Floating and Sustained-Release Characteristics of Effervescent Tablets Prepared with a Mixed Matrix of Eudragit L-100-55 and Eudragit E PO

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The aim of this study was to evaluate the influence of Na-bicarbonate as an effervescent agent on the floating and sustained-release characteristics in 0.1 M HCl of tablets made of Eudragit E PO (EE) and/or Eudragit L-100-55 (EL) as matrix formers at different EE : EL weight ratios: 0 : 100, 25 : 75, 50 : 50, 75 : 25, and 100 : 0. The tablets were made by direct compression utilizing metronidazole as a model drug. Effervescent tablets with 50EE/50EL (w/w) showed the best floating and sustained drug release properties in the dissolution medium. The corresponding noneffervescent tablets were nonfloating and showed significantly faster drug release. Effervescent tablets with single polymers showed an immediate drug release pattern. These results were explained by Fourier-transform infrared spectroscopy and elemental analysis, which showed strong evidence of interpolyelectrolyte complexation between EE and EL when they were exposed to 0.1 M HCl as an effervescent hybrid matrix, but not as a noneffervescent hybrid matrix. The role of Na-bicarbonate in allowing EE–EL complexation during dissolution was explained as due to raising the pH around EL particles for sufficient polymer ionization and ionic-interaction with the ionized EE.

Key words Eudragit E; Eudragit L; floating tablet; gastroretentive system; sustained release

Several approaches are used to prolong gastric retention time. These include polymeric bioadhesive systems,[1] swelling and expanding systems,[2,3] and floating drug delivery systems.[4,5] The principle of buoyant preparation offers a simple, practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[6] In addition, it offers a greater safety for clinical uses than some other approaches.[7] To achieve an intragastric floating system, low-density additives (*e.g.*, fatty acids and fatty alcohols) and gas-generating agents (effervescent type) are used.[8] The effervescent type consists of a polymeric matrix containing effervescent components, such as Na-bicarbonate. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in a gelling hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy.[9] Among the hydrocolloids used for this purpose are hydroxypropyl methylcellulose, chitosan, and carboxymethylcellulose.

The use of two polymers having opposite charges to form an interpolyelectrolyte complex has recently achieved attention because of the capability of the interpolyelectrolyte complex to achieve more extended drug release than single polymers. The interpolyelectrolyte complex can be synthesized and then used as a matrix former, which was studied for chitosan and polyacrylic acid for the purpose of stomach-controlled antibiotic delivery.[10] Alternatively, the two polymers are physically mixed to form the matrix, and the interpolyelectrolyte complex is formed *in situ* during exposure to a simulated gastric fluid. The later approach was studied for chitosan and carboxymethylcellulose as a gastric-specific delivery system for clarithromycin.[11]

Polymethacrylates are synthetic cationic or anionic polymers of dimethyl-aminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. They are used in pharmaceutical formulations as film coating agents, bindings, direct-compression excipients, and gel bases.[12] Eudragit E (EE) is a cationic polymer prepared by copolymerization of butyl methacrylate, 2-dimethylaminoethyl-methacrylate, and methyl methacrylate with mole ratio of 1 : 2 : 1.[13] It is soluble in gastric fluid below pH 5.0.[13] Eudragit® L-100-55 (EL) is an anionic copolymer based on methacrylic acid and methyl methacrylate.[14] It exhibits pH dependent solubility and is soluble at pH values higher than 5.5.[14] Although polymethacrylates are widely used in pharmaceutical delivery systems for sustained drug release, their use as matrix former in floating tablets for local drug delivery in the stomach was not routinely addressed in the literature. The influence of Na-bicarbonate on the physicochemical properties of controlled-release hot-melt extruded (HME) tablets containing Eudragit RS PO and/or EE, in comparison with corresponding tablets made using direct compression, was previously investigated.[15] HME tablets prepared from a powder blend containing both Eudragit RS PO and Na-bicarbonate exhibited sustained-release properties and the tablets floated on the surface of the media for 24 h. The inclusion of EE in these tablets accelerated the drug release. In contrast, all direct compression tablets prepared showed no buoyancy and rapid drug release in the dissolution media. These results were attributed to the thermal degradation of Na-bicarbonate in the softened Eudragit RS at elevated temperature during the extrusion process.

This study aimed to evaluate the mixed matrix system of EE and EL as an effervescent buoyant drug-delivery system and the sustained drug-release characteristics of the system in comparison to single polymers. The reason for choosing these two polymers with opposite charges was the possibility of ionic interaction during tablet exposure to simulated gastric fluid, which could affect buoyancy and the drug-release pattern in the medium. The production method was direct compression as a low-cost method with no drug exposure to harsh conditions such as high temperature. Accordingly, the main objectives of this study were to study 1) the effects of Na-bicarbonate as an effervescent agent on the gastric buoy-

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ancy of tablets made of EE and EL at different EE : EL weight ratios; 2) study the drug-dissolution pattern from the best buoyant system(s) in 0.1 M HCl; and 3) evaluate possible ionic interaction between the two polymers during dissolution in the medium.

Experimental

Materials EE and EL were obtained from Röhm Pharma, Darmstadt, Germany. Metronidazole was a gift from the Jordanian Pharmaceutical Co., Naur, Jordan. Distilled water was used for all experiments, and all other chemicals were of pure laboratory grade.

Evaluation of Interpolyelectrolyte Complexation. Fourier Transform Infrared Spectroscopy EE and EL at a 1 : 1 weight ratio were physically mixed with and without Na-bicarbonate (20 mg per each 100 mg of the polymers) using a mortar and pestle. Tablets with 200 mg of the polymers were made from the physical mixtures in a 9-mm die using a manual tableting hydraulic press at compression force of 34.5 MPa. The tablets were exposed to 100 ml of 0.1 M HCl using glass beakers in a water bath shaker at 37 °C for 1 h, with subsequent filtration. The filtered solids were allowed to dry at room temperature in glass Petri dishes, ground into powder in a mortar and pestle, and then analyzed by Fourier Transform Infra-Red (FT-IR) spectroscopy according to the KBr disk method using a Shimadzu FT-IR spectrometer (Japan). For comparative purposes, FT-IR analysis was also performed on pure EE, pure EL, and an unexposed physical mixture of the polymers. To evaluate for the effects of the Na-bicarbonate amount on EE-CG interpolyelectrolyte complexation (IPEC), EE-CG physical mixtures (50EE/50CG) with different levels of Na-bicarbonate (0, 10, 20, and 40 mg per 100 mg of the polymers) were kneaded with the same volume of 0.1 M HCl, dried at 37 °C, and then used for the above FT-IR analysis.

Elemental Analysis Effervescent and noneffervescent EE–EL tablets were exposed to 0.1 M HCl for 4 or 8 h using a Vankel dissolution tester (U.S.A.) at a paddle speed of 100 rpm and temperature of 37±0.1 °C. After soaking and filtration, the tablets were left to dry at room temperature and then ground into powders. The obtained powders and physical mixtures with the same composition as the tablets before soaking were investigated for the elemental composition using a Euro EA 3000 elemental analyzer (Eurovector, Milan, Italy).

Tablet Preparation Five different mixtures of EE and/or EL, metronidazole as a model drug, and magnesium stearate were prepared in a mortar and pestle at EE : EL weight ratios of 0 : 100, 25 : 75, 50 : 50, 75 : 25, and 100 : 0, a polymer(s) : drug weight ratio of 1 : 1, and magnesium stearate concentration of 1% of each total mixture. Five more corresponding effervescent mixtures were prepared with the same drug–polymer compositions, but Na-bicarbonate was included with no ingredient replacement at a level of 20 mg for each 100 mg of the polymer(s). Powder quantities equivalent to 100 mg of metronidazole were compressed into tablets in a 9-mm die using a manual tableting hydraulic press at a compression force of 34.5 MPa.

***In Vitro* Buoyancy Studies** The tablets were placed in 100 ml of 0.1 M HCl using glass beakers in a water bath shaker at 37 °C. The tablets were observed for floating for 8 h. The time required for the tablets to rise to the surface and float was determined to be the floating lag-time (T-lag), and the floating tablets were then observed for the duration of floating (floating time).

Dissolution Studies The dissolution studies were performed in triplicate using a type II (paddle method) dissolution apparatus (Vankel dissolution tester, U.S.A.). The dissolution medium was 0.1 M HCl, and the stirring rate and temperature were adjusted to 50 rpm and 37±0.1 °C, respectively. Samples (5 ml) were drawn at suitable time intervals with volume replacement and then assayed for drug release using UV spectrophotometery at a wavelength of 280 nm.

Results and Discussion

Evaluation of IPEC. FT-IR Spectroscopy The spectrum of EL (Fig. 1A) exhibited a characteristic absorption band at 1720 cm^{-1}, which corresponds to the absorption by carboxy groups of the acrylic copolymer in agreement with data presented in the product specifications of Röhm Pharma. In accordance with these specifications, the spectrum also showed a wide absorption range of the associated OH groups between 2500 and 3500 cm^{-1} superimposed by CHX vibrations at 2900—3000 cm^{-1}. The spectrum of EE (Fig. 1B) showed a C=O ester vibration band at 1728 cm^{-1}. In addition, the bands at 2769 and 2823 cm^{-1} can be assigned to the dimethylamino groups. The physical mixture (Fig. 1C) showed the bands for the single components. The spectra of the effervescent and noneffervescent EE–EL tablets exposed to 0.1 M HCl are shown in Fig. 2. The spectrum of the noneffervescent tablet matched that of the physical mixture (Fig. 1C). However, major changes in the spectrum of the effervescent tablet compared with that of the noneffervescent tablet were seen: 1) disappearance of the OH absorption bands of EL at 3255 and 2600 cm^{-1}; 2) reduction in the intensity of bands associated with the dimethylamino groups of EE at 2823 and 2769 cm^{-1}; 3) reduction in the intensity of the car-

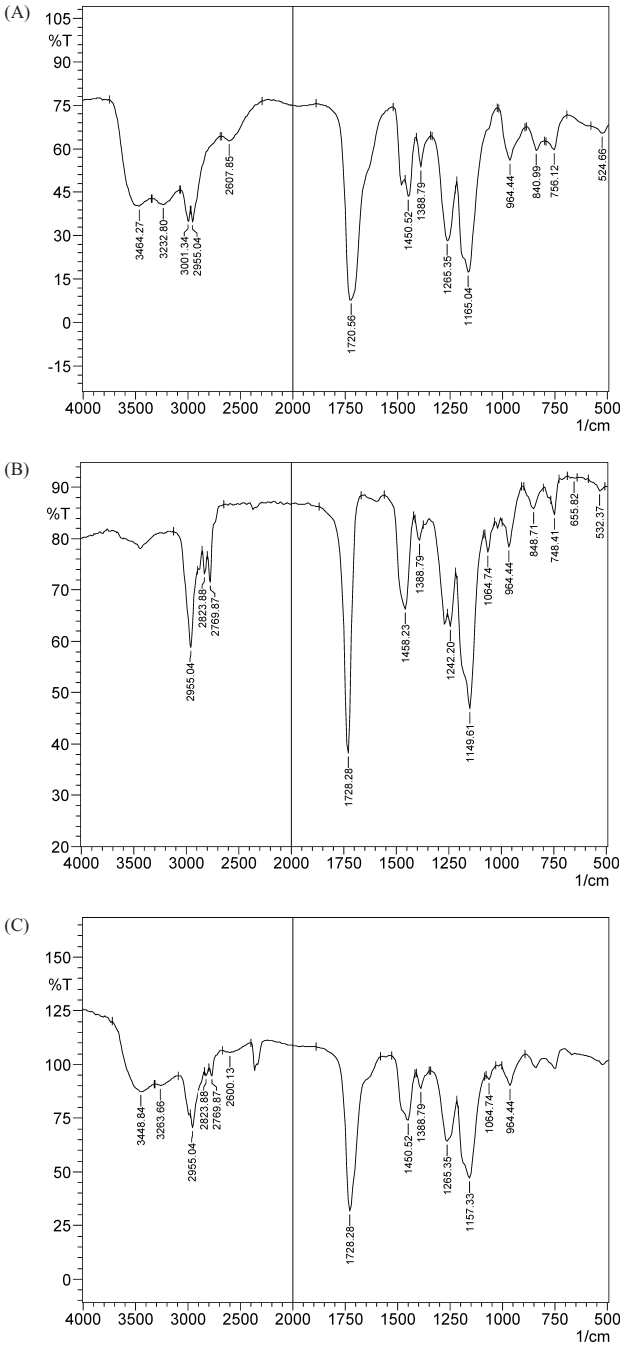

Fig. 1. FT-IR Spectra of EL (A), EE (B) and EE–EL Physical Mixture (C)

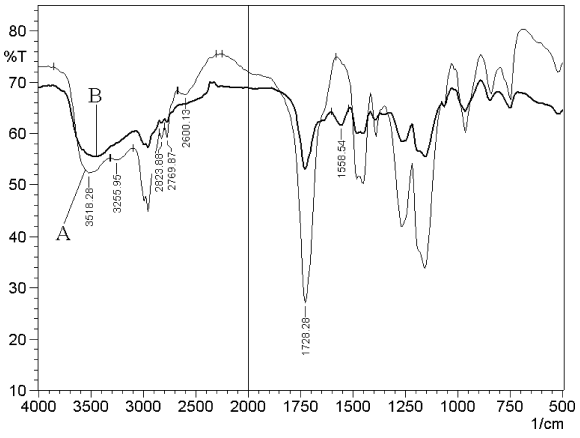

Fig. 2. FT-IR Spectra of EE–EL Matrices upon 1 h of Exposure to 0.1 M HCl: Non-effervescent: A and Effervescent: B

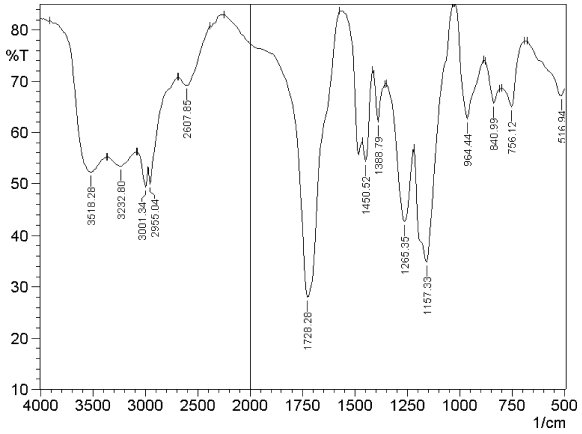

Fig. 3. FT-IR Spectrum of Effervescent EL Matrices upon 1 h of Exposure to 0.1 M HCl

bonyl absorption band at 1720 cm^{-1}; and 4) the emerge of a new absorption band at 1558 cm^{-1}, which was attributed to the formation of ammonium salt of EE. These changes suggest that there was sufficient ionization of both EE and EL in the exposed effervescent tablets, but not in the corresponding noneffervescent tablet, leading to an interaction between the ionized carboxy groups of EL and dimethylamino groups of EE. To rule out that these FT-IR changes were simply due to a reaction between EL and Na-bicarbonate, effervescent EL-tablet with no EE incorporated was run for the same experiment and the obtained FT-IR spectrum is shown in Fig. 3, which showed no major changes from that of pure EL (Fig. 1A). The role of Na-bicarbonate in allowing EE–EL complexation during exposure to 0.1 M HCl was likely due to raising the microenvironment pH around the EL particles and consequently sufficient ionization of EL for electrostatic interaction with the ionized EE occurred. In the absence of Na-bicarbonate, the pH would be too low for simultaneous, sufficient ionization of both EE and EL.

To confirm the role of Na-bicarbonate in allowing EE–EL complexation, FT-IR spectra of EE-CG physical mixtures with various levels of Na-bicarbonate after kneading with 0.1 M HCl are shown in Fig. 4. As Na-bicarbonate was increased in these mixtures, more spectral changes between 1500 to 1800 cm^{-1} were apparent, particularly as a reduction in the intensity of the carbonyl absorption band (at about 1750 cm^{-1}). This reduction in intensity was progressively increased as the level of Na-bicarbonate was increased from 0 to 40 mg.

Elemental Analysis EE is highly soluble in 0.1 M HCl making tablets of the polymer dissolve completely within 3 h of soaking in the acidic medium. When EE is combination with EL in effervescent tablets, then EE leaching out the tablets during the acidic soaking should be prevented or at least slowed by IPEC. As shown in Table 1, EE was retained significantly in the effervescent tablets for more than 8 h of the acidic soaking as N% (contributed only by EE) in the dried-soaked tablets decreased to about 80% and 59% of the initial N% before soaking after 4 and 8 h of soaking, respectively. This means that more EE is retained than released into the soaking medium after 8 h. The retention of EE could be attributed the conversion of the soluble EE into an insoluble form by complexation with EL. The slow release of EE into the medium was likely due to the fact that the complex was in equilibrium with the free polymers, and the free fraction of EE was responsible for this slow release. Interestingly, noneffervescent EE/EL tablet yielded 0% of nitrogen after 4 h of soaking (Table 1). This indicates that EE was rapidly dissolved and completely leaked out of the tablet as a result of insignificant IPEC, which emphasizes the role of Na-bicarbonate in allowing for EE–EL IPEC.

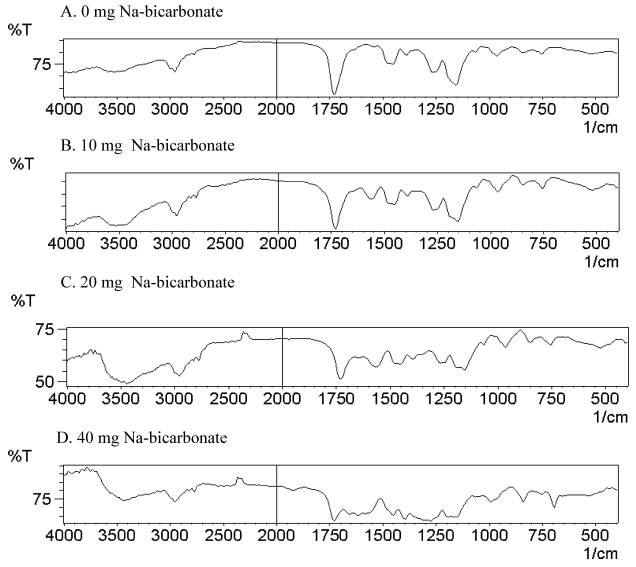

Fig. 4. FT-IR Spectra of EE/EL Physical Mixtures Having Various Levels of Na-Bicarbonate (mg per 100 mg of the Polymers) after Kneading with 0.1 M HCl

Table 1. Elemental Analysis of Dried Powders of Effervescent and Noneffervescent EE–EL Tablets upon Soaking in 0.1 M HCl for 4 and 8 h, in Comparison with EE–EL Physical Mixtures with Compositions Corresponding to Tablets before Soaking (0 h)

Soaking time (h)	Effervescent tablet			Non-effervescent tablet		
	N%	C%	H%	N%	C%	H%
0	2.099	53.247	8.392	2.332	8.392	8.384
4	1.683	52.572	9.501	0	9.501	7.337
8	1.236	51.901	9.192	0	9.192	7.581

Table 2. Effect of Na-Bicarbonate Level on Floating Parameters of Matrices Made of EE and/or EL at Different EE : EL Weight Ratios

EE : EL weight ratio	Na-bicarbonate (mg/100 mg polymer(s))	Lag time	Floating time
0 : 100	0	NF[a)]	NF[a)]
25 : 75	0	NF[a)]	NF[a)]
50 : 50	0	NF[a)]	NF[a)]
75 : 25	0	NF[a)]	NF[a)]
100 : 0	0	NF[a)]	NF[a)]
0 : 100	20	10.3±6.1 s	2.66±0.577 min
25 : 75	20	14.3±4.2 s	<3 h
50 : 50	20	16.6±1.5 s	>8 h
75 : 25	20	>30 min	<6 h
100 : 0	20	NF[a)]	NF[a)]

a) No floatation observed.

***In Vitro* Buoyancy Studies** The floating results of the different matrices are reported in Table 2. All the matrices with no Na-bicarbonate incorporated were nonfloating. However, inclusion of Na-bicarbonate at a level of 20 mg per tablet rendered most of the matrices rapidly floating (T-lag of less than 2 min) as a result of CO_2 generation and entrapment inside the matrix, thus decreasing the density of the tablets. As the density of tablets falls below 1, the tablets become buoyant. As this entrapment is more stable, persistent floating should occur. Effervescent tablets made of 100% EL as matrix former likely entrapped the gas inside the microporous structure of the insoluble polymer, leading to rapid floatation. However, these tablets showed rapid and complete disintegration within 5 min of the acidic soaking. This could be explained based on the fact that EL is not soluble in 0.1 M HCl, and thus cannot form a gel with sufficient strength to resist the bursting effect of the evolved CO_2. On the other hand, the corresponding effervescent tablets based on 100% EE as polymeric matrix were nonfloating, which was attributed to the high aqueous solubility of EE at pH around 1, leading to rapid leaching of the polymer out of the tablets, and consequently poor gelling. This explanation was supported by visual observation of the tablets, which completely dissolved within 2 h of the acidic soaking. In general, hybrid EE–EL matrices achieved better floating parameters than single polymers, which could be attributed to the evident complexation between EE and EL in effervescent tablets during exposure to 0.1 M HCl as shown by the previous FT-IR analysis. This complexation likely gave better matrix integrity and thus led to higher and longer entrapment of CO_2 in the matrices. The best floating system was 50EE : 50EL (w/w) with T-lag of less than 30 s and floating time of more than 8 h, and thus it was chosen for the dissolution studies. Photographs taken with a digital camera of noneffervescent and effervescent EE/EL matrices are shown in Fig. 5, which show that the effervescent tablet achieved greater swelling and increase in size, likely as a result of gelling and CO_2 entrapment.

Dissolution Studies Metronidazole release in 0.1 M HCl was studied from nonfloating (noneffervescent) Eudragit matrices (hybrid and of single polymers) to illustrate how combining EE and EL in tablets affect drug release in comparison with single polymers. This provides useful information to explain the release data from the corresponding effervescent floating matrices. Noneffervescent tablets with EE or EL as a single matrix former showed rapid drug release with more than 90% average drug release at 2 h (Fig. 6). This could be attributed to the high drug : polymer weight ratio (1 : 1) and high aqueous solubility of the drug. For EE-tablets, the high solubility of the polymer in 0.1 M HCl can be added as one more reason. Indeed, EE tablets completely dissolved and EL tablets showed rapid disintegration during dissolution. When the two polymers were combined (50EE : 50EL weight ratio) in the tablets at the same drug : polymer weight ratio (1 : 1), slower drug release was achieved as an average of 86% of loaded-drug was released over 4 h. This better performance of the noneffervescent hybrid matrices could be due to a cooperative effect of the soluble polymer (EE) and insoluble polymer (EL) during dissolution. Because no evidence of EE–EL complexation in 0.1 M HCl was seen for the hybrid matrices with no Na-bicarbonate incorporated, it is likely that the cooperative effect was due to the fact that EE is an adhesive polymer, and consequently when dissolved in the tablets by the dissolution medium (0.1 M HCl) it could bond the insoluble EL particles and prevent tablet disintegration.

Incorporation of Na-bicarbonate did not significantly affect the rapid drug release from EE or EL matrices (Fig. 7). Interestingly, incorporation of Na-bicarbonate into the hybrid EE–EL system did not lead to acceleration of drug release by the effervescent action (Fig. 7). Instead, further slowing of drug release was obtained by this incorporation, which can be confirmed by comparing the corresponding profiles in Figs. 6 and 7. This slowing of drug release meant that only 64% of the drug was released over 8 h from the effervescent hybrid matrices, compared with 86% over only 4 h from the corresponding noneffervescent matrices. Since EE is mostly ionized in 0.1 M HCl, ionization of EL would be the limiting

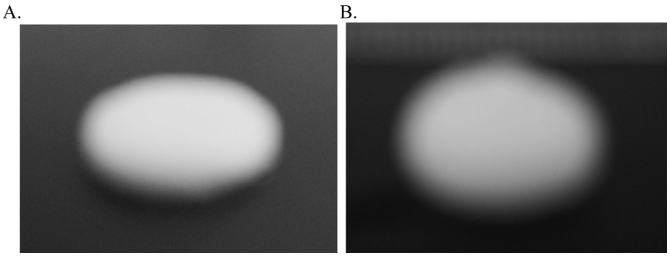

Fig. 5. Photographs of Noneffervescent (A) and Effervescent (B) EE/EL Matrices after 2 h of Soaking in 0.1 M HCl

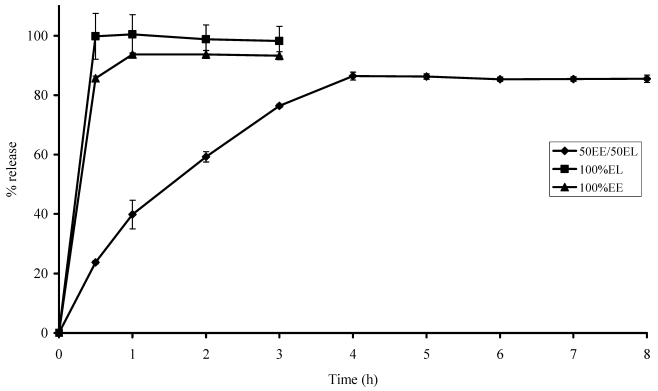

Fig. 6. Metronidazole Release in 0.1 M HCl from Noneffervescent Matrices

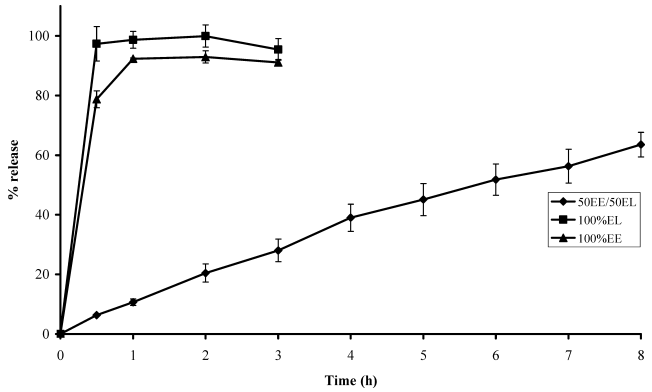

Fig. 7. Metronidazole Release in 0.1 M HCl from Effervescent Matrices

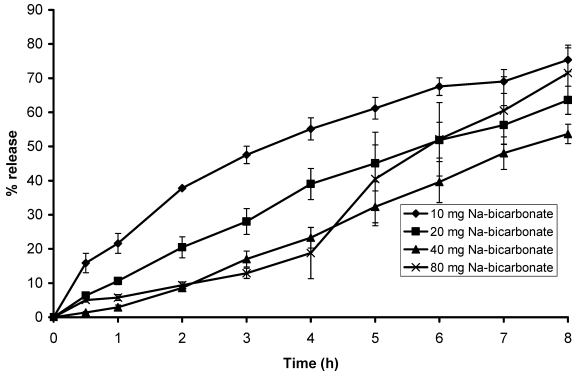

Fig. 8. Effect of Na-Bicarbonate Level (mg/tablet) on Metronidazole Release in 0.1 M HCl from 50EE/50EL Polymeric Matrices

factor for an ionic interaction between the two polymers in the acidic medium. Incorporation of Na-bicarbonate likely provided a microenvironment of higher pH around EL particles, leading to significant ionization of the polymer and consequently significant EE–EL complexation. This complexation probably slowed the drug release by controlling the solvent penetration into the tablets and drug diffusion out of the tablets. To confirm for this effect of Na-bicarbonate, EE–EL tablets were made with four increasing levels of Na-bicarbonate: 10, 20, 40, and 80 mg per each 100 mg of the polymers. These tablets were examined for drug dissolution and observed for floating during dissolution. T-lags (average of 3 tablets) were 298, 21, 20, and 15 s for the four levels, respectively, and floating time was more than 8 h for all levels. The dissolution performance as a function of these levels is illustrated in Fig. 8. Except for the 80-mg Na-bicarbonate level, as the Na-bicarbonate level increased, slower drug release was obtained. Similarity factor (SF) calculations[16] were performed for the different profile pairs at different Na-bicarbonate levels, which had the following results (Na-bicarbonate level combination: SF): 10—20 mg: 41.5, 10—40 mg: 29.6, 10—80 mg: 32.6, 20—40 mg: 48.0, 20—80 mg: 50.0, and 40—80 mg: 51.8. A significant effect of the Na-bicarbonate level on the dissolution performance can be concluded as four out of the six total profile combinations showed dissimilarity (SF$<$50). Similarity in dissolution was seen when the data for 80 mg Na-bicarbonate were compared with those for 40 or 20 mg Na-bicarbonate (SF$>$50). $t_{50\%}$ values were calculated using the Korsmeyer–Peppas model for the dissolution data at each Na-bicarbonate level and were found to be 218$\pm$20, 354$\pm$42, 430$\pm$34, and 445$\pm$80 min at levels of 10, 20, 40, and 80 mg, respectively. Except for the comparison between the data at 80 mg and those at 20 or 40 mg, p values obtained by the t-test for the differences in $t_{50\%}$ were less than 0.05. The previous analyses indicated that as the Na-bicarbonate increased from 10 to 40 mg, drug release became significantly slower, which is consistent with the proposed effect of Na-bicarbonate on the microenvironment pH leading to greater ionization of EL and consequently greater complexation between EE and EL. However, a further increase in Na-bicarbonate to 80 mg did not significantly change the dissolution performance. By careful examination of the dissolution profile at 80 mg Na-bicarbonate, one can see that the drug release was slow up to 4 h, beyond which the dissolution was accelerated. The initial slow phase was attributed to EE–EL complexation, while the following faster release phase was likely due to the disintegration effect of the built-up CO_2 that is expected to be the highest at the highest level of Na-bicarbonate studied.

To understand the *in vitro* release pattern, dissolution data were fitted to different models: the zero-order release kinetics Eq. 1; first-order release kinetics[17,18] Eq. 2; Higuchi's square root of time equation[19] Eq. 3; Hixson–Crowell's cube root of time equation[20] Eq. 4; and Korsmeyer–Peppas' power law equation[21,22] Eq. 5. The goodness of fit was evaluated using r (correlation coefficient) values.

$$Q_t = Q_0 + K_0 t \tag{1}$$

where Q_t is the fractional amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution (mostly Q_0=0), K_0 is the zero-order release constant, and t is release time.

$$Q_t = Q_0 e^{-K_1 t} \tag{2}$$

where Q_t is the fractional amount of drug dissolved in time t, Q_0 is the initial amount of drug in the solution, K_1 is the first-order release constant, and t is release time.

$$Q_t = K_H \sqrt{t} \tag{3}$$

where Q_t is the fractional amount of drug dissolved in time t, K_H is the Higuchi dissolution constant, and t is release time.

$$(Q_0)^{1/3} - Q_t^{1/3} = K_s t \tag{4}$$

where Q_0 is the initial amount of drug in the pharmaceutical dosage form, Q_t is the remaining amount of drug in the pharmaceutical dosage form at time t, K_s is a constant incorporating the surface–volume relation, and t is release time.

$$Q_t / Q_\infty = Kt^n \tag{5}$$

where Q_t is the amount of drug dissolved in time t, Q_∞ is the amount of drug dissolved in ∞ time (the drug loaded in the formulation), Q_t/Q_∞ is the fractional release of the drug in time t, K is a constant incorporating structural and geometric characteristics of the dosage form, n is the release (diffusional) exponent that depends on the release mechanism and the shape of the matrix tested, and t is release time. A value of n=0.45 indicates case I (Fickian) diffusion or square of time kinetics, 0.45$<n<$0.89 indicates anomalous (non-Fickian) diffusion, n=0.89 indicates case II transport, and $n$$>$0.89 indicates super case II transport.[21] Case II generally

Table 3. Fitting Parameters of Drug Release Data of EE–EL (50 : 50) Matrices Containing Various Levels of Na-Bicarbonate (mg/each 100 mg of the Polymers)

Na-bicarbonate level (mg)	Release model										
	Zero order		First order		Higuchi matrix		Korsmeyer–Peppas			Hixson–Crowell	
	K_0	r_0	K_1	r_1	K_H	r_H	n	K_k	r_k	K_s	r_s
10	0.111±0.005	0.697±0.046	0.189±0.014	0.833±0.028	0.268±0.012	0.983±0.009	0.623±0.076	0.235±0.027	0.989±0.007	0.046±0.002	0.873±0.024
20	0.085±0.008	0.970±0.041	0.282±0.012	0.861±0.031	0.199±0.019	0.900±0.010	0.859±0.068	0.111±0.005	0.993±0.003	0.059±0.003	0.924±0.023
40	0.065±0.007	0.977±0.004	0.456±0.024	0.864±0.018	0.148±0.015	0.757±0.014	1.413±0.133	0.033±0.005	0.993±0.004	0.076±0.003	0.948±0.012
80	0.081±0.013	0.902±0.045	0.382±0.020	0.961±0.020	0.182±0.030	0.660±0.058	0.916±0.070	0.066±0.007	0.840±0.075	0.076±0.007	0.962±0.018

refers to the erosion of the polymeric chain and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release. Fitting was performed for $Q_t/Q_\infty \leq 0.6$.

The results of the previous fittings are reported in Table 3. At the Na-bicarbonate level of 10 mg, the dissolution data best fitted the Korsmeyer–Peppas model. The value of n was 0.623, confirming that the formulation followed non-Fickian diffusion kinetics (anomalous transport), *i.e.*, the release was ruled by both diffusion of the drug and matrix erosion. However, the formulation showed a higher R^2 value by fitting to the Higuchi model than to the zero-order model, indicating that the release is principally controlled by diffusion. At 20 and 40 mg of Na-bicarbonate, the dissolution data followed the Korsmeyer–Peppas model ($R^2 > 0.99$). However, the n value increased from 0.859 for 20 mg Na-bicarbonate to 1.413 for 40 mg Na-bicarbonate, indicating that the release mechanism shifted from anomalous transport to super case-II. As Na-bicarbonate was increased from 10 to 40 mg in the matrices, a decrease in k and an increase in n were apparent, indicating a lowering of polymer chain relaxation, which was in correlation with the proposed increase in EE–EL complexation with the increase in Na-bicarbonate level. At these levels, the order of drug release was best described as zero-order release ($R^2 > 0.977$), which indicated that the rate of surface erosion is controlling the rate of drug release rather than drug diffusion. At 80 mg, the dissolution data were best fitted according to the Hixon–Crowell model ($R^2 = 0.962$), which indicated a change in surface area and diameter of the tablets, and to the first-order model ($R^2 = 0.961$), which indicated that the drug release rate was changing likely as a result of the progressive increase in the built-up CO_2 that accelerated matrix erosion with time.

Conclusion

As single polymers, EE and EL are not suitable for the development of floating effervescent matrices with good floating and sustained-release properties. Hybrid effervescent matrices of the polymers at the optimum EE : EL weight ratio (50 : 50) achieve superior floating and sustained drug release properties in 0.1 M HCl. IPEC apparent to be the key factor for the superior performance of the hybrid matrices, and Na-bicarbonate inclusion in these matrices likely mediates the IPEC by raising the microenvironment pH around EL particles, which allows for significant ionization of EL and its interaction with EE.

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