid release mechanism where polymer swelling and erosion as well as drug diffusion all controls drug release from the matrices when n values between 0.45 and 0.89 are obtained.

For IB# 13, the drug release data in acidic medium were not fitted since about 10% cumulative drug release was obtained throughout the dissolution time. However, in the buffered medium (pH 6.8), the power law model fitted the data with regression coefficient (R^2) was 0.9987, the constant K was 0.0821, while n value was 0.8636. For MD#15 in the acidic medium, the regression coefficient, the constant K and n value were 0.9981, 4.6315 and 0.6041 respectively, whereas, in the buffered medium (pH 6.8), these values were 0.9962, 1.1435 and 0.7073 respectively. Therefore, the n values for both formulations (IB#13 and MD#15) were between 0.45 and 0.89, indicating a combined mechanism of diffusion, polymer swelling and/or matrix erosion at later stages of dissolution process. The drugs release rates in the respective media decreased with time which is attributed to the increase in the diffusional path length due to polymer relaxation and matrix swelling as well as drug depletion from the tablets (53).

3.4. Differential Scanning Calorimetry Analysis

Figure 9 shows the DSC traces for plain Ibuprofen (IB), individual polymers (EL and EE), mixtures of IB and EL, mixtures of IB and EE at various ratios (1:1, 2:1 and 1:2), and mixtures of IB and EEHCl at 1:1 ratio. Mixtures

containing ES exhibited similar pattern as those containing EL, therefore were not shown here.

Insert Figure 9 here

IB exhibited a sharp endothermic peak at about 77 °C attributed to the melting of plain IB. It was apparent from the figure that a peak broadening or early melting occurred in the region of IB melting peak when combined with EE at the different ratios. As mentioned earlier, it was observed that IB tablets containing EE polymer exhibited softening process shortly after their manufacture. This can be attributed to an acid-base interaction between the acidic drug IB and the basic polymer EE that lead to plasticization or softening of the tablets. The endotherm of plain IB was found to exhibit broadening and shifting to lower temperatures upon mixing with EE base at different ratios, as confirmed by differential scanning calorimetry (DSC). The DSC thermograms for the dried granules containing IB and the polymer in its salt form at 1:1 ratio (IB:EEHCl) exhibited a sharp endotherm at 77°C. The slight peak broadening or early melting in the latter case is indicative of absence or significantly lower drug-polymer interactions and therefore, the compatibility of such combination.

The DSC thermograms for MD and polymeric combinations were also conducted (data not shown). MD exhibited a sharp endotherm at about 170 °C attributed to its melting. In contrast to the behavior of IB, MD did not exhibit significant interactions with any of the polymers employed in tablets formulations, including EE base. This was confirmed by both visual examinations as well as differential scanning calorimetry (DSC) results. The endothermic peak of MD was found to be preserved with slight lowering when combined with EE, EL, or when MD was granulated with EE/ 0.1N HCl solution. The slight lowering of MD melting point did not reveal any changes on the visual appearance of the tablets. Therefore, these results indicated the compatibility of MD with all employed polymers.

3.5. Fourier transform infrared analysis (FT-IR)

Figure 10 shows the FT-IR spectra of moisture-free pure EE and EL powdered polymers, EE and EL granules, physical mix of EE and EL at 1:1 ratio, and physical mix of EE and EL granules at 1:1 ratio. ES spectra exhibited similar pattern to EL, therefore were not shown here.

Insert Figure 10 here

Since EE and EL (or ES) are derivatives of methacrylic acid copolymers, the FT-IR spectra would exhibit many common features. EE showed characteristic band at 1728 cm^{-1} which corresponds to absorption of ester groups in addition to two more absorption bands at 2769 and 2823 cm^{-1} which corresponds to the optical absorption due to non-ionized dimethylamino groups. On the other hand, the spectrum of EL showed similar but broader absorption band for the non-ionized carboxylic acid groups at 1728 cm^{-1} than that found

in EE due to the intra- and intermolecular hydrogen bonding between the carboxylic acid groups [54]. In addition, EL [or ES] also showed a wide absorption range of the associated hydroxyl groups between 2500 and 3500 cm^{-1} shown as several minor peaks. The FT-IR spectrum of the physical mixture EE and EL seemed to be a 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. On the other hand, the FT-IR spectrum of the physical mixture EE and EL granules seemed to exhibit a shift in the absorption peak from 1728 cm^{-1} to about 1620 cm^{-1} , and minimization or disappearance of the absorption peaks at 2769 and 2823 cm^{-1} compared to the pure polymers. These shifts and minimization in absorption peaks could be explained by the ionization of carboxylic acids in EL polymer, and the protonation of dimethylamino groups of EE polymer [15, 35]. However, despite these changes in the FT-IR spectra of EE-EL granules compared to the powdered mixtures, there was no evidence of any interaction between the two polymers in the dry granules mixture.

4. CONCLUSION

The combination of anionic and cationic polymethacrylate polymers in their salt (individual granules) at 1:1 ratio and at total polymers concentrations of 5% was found to be effective in extending the release of model acidic and basic drugs from matrix tablets. For Ibuprofen, the drug release rates from such matrices were decreased when shifting the pH values from acidic to neutral compared to plain Ibuprofen tablets. For Metronidazole, the drug release rates from such matrices were significantly lowered in both acidic and neutral media compared to plain metronidazole tablets. The polymeric combinations in their salt forms were found superior in extending release throughout the dissolution profile of model acidic and basic drugs as compared to single polymers in their free or salt forms, and to the polymeric combinations in their free forms that were either directly compressed as powders or granulated using isopropyl alcohol. It appears that upon dissolution, a possible formation of an interaction between polymeric salts of EE and EL with characteristics different from the individual polymers is the basis for the significant drug release extension.

The current findings along with the previously reported work suggests that the combination of EE with EL or with ES in their salt form could be suitable for formulating matrix tablets for drugs of different physicochemical properties. Therefore, such a polymeric combination has the potential to be used as a universal carrier for controlling the release of drugs from matrix tablets.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

6. ACKNOWLEDGEMENTS

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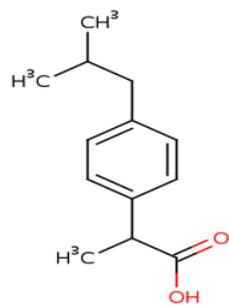
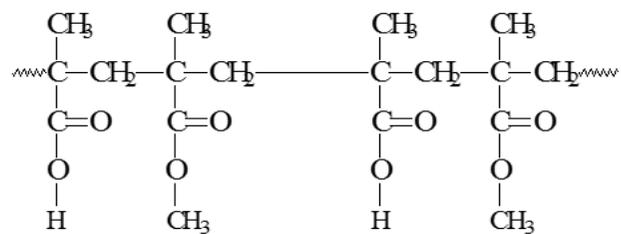
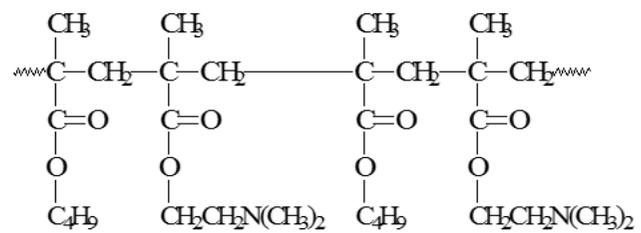
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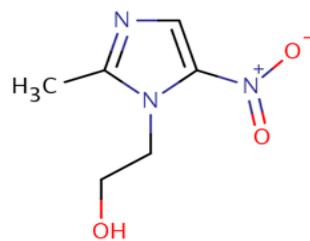
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(c)



(d)

Figure 1

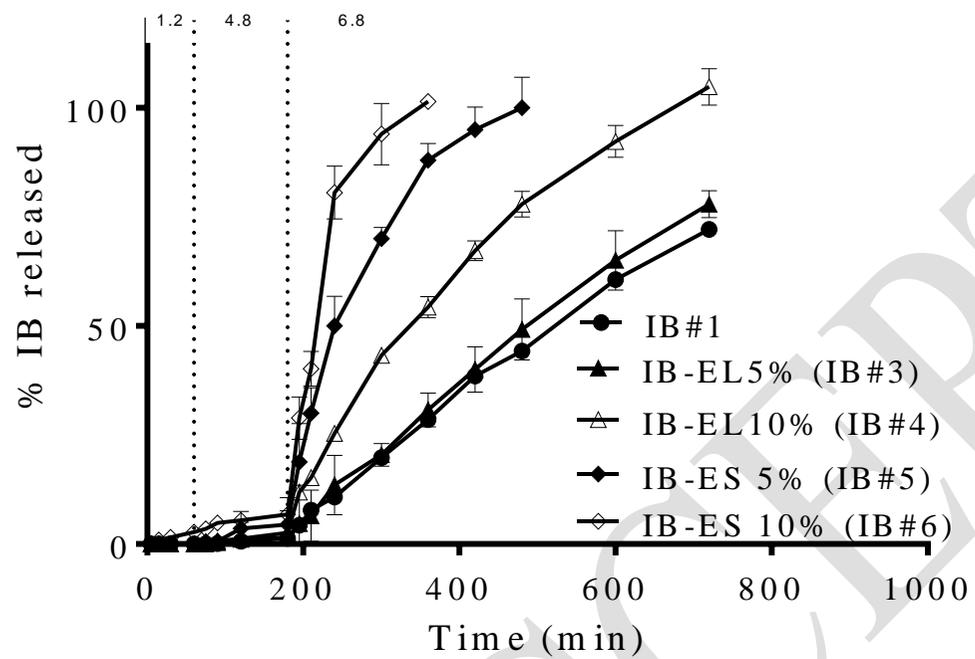


Figure 2

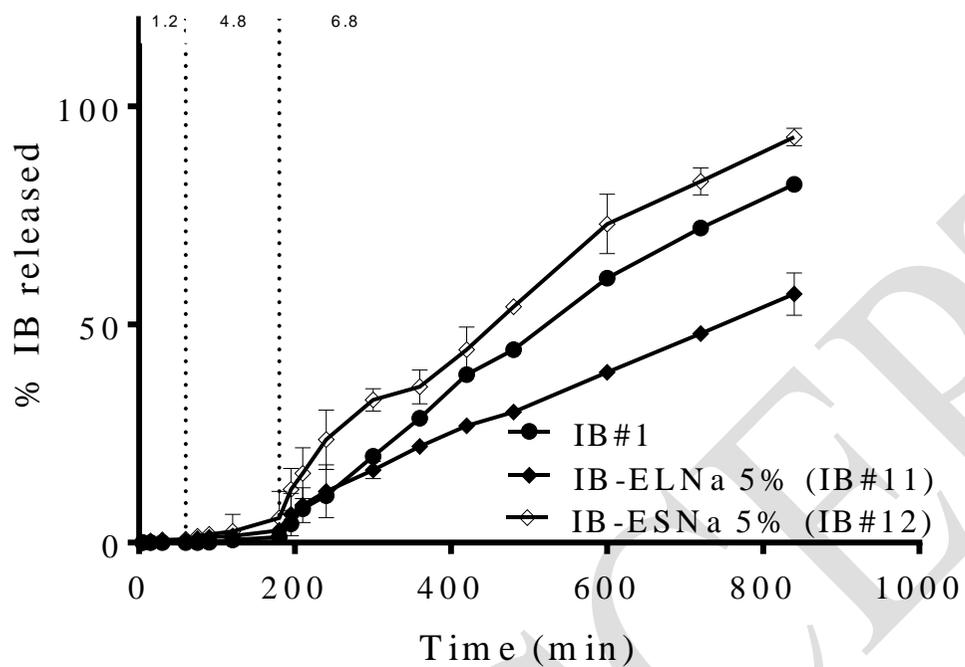


Figure 3

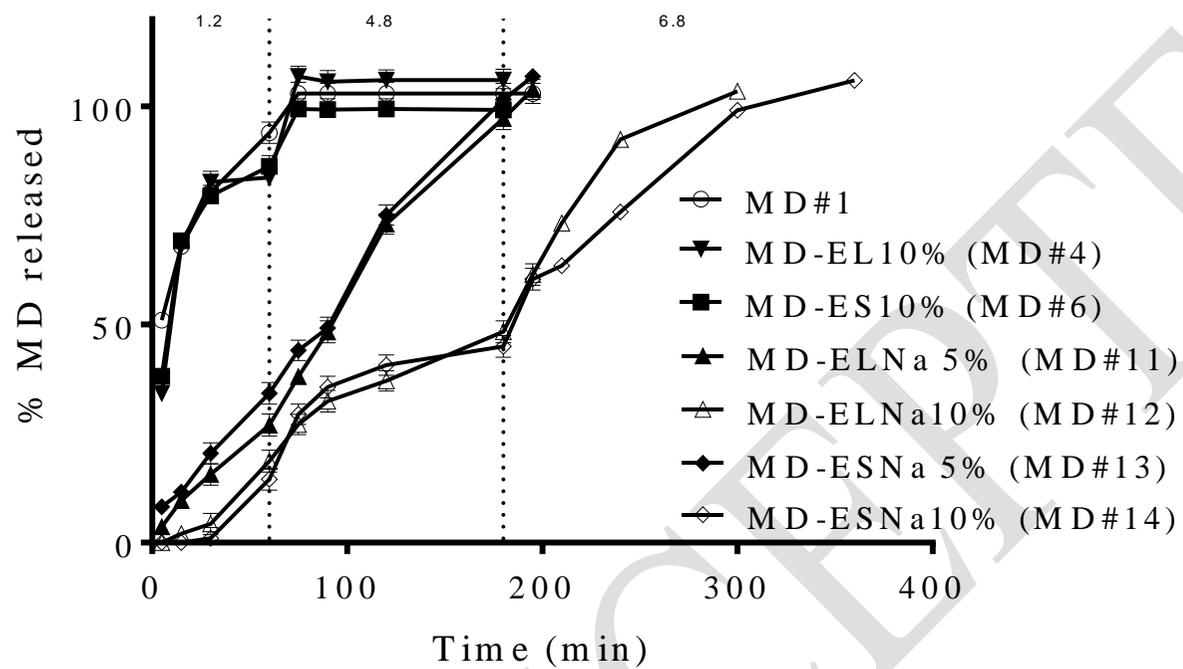


Figure 4

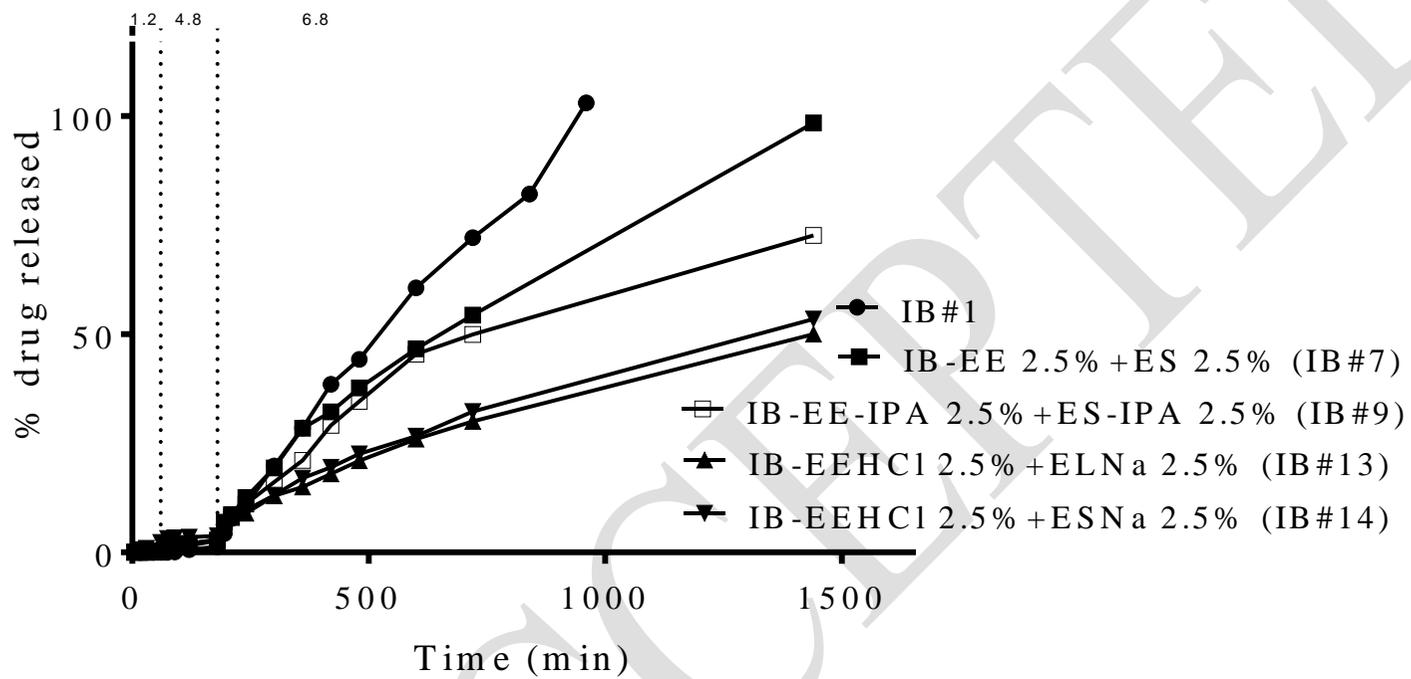


Figure 5

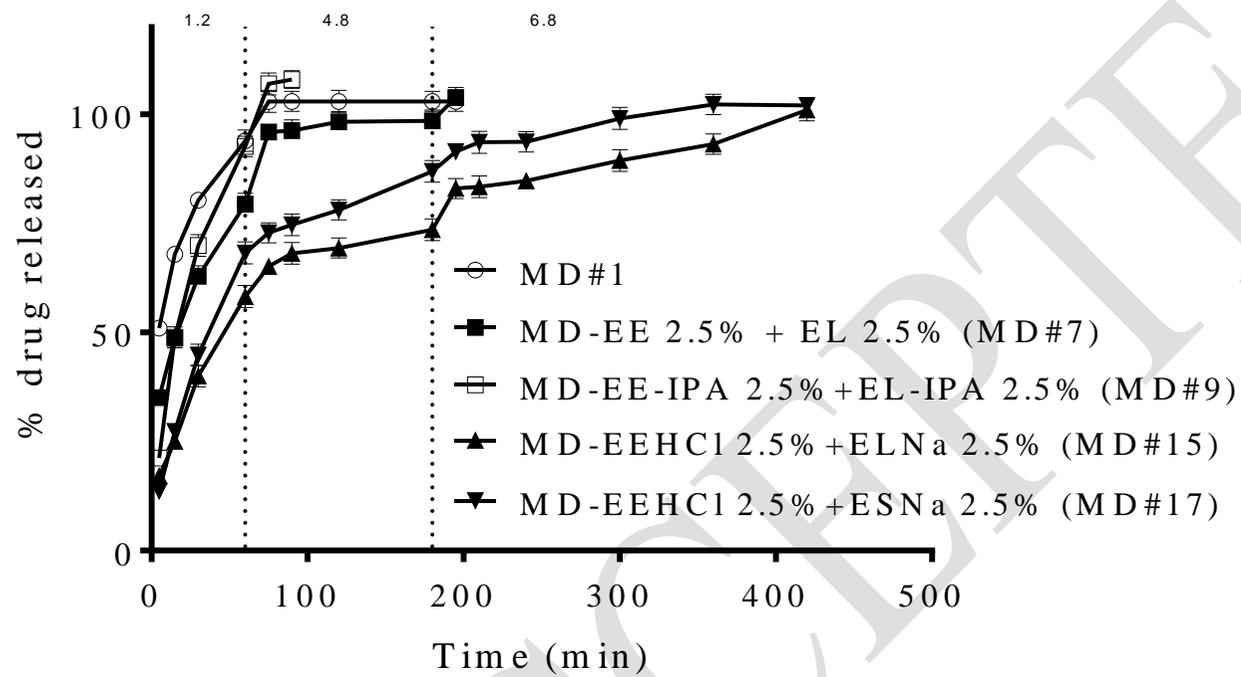


Figure 6

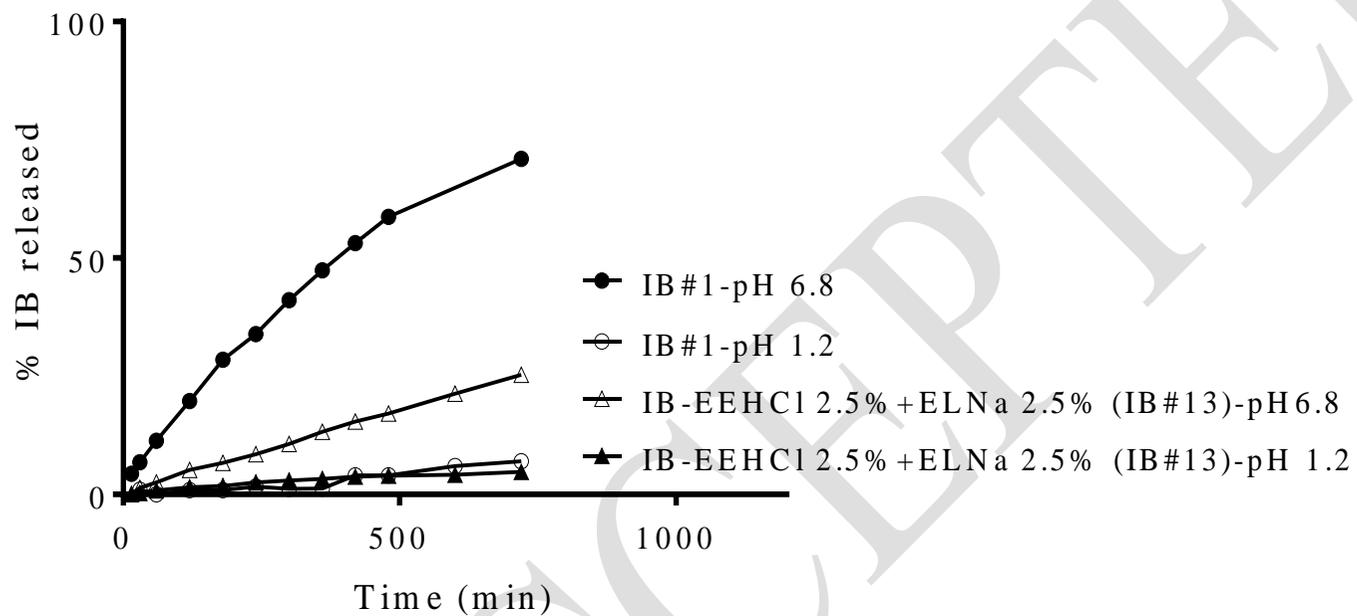


Figure 7

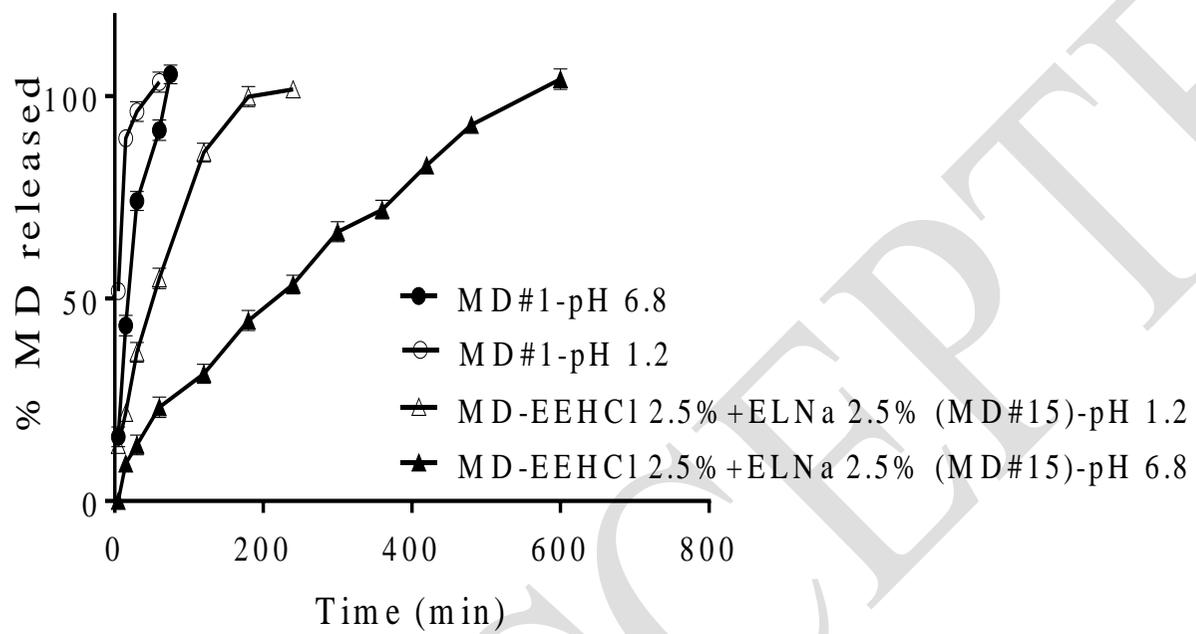


Figure 8

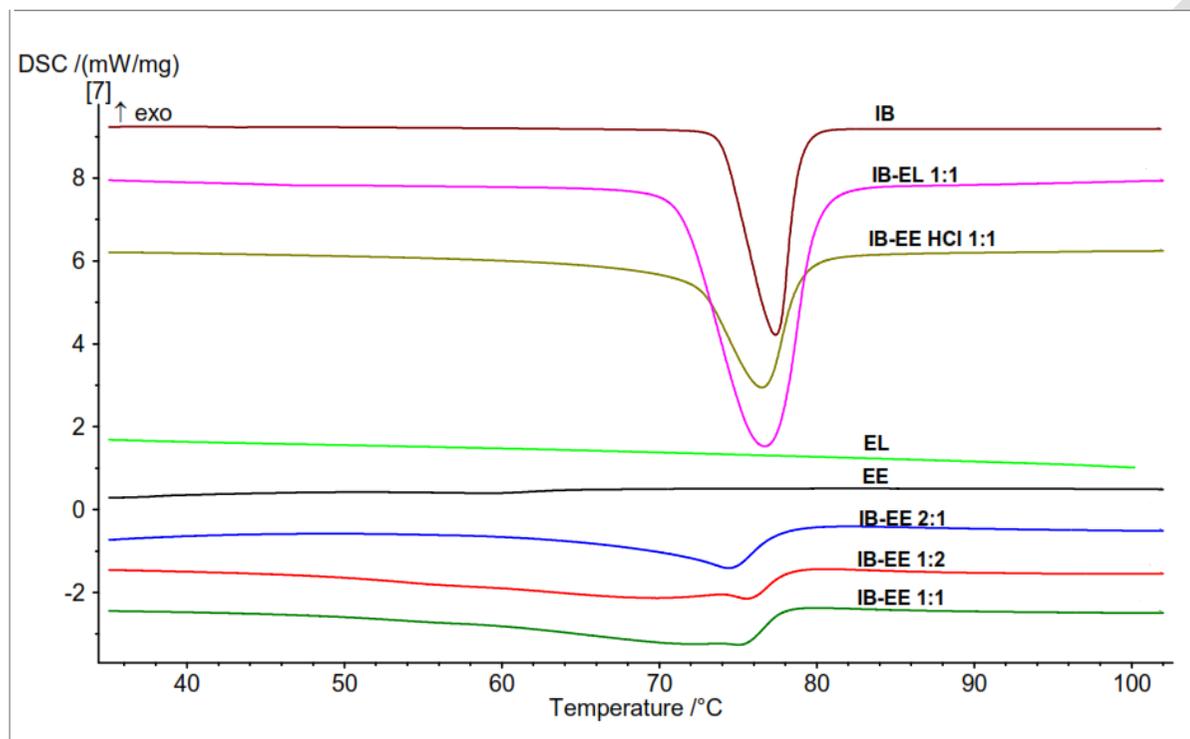


Figure 9

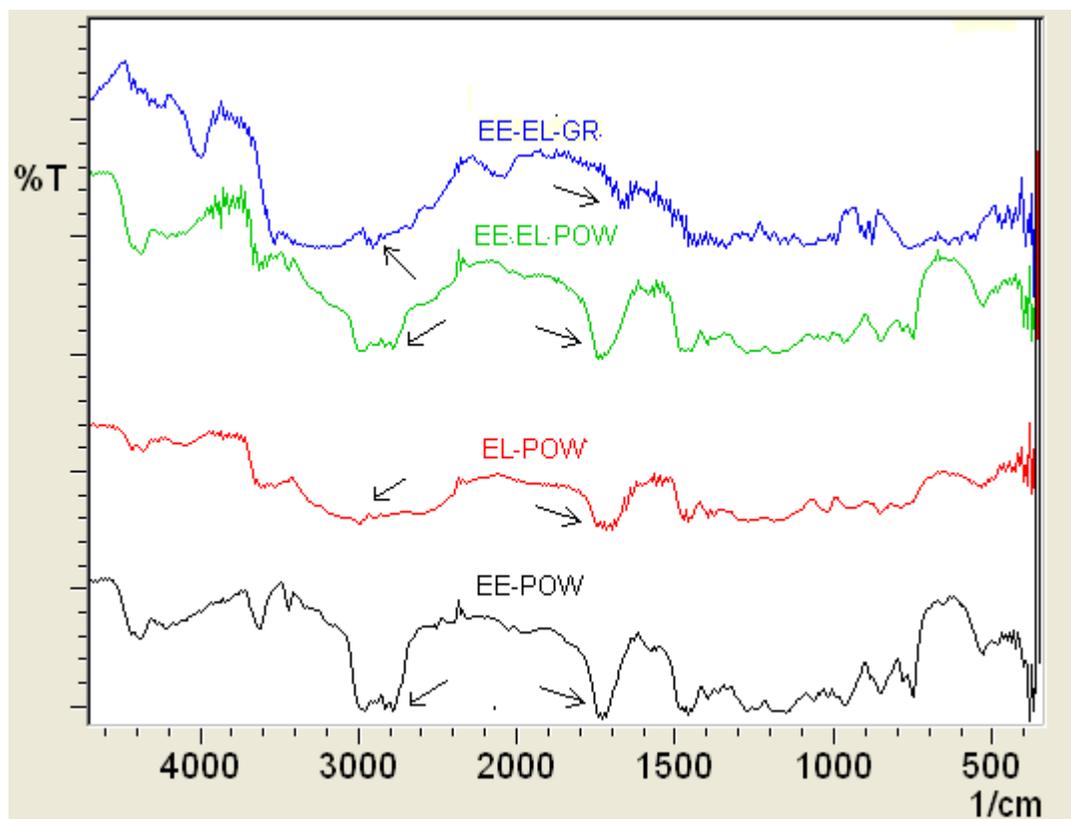


Figure 10

Table 1a

Name	Formula No.															
	IB1		IB2		IB3		IB4		IB5		IB6		IB7		IB8	
	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)
Ibuprofen	400	80	400	80	400	80	400	80	400	80	400	80	400	80	400	80
Lactose	97.5	19.5	72.5	14.5	72.5	14.5	47.5	9.5	72.5	14.5	47.5	9.5	72.5	14.5	72.5	14.5
Mg stearate	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
Talc	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
EE			25	5									12.5	2.5	25	5
EL					25	5	50	10								
ES									25	5	50	10	12.5	2.5	25	5
Total (mg)	500	100	500	100	500	100	500	100	500	100	500	100	500	100	550	100

Table 1b

Name	Formula No.															
	IB9		IB10		IB11		IB12		IB13		IB14		IB15		IB16	
	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)
Ibuprofen	400	80	400	80	400	80	400	80	400	80	400	80	400	80	400	80
Lactose	72.5	14.5	72.5	14.5	72.5	14.5	72.5	14.5	72.5	14.5	72.5	14.5	72.5	14.5	72.5	14.5
Mg stearate	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
Talc	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
EE-HCl			25 ^a	5					12.5 ^d	2.5	12.5 ^d	2.5	25 ^a	5	25 ^a	5
EL-Na					25 ^b	5			12.5 ^e	2.5			25 ^a	5		
ES-Na							25 ^c	5			12.5 ^f	2.5			25 ^c	5
EE-IPA	12.5	2.5														
ES-IPA	12.5	2.5														
H ₂ O			q.s		q.s		q.s	q.s		q.s				q.s		
Total (mg)	500	500	500	100	500	100	500	500	100	500	100	100	100	500	100	100
	(a) Equivalent to 17.20 mg of EE		(b) Equivalent to 19.70 mg of EL		(c) Equivalent to 19.70 mg of ES											
	(d) Equivalent to 8.60 mg of EE		(e) Equivalent to 9.85 mg of EL		(f) Equivalent to 9.85 mg of ES											

Table 2b

Name	Formula No.																	
	MD10		MD11		MD12		MD13		MD14		MD15		MD16		MD17		MD18	
	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)	mg/tab	%(w/w)								
Metronidazole	400	80	400	80	400	80	400	80	400	80	400	80	400	80	400	80	400	80
Lactose	60	12	60	12	60	12	60	12	60	12	60	12	60	12	60	12	60	12
Methocel	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5	12.5	2.5
Mg stearate	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
Talc	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25	1.25	0.25
EE-HCl	25 ^a	5									12.5 ^f	2.5	25 ^a	5	12.5 ^f	2.5	25 ^a	5
EL-Na			25 ^b	5	50 ^e	10					12.5 ^g	2.5	25 ^b	5				
ES-Na							25 ^d	5	50 ^e	10					12.5 ^h	2.5	25 ^d	5
H ₂ O	q.s		q.s		q.s		q.s		q.s									
Total (mg)	500	100	500	100	525	100	500	100	525	100	500	100	525	100	500	100	525	100
(a) Equivalent to 17.20 mg of EE (b) Equivalent to 19.70 mg of EL (c) Equivalent to 39.40 mg of EL (d) Equivalent to 19.70 mg of ES (e) Equivalent to 39.40 mg of ES (f) Equivalent to 8.60 mg of EE (g) Equivalent to 9.85 mg of EL (h) Equivalent to 9.85 mg of ES																		

Table 3

IB Formula #	Crushing strength (Kp)	Tablet thickness (mm)	Tablet diameter (mm)	MD Formula #	Crushing strength (Kp)	Tablet thickness (mm)	Tablet diameter (mm)
IB#1	5.6±0.1	3.41±0.01	12.97±0.08	MD#1	12.1±0.5	2.82±0.03	12.97±0.08
IB#2	4.9±0.2	3.69±0.01	12.98±0.06	MD#2	11.4±0.5	2.84±0.03	13.08±0.07
IB#3	4.8±0.2	3.54±0.02	13.09±0.06	MD#3	11.3±0.2	2.80±0.02	13.05±0.05
IB#4	4.2±0.2	3.57±0.01	13.02±0.06	MD#4	10.2±0.4	2.82±0.02	13.06±0.06
IB#5	6±0.2	3.53±0.01	13.02±0.06	MD#5	9.4±0.4	2.80±0.02	12.95±0.12
IB#6	5.5±0.3	3.64±0.02	12.98±0.12	MD#6	11.8±0.6	2.86±0.03	13.05±0.10
IB#7	9.8±0.3	3.63±0.01	13.04±0.10	MD#7	11.6±0.7	2.88±0.03	12.97±0.05
IB#8	12±0.4	3.54±0.01	13.02±0.05	MD#8	12.0±1.3	2.87±0.04	12.98±0.11
IB#9	9.8±0.4	3.64±0.01	12.98±0.11	MD#9	8.8±0.5	2.83±0.02	13.09±0.07
IB#10	8.4±0.4	3.46±0.02	13.04±0.07	MD#10	12.1±0.5	2.82±0.03	13.02±0.05
IB#11	11±0.1	3.49±0.03	13.05±0.08	MD#11	11.4±0.5	2.84±0.03	13.02±0.08
IB#12	10.2±0.4	3.57±0.02	13.06±0.05	MD#12	11.3±0.2	2.80±0.02	12.98±0.06
IB#13	11.7±0.3	3.56±0.02	12.95±0.06	MD#13	10.2±0.4	2.82±0.02	13.04±0.06
IB#14	11.5±0.3	3.58±0.01	13.04±0.06	MD#14	9.4±0.4	2.80±0.02	12.98±0.12
IB#15	11.2±0.5	3.56±0.02	13.04±0.06	MD#15	9.5±0.4	2.82±0.02	12.97±0.12
IB#16	11.5±0.4	3.57±0.01	13.04±0.06	MD#16	9.8±0.2	2.87±0.02	12.94±0.07
				MD#17	9.2±0.4	2.86±0.02	13.02±0.12
				MD#18	9.6±0.2	2.87±0.04	13.02±0.14

Table 4

IB Formula #	Formula Composition	Mean AUC	SD	Ratio of Mean AUC** values	p-value
IB#1	Plain IB	62.98	2.65	1	----
IB#2	IB-EE 5%	62.24	2.45	1.332064298	0.006
IB#3	IB-EL 5%	60.68	3.22	1.037903757	0.655
IB#4	IB-EL 10%	25.07	2.78	2.512165935	0.00007
IB#5	IB-ES 5%	15.08	3.25	4.176392573	0.00004
IB#6	IB-ES 10%	14.26	2.66	4.41654979	0.00005
IB#7	IB-EE 2.5%+ES 2.5%	50.85	3.88	1.238544739	0.011
IB#8	IB-EE 5%+ES 5%	47.9	4.22	1.314822547	0.006
IB#9	IB-EE-IPA 2.5%+ES-IPA 2.5%	42.15	1.78	1.494187426	0.004
IB#10	IB-EEHCl 5%	47.28	2.66	1.331188946	0.006
IB#11	IB-ELNa 5%	14.96	1.21	4.209893048	0.00004
IB#12	IB-ESNa 5%	26.36	2.78	2.3892261	0.00007
IB#13	IB-EEHCl 2.5%+ELNa 2.5%	27.65	3.34	2.277757685	0.00006
IB#14	IB-EEHCl 2.5%+ESNa 2.5%	29.32	2.96	2.148021828	0.00006
IB#1 (pH 6.8)	Plain IB	23.41	2.44	2.690303289	0.00005
IB#13 (pH 6.8)	IB-EE-HCl 2.5%+EL-Na 2.5%	7.53	0.87	8.363877822	0.000006
MD#1	Plain MD	4.03	0.39	1	-----
MD#2	MD-EE 5%	4.24	0.48	0.9504717	0.588
MD#3	MD-EL 5%	4.11	0.44	0.98053528	0.825
MD#4	MD-EL 10%	3.95	0.33	1.02025316	0.97
MD#5	MD-ES 5%	4.15	0.55	0.97108434	0.773
MD#6	MD-ES 10%	4.09	0.44	0.98533007	0.868
MD#7	MD-EE 2.5% EL 2.5%	10.97	1.56	0.36736554	0.002
MD#8	MD-EE 5% EL 5%	10.38	1.68	0.38824663	0.003
MD#9	MD-EE-IPA 2.5%+EL-IPA	3.63	0.85	1.11019284	0.499
MD#10	MD-EE-HCl 5%	3.59	0.24	1.12256267	0.447
MD#11	MD-ELNa 5%	7.28	1.01	0.55357143	0.007
MD#12	MD-ELNa 10%	10.42	1.88	0.38675624	0.002
MD#13	MD-ESNa 5%	7.78	1.22	0.51799486	0.008
MD#14	MD-ESNa 10%	11.83	2.2	0.34065934	0.004
MD#15	MD-EEHCl 2.5%+ELNa 2.5%	22.2	2.15	0.18153153	0.0007
MD#16	MD-EEHCl 5%+ELNa 5%	22.05	1.88	0.18276644	0.0008
MD#17	MD-EEHCl 2.5%+ESNa 2.5%	22.3	2.81	0.18071749	0.0008
MD#18	MD-EEHCl 5%+ESNa 5%	22.3	2.65	0.18071749	0.0008
MD#1 (pH 1.2)	Plain MD	3.53	0.62	1.14164306	0.445
MD#1 (pH 6.8)	Plain MD	3.59	0.81	1.12256267	0.432
MD#15 (pH 1.2)	MD-EEHCl 2.5%+ELNa 2.5%	10.36	1.14	0.38899614	0.003
MD#15 (pH 6.8)	MD-EEHCl 2.5%+ELNa 2.5%	21.45	3.87	0.18787879	0.0008

List of Figures

Figure 1: Chemical structures of Eudragit E (a), Eudragit L and Eudragit S (b), Ibuprofen (c), and Metronidazole (d).

Figure 2. pH dissolution profiles at 50 rpm and 37 °C of IB#3, IB#4, IB#5 and IB#6 tablets compared to that of IB#1 tablets, all compressed at 500 Kg. The profile was at pH 1.2, 4.8, and 6.8 as indicated on graph.

Figure 3. pH dissolution profiles at 50 rpm and 37 °C of IB#11 and IB#12 tablets compared to that of IB#1 tablets, all compressed at 500 Kg. The profile was at pH 1.2, 4.8, and 6.8 as indicated on graph.

Figure 4. pH dissolution profiles at 50 rpm and 37 °C of MD#4, MD#6, MD#11, MD#12, MD#13 and MD#14 tablets compared to that of MD#1 tablets, all compressed at 5000 Kg. The profile was at pH 1.2, 4.8, and 6.8 as indicated on graph.

Figure 5. pH dissolution profiles at 50 rpm and 37 °C of IB#7, IB#13, IB#14 and IB#9 compared to that of IB#1 tablets, all compressed at 500 Kg. The profile was at pH 1.2, 4.8, and 6.8 as indicated on graph.

Figure 6. pH dissolution profiles at 50 rpm and 37 °C of MD#7, MD#15, MD#17 and MD#9 tablets compared to that of MD#1 tablets, all compressed at 5000 Kg. The profile was at pH 1.2, 4.8, and 6.8 as indicated on graph.

Figure 7. Dissolution at 50 rpm and 37 °C, of IB#13 compared to that of IB #1 tablets in 0.1 N HCl (pH 1.2) and in phosphate buffer (pH 6.8), all compressed at 500 Kg.

Figure 8. Dissolution at 50 rpm and 37 °C of MD#15 compared to that of MD#1 tablets in 0.1 N HCl (pH 1.2) and in phosphate buffer (pH 6.8), all compressed at 5000 Kg.

Figure 9. DSC thermograms for plain Ibuprofen (IB), individual polymers: Eudragit®L100 (EL) and Eudragit®E100 (EE), mixtures of IB and Eudragit®L100 (IB-EL 1:1), mixtures of IB and Eudragit®E100 (IB-EE) at various ratios (1:1, 2:1 and 1:2), and mixtures of IB and Eudragit®E100-HCl (IB-EE HCl 1:1).

Figure 10. FT-IR spectra of pure EE and EL powdered polymers (EL-POW and EE-POW), physical mix of EE and EL (EE-EL-POW), and physical mixture of EE and EL granules (EE-EL-GR). All physical mixtures were at 1:1 ratios.

List of Tables

Table 1a. Composition (mg/tablet) and percentage (% w/w) and of Ibuprofen (IB) tablet formulations prepared by direct compression of powders.

Table 1b. Composition (mg/tablet) and percentage (% w/w) and of Ibuprofen (IB) tablet formulations prepared by wet granulation method.

Table 2a. Composition (mg/tablet) and percentage (% w/w) and of Metronidazole (MD) tablet formulations prepared by direct compression of powders.

Table 2b. Composition (mg/tablet) and percentage (% w/w) and of Metronidazole (MD) tablet formulations prepared by wet granulation method.

Table 3. Average tablet crushing strength (n=3), thickness (n=3) and diameter (n=3) for IB and MD tablets formulations.

Table 4. Mean area under the curve (AUC), standard deviations (SD), and the ratio of AUC of reference tablet formulations (IB #1 or MD#1) to the AUC of IB or MD tablet formulations, respectively.

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