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Comparative study of three structurally related acid polyelectrolytes as carriers of basic drugs: Carbomer, Eudragit L-100 and S-100

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A detailed description of equilibrium and drug release properties of aqueous dispersions of complexes of model basic drugs (D) [lidocaine (Ld), atenolol and metoclopramide (Me)] with three structurally related acid polyelectrolytes (PE) is reported. Thus, affinity constants for ionic pair formation (K_{ip}) of dispersions of polymetacrylates, Eudragit L-100 and Eudragit S-100, neutralised with increasing proportions of Ld and Me, were determined and compared with those of Carbomer previously reported. Affinity constants were calculated from the concentration of D condensed with PE ($\text{RCOO}^- \text{DH}^+$) and those of free species (D and DH^+). In agreement with the high degree of counterionic condensation observed, the three PE–D complexes placed on Franz-type cells released D at slow rates as water was placed as receptor medium. Rates increased over three times as water was replaced by 0.9% NaCl solution. Similar average of diffusional exponent n (water, 0.61 and NaCl, 0.69) was found in both media. The overall kinetic behaviour suggests that, under the conditions assayed, the dissociation of $\text{RCOO}^- \text{DH}^+$ is the factor that controls releasing rates. Structure-related properties of the PE–D systems were identified in order to expand their potential uses as drug carriers.

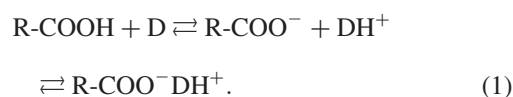
Keywords: drug–polyelectrolyte complex; ionic pairs; affinity; species distribution; drug release

Introduction

Polyelectrolytes (PE) under the form of ionic exchange resins (insoluble PE) or dispersible hydrophilic polymers (soluble PE) have been largely used in pharmaceutical formulations (1–3).

The unique properties arising from the interaction of soluble PE with inorganic or organic counterions have been exploited for a variety of purposes such as drug delivery modulation (4–6), taste masking (7), drug compatibility (8), drug stability improvement (9), viscosity building (10), metabolite trapping (11), etc.

Aqueous dispersions of PE having acid or basic pending groups react, respectively, with molecules having basic or acid groups, yielding a high proportion of counterionic condensation. Equation (1) depicts the reaction between the carboxylic groups of a PE (R-COOH) with the basic groups of a drug D, where D and DH^+ are the neutral and protonated species,



In the same way, PE having protonable amino groups react with an acid group of a drug generating an analogue process of counterion condensation (12).

The knowledge about the factors that determine the interaction between ionic or ionisable drugs and PE is relevant in the design of pharmaceutical dosage forms. At present, a detailed description about the factors governing such interaction is not fully available.

Classical description of ion–ion interaction recognises two relative stable regions: one referred to as a *solvent-separated ion pair*, or as a *loose ion pair*, and the other referred to as a *contact ion pair*, which is also known as a *tight ion pair* (13).

In the same line, within the framework of the counterion condensation theory of PE, a common point in the theoretical treatments proposed is the recognition of two extreme modes of counterion association with the PE, currently referred to as *loose* and *covalent bonding*. The former is the delocalised confinement of the counterions within a condensation volume in the immediate vicinity of the PE, due only to long-range interactions, while the latter is a short range, site-specific interaction (14–16).

Theoretical treatments mainly address the interaction of acid linear PE with inorganic cations. However, with organic counterions, although the main contribution to the overall interaction arises from the electrostatic attraction, non-electrostatic contributions would also play a role in the association process.

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In this context, we have previously reported results concerning the properties of aqueous dispersions as well as solid matrices of PE–D systems. Such results were obtained with the acid PE carbomer, alginic acid, carboxymethylcellulose and a variety of drugs having basic groups (4, 6, 17, 18). In addition, the interaction between the basic polymethacrylate Eudragit® E-100 (EE) and a set of DH was also addressed (12).

The polyacrylic acid, Carbomer 934 (CB), was used as a model PE in several of the referenced reports. In this step, it was considered of interest to perform a comparative study of CB with two structurally related PE: the polymethacrylates Eudragit® L and S (EL and ES). Therefore, this paper reports some relevant properties of PE–D aqueous dispersions of the three PE with three model drugs: lidocaine (Ld, $pK_a = 7.92$), metoclopramide (Me, $pK_a = 9.71$) and atenolol (At, $pK_a = 9.55$).

Materials and methods

Materials

The following materials were used: EL-100, ES-100 (Roehm, Darmstadt, Germany) and Carbomer 934-P (CB) (Carbopol® 934-P, BFGoodrich, Cleveland, OH, USA), kindly supplied by Etilfarma (Buenos Aires, Argentina) and BFGoodrich (Buenos Aires, Argentina). Me hydrochloride, At and Ld all are of USP grade (Parafarm, Buenos Aires, Argentina).

Me as free base was obtained by neutralisation of its hydrochloride solutions with 1.0 N NaOH solution (Anedra, Buenos Aires, Argentina). The solid product was filtered, washed with distilled water and dried (50°C) to constant weight.

The carboxylic group content of each PE was assayed by acid–base titration with 0.1 N NaOH solution on samples of about 50 mg dispersed in water and reported in Table 1 as meq/g.

Preparation of Eudragit–basic drug dispersions

Two series of complexes, (EL–D)_x and (ES–D)_x, were prepared by neutralising 1.0% aqueous dispersion of each Eudragit® with the appropriate amount of D. Subscript ‘x’ (x = 50, 75 and 100) refers to the mole% of D that neutralises the carboxylic groups of PE. Also, dispersions at 0.50, 0.25 and 0.10% of (EL–Ld)₅₀ and (EL–Me)₅₀ were prepared.

Neutralisation was carried out by addition of the adequate amount of D as a fine powder on the PE dispersion under constant stirring for about 6 h. In addition, each dispersion was sonicated for 15 min every 1 h. After that, the resulting dispersion was kept at room temperature for 24 h before being used.

Electrokinetic potential (ζ) was measured by dynamic light scattering using a DelsaNano C instrument (Beckman

Coulter, Osaka, Japan) equipped with laser diode at 658 nm and a scattering angle of 165°. Measurements were performed at 25°C, without dilution, allowing the instrument to automatically optimise signal intensity of the sample. With a specific software (DelsaNano C, version 2.20), by applying Smoluchowski approximation, the ζ -potential of samples was calculated.

Optical density (transparency) of (PE–D)_x dispersions was determined at a wavelength of 600 nm (Nicolet Evolution 300, Spectrophotometer, Thermo Sci. Ins., Madison, WI, USA). Such measurements were performed on samples of 5.0 ml of each (PE–D)₅₀ dispersion at 1.0% of Eudragit®. Volumes from 15 to 77 μ l of 1.0 N NaOH were added in order to neutralise the remaining 50 mole% of Eudragit® carboxylic groups.

On the other hand, increasing volumes of ethanol or propyleneglycol were added to increase transparency of (PE–D)₅₀ dispersions and data were expressed as volume % of cosolvent added.

Partition equilibrium with organic solvent

Samples of (PE–D)_x at 0.10, 0.25, 0.50 and 1.0% (D = Me or Ld) were prepared and shake flask partitioned with cyclohexane for (EL–Ld)_x and (ES–Ld)_x and 1,2-dichloromethane for (EL–Me)_x and (ES–Me)_x in a ratio of 1:2. After equilibrium, the concentration of D in the organic solvents was spectrophotometrically assayed (Nicolet® Evolution 300, Thermo-Electron Corp.) at 261 and 302 nm for Ld and Me, respectively, and the pH of the aqueous phases was recorded.

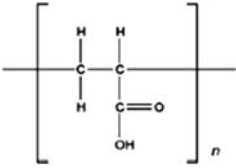
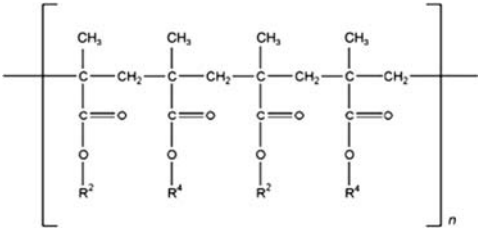
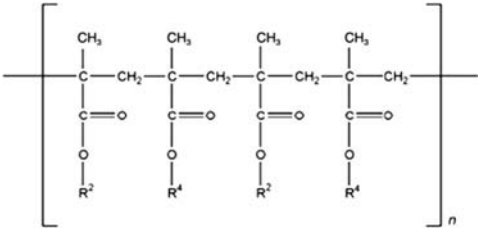
Drug release

The extent and rate of *in vitro* release of D from aqueous (PE–D)_x dispersions were determined in diffusion Franz cells with artificial cellulose membranes (12,000 Da; Sigma®, St Louis, MA, USA). The effective diffusion area was 4.52 cm². The donor compartment was filled with an amount exactly weighed, close to 4.0 g, of each dispersion and sealed with Parafilm®. The receptor compartment, filled with 75 ml of distilled water or 0.9% NaCl solution, was maintained at 37.0 \pm 0.5°C.

Samples of 4.0 ml of the receptor medium were withdrawn at predetermined time intervals and immediately replaced with an equal volume of fresh medium. Collected samples were acidified with one drop of 1 M HCl solution and then spectrophotometrically assayed at the wavelength of maximum absorbance of each D (At, 263 nm; Me, 272 nm; Ld, 263 nm). All the experiments were conducted in triplicate and release data were processed by the Korsmeyer–Peppas equation,

$$M_t/M_\infty = kt^n, \quad (2)$$

Table 1. Relevant properties of PE selected as a drug carrier.

Acid PE	CB	EL	ES
Molecular formula			
Average molecular weight ^a	6.0×10^6	135,000	
Type	Cross-linked	Linear	Linear
Ratio	Polyacrylate homopolymer	Methacrylic acid–methyl methacrylate copolymer (1:1)	Methacrylic acid–methyl methacrylate copolymer (1:2)
COOH content	(meq/g) ^b (%) ^c		
	12.0 58.0–68.0	4.85 46.0–50.6	3.07 27.6–30.7

^a Average molecular weight taken from (23, 24).

^b Determined by potentiometric titration.

^c Specifications from PhEur 2005 for the content of carboxylic acid (COOH) groups calculated on the dry basis.

where M is the amount of D permeated at time t ; M_{∞} , the initial amount of D in the donor compartment; k , the kinetic constant and n , an exponent which characterises the mechanism of release (19). Based on the diffusional exponent, n , the drug transport is essentially classified as Fickian diffusion for $n \leq 0.5$, anomalous (non-Fickian) diffusion for $0.5 < n < 1.0$, case II transport or zero order for $n = 1.0$ (20).

Results and discussion

Table 1 reports the structural characteristics of the three PE. The proportion of carboxylic groups in meq/g of each PE follows the sequence $CB > EL > ES$, whereas the proportion of structural hydrophobic moieties follows the reverse sequence. In fact, both Eudragit[®] have a $-\text{CH}_3$ instead of the $-\text{H}$ placed in the CB backbone. Also, in both polymethacrylates, a number of carboxylic groups are esterified as indicated in the table. Additionally, CB is cross-linked while EL and ES are linear polymers.

A set of 1.0% dispersions of EL and ES loaded with different proportions of each model D (At, Ld and Me) (Eudragit[®]-D)_x were prepared as described in the previous section and their compositions are reported in Tables 2 and 3. Such systems are physically stable dispersions that exhibit low viscosity and quasi-Newtonian flux. In contrast, as it was earlier reported, analogue (CB-D)_x dispersions exhibit high viscosity and plastic or pseudoplastic flux (17).

(Eudragit[®]-D)_x dispersions also exhibit a high negative electrochemical potential similar to the (CB-D)_x ones [i.e. -22.9 ± 0.71 and -25.5 ± 2.7 mV for (EL-Ld)₅₀ and (ES-Ld)₅₀, respectively], which contribute to the physical stability observed.

While (CB-D)_x are transparent or quasi-transparent systems, (Eudragit[®]-D)_x with lower D loading ($x = 25, 50$ mole%) are non-transparent dispersions, however higher D loading increases their transparency.

The introduction of a second inorganic counterion in (Eudragit[®]-D)₅₀, through the addition of increasing amounts of NaOH, also promotes transparency. It seems that the degree of carboxylic acid dissociation exerts a significant contribution on the physical stability of these systems based on PE with lower water affinity than CB.

In the same way, addition of cosolvents such as ethanol or propyleneglycol also yields light isotropic systems, as shown in Figure 1. It can be seen there that EL, having higher proportion of carboxylic groups than ES, generates dispersions more sensitive towards the addition of NaOH or cosolvents.

The differences and similarities observed in the properties of the dispersions are in agreement with the structural characteristics of the PE summarised in Table 1.

Species distribution and counterionic condensation

As depicted in Equation (1), aqueous (PE-D)_x dispersions, the drug is distributed as free species D and DH^+ and PE condensed as RCOO^-DH^+ . Then, the total drug molar concentration $[\text{D}_T]_w$ is distributed as

$$[\text{D}_T]_w = (\text{D})_w + (\text{DH}^+)_w + (\text{RCOO}^-\text{DH}^+)_w \quad (3)$$

The proportions in which such species are distributed in (Eudragit[®]-D)_x dispersions were determined according to previously described methods by Jimenez-Kairuz et al. (4)

Table 2. Composition of (PE–D)_x complexes and species distribution after partition equilibrium with an organic solvent.

Complex dispersions	Stoichiometric composition ^a		pH ^b		[D _T] _w ^c (mole%)	Distribution at equilibrium ^d (%)			Log K _{ip}
	[PE] (eq/l)	[D _T] (M)	Before	After		(D) _w	(DH ⁺) _w	(RCOO ⁻ DH ⁺) _w	
(EL–Ld) ₂₅	4.85 × 10 ⁻²	1.20 × 10 ⁻²	6.95	6.73	21.0	0.80	12.40	86.80	3.45
(EL–Ld) ₅₀	4.85 × 10 ⁻²	2.40 × 10 ⁻²	6.92	6.75	36.7	1.45	22.31	76.24	3.23
(EL–Ld) ₇₅	4.85 × 10 ⁻²	3.60 × 10 ⁻²	6.75	6.50	52.2	1.76	45.6	52.64	3.11
(EL–Ld) ₁₀₀	4.85 × 10 ⁻²	4.90 × 10 ⁻²	7.33	6.80	63.7	2.4	32.04	65.56	3.17
(ES–Ld) ₂₅	3.07 × 10 ⁻²	7.50 × 10 ⁻³	8.09	7.44	15.1	2.80	8.60	88.60	3.02
(ES–Ld) ₅₀	3.07 × 10 ⁻²	1.50 × 10 ⁻²	7.60	7.33	27.4	3.49	13.64	82.86	3.02
(ES–Ld) ₇₅	3.07 × 10 ⁻²	2.30 × 10 ⁻²	7.68	7.26	36.07	4.60	21.27	74.13	2.9
(ES–Ld) ₁₀₀	3.07 × 10 ⁻²	3.10 × 10 ⁻²	7.64	7.16	49.7	4.22	24.66	71.12	3.7
(CB–Ld) ₂₅	1.20 × 10 ⁻²	3.01 × 10 ⁻³	7.44	6.48	23.3	0.36	26.00	73.64	4.41
(CB–Ld) ₅₀	1.20 × 10 ⁻²	6.02 × 10 ⁻³	7.44	6.48	37.7	1.38	37.94	60.67	3.77
(CB–Ld) ₇₅	1.20 × 10 ⁻²	9.00 × 10 ⁻³	8.09	7.16	43.6	3.03	17.48	79.48	3.58
(CB–Ld) ₁₀₀	1.20 × 10 ⁻²	1.20 × 10 ⁻²	8.41	7.34	52.4	3.81	14.49	81.69	3.56
(EL–Me) ₅₀	4.85 × 10 ⁻²	2.40 × 10 ⁻²	6.80	6.71	42.56	0.04	50.22	49.74	4.55
(ES–Me) ₅₀	3.07 × 10 ⁻²	1.50 × 10 ⁻²	7.40	7.18	38.1	0.09	31.41	68.5	4.59
(CB–Me) ₅₀	1.20 × 10 ⁻²	6.00 × 10 ⁻³	6.96	6.91	43.9	0.08	51.19	48.73	4.89

^a Stoichiometric composition of the (PE–D)_x complexes in the dispersions prepared at 1.0% p/v of Eudragit[®] and 0.1% p/v of CB.

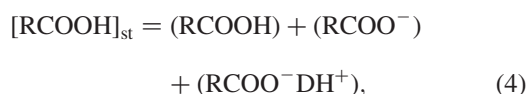
^b pH values of the aqueous phase before and after partition extraction.

^c Percentage (mole%) of drug-forming complexes with the PE remaining in the aqueous phase after partition extraction.

^d Distribution of species expressed as the percentage of total drug remaining in the aqueous phase after partition extraction.

through the selective extraction of D by an appropriate organic solvent. The results, quoted in Table 2, together with those previously reported on (CB–D)_x dispersions, reveal that a high proportion of D is ionically condensed with PE in all cases. Such proportion was always above 50%.

In concordance with D speciation, the carboxylic groups (RCOOH) of the PE are speciated as



where the subscript 'st' means the stoichiometric concentration of PE.

Then, according to the equilibrium depicted in Equation (1), the affinity constant of ion-pair formation

(K_{ip}) is given by

$$K_{\text{ip}} = (\text{RCOO}^- \text{DH}^+) / (\text{RCOOH})(\text{D}) \quad (5)$$

or

$$K_{\text{ip}} = (\text{RCOO}^- \text{DH}^+)(\text{H}^+) / (\text{RCOOH})K_{\text{a}}(\text{DH}^+). \quad (6)$$

The following considerations let to calculate K_{ip} in aqueous (PE–D)_x dispersions:

$$(\text{RCOO}^-) + (\text{OH}^-) = (\text{H}^+) + (\text{DH}^+). \quad (7)$$

Moreover, under the present experimental conditions, (RCOO⁻) ≫ (OH⁻) and (DH⁺) ≫ (H⁺); then Equation (7) can be reduced to

$$(\text{RCOO}^-) = (\text{DH}^+). \quad (8)$$

Table 3. Kinetic data obtained according to the Korsmeyer–Peppas model.

Complex dispersions ^a	Water			0.9% NaCl solution			k _{NaCl} /k _w ratio
	k _w (%/h ⁿ)	n	R ²	k _{NaCl} (%/h ⁿ)	n	R ²	
(EL–At) ₅₀	0.090	0.66 (±0.02)	0.998	0.369	0.78 (±0.02)	0.998	4.10
(ES–At) ₅₀	0.162	0.64 (±0.03)	0.995	0.473	0.74 (±0.03)	0.995	2.92
(CB–At) ₅₀	0.066	0.59 (±0.03)	0.995	1.670	0.58 (±0.02)	0.998	25.30
(EL–Ld) ₅₀	0.434	0.60 (±0.02)	0.997	1.361	0.57 (±0.03)	0.995	3.13
(ES–Ld) ₅₀	0.865	0.59 (±0.02)	0.996	0.935	0.61 (±0.01)	0.999	1.08
(CB–Ld) ₅₀	0.083	0.63 (±0.05)	0.990	0.737	0.61 (±0.04)	0.990	8.88
(EL–Me) ₅₀	0.110	0.61 (±0.04)	0.990	0.522	0.78 (±0.02)	0.999	4.74
(ES–Me) ₅₀	0.432	0.51 (±0.04)	0.982	0.817	0.64 (±0.02)	0.999	1.89
(CB–Me) ₅₀	0.179	0.69 (±0.03)	0.996	1.266	0.63 (±0.02)	0.998	7.07

^a The initial concentration of D in the complexes was different according to PE associated with EL, 2.43 × 10⁻² M; ES, 1.54 × 10⁻²; CB, 3.00 × 10⁻².

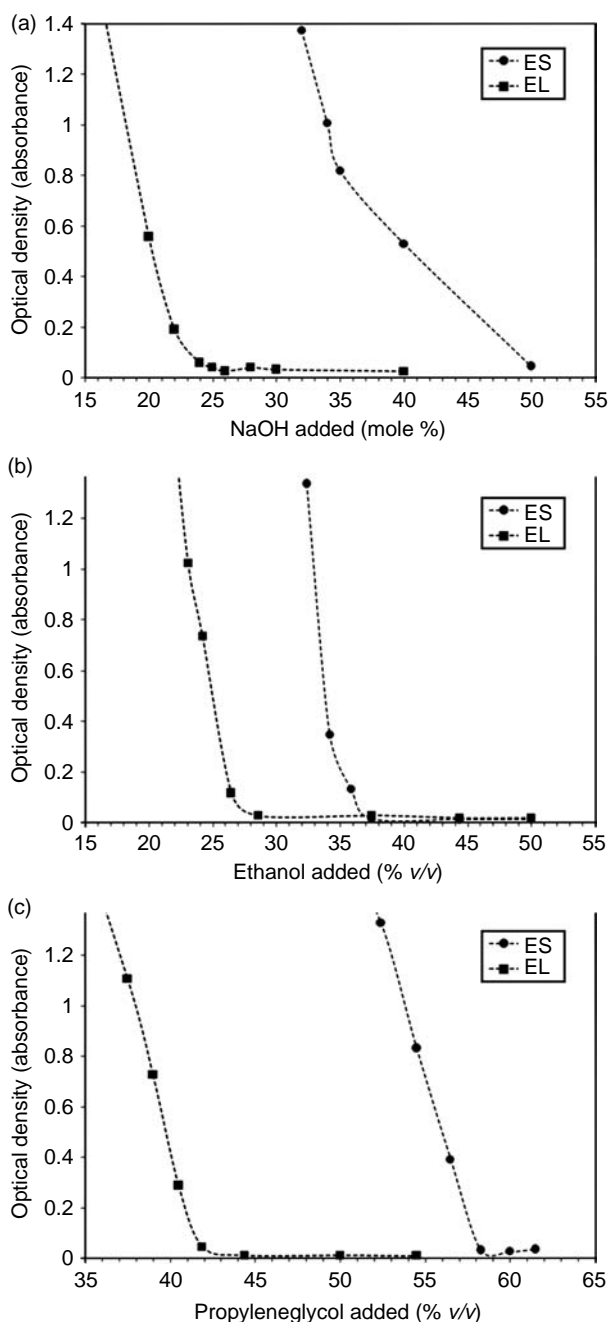


Figure 1. Increase of transparency of (ES-Me)₅₀ and (EL-Me)₅₀ dispersions at 1.0% of Eu, upon addition of: (a) 1.0 N solution of NaOH expressed as mole % of PE carboxylic groups; (b) ethanol or (c) propylene glycol.

Then, to calculate (RCOOH) in Equation (4), (DH⁺) was introduced instead of (RCOO⁻). Thus, K_{ip} was calculated through Equation (6) with data quoted in Table 2. Figure 2 shows K_{ip} of the three (PE-D)_x systems loaded with increasing proportions of Ld, which was used as the model drug. It is worth emphasising that, in these systems, the

increase in the degree of neutralisation of the acid groups of the PE with model drugs produces an increase in properties such as specific conductivity (21), viscosity (17) and transparency. Also, the resulting dispersions exhibit high negative electrokinetic potentials. Such observations are consistent with the idea that a significant population of the condensed counterions keeps some degree of hydration and that charges are not fully neutralised. Therefore, the counterionic condensation generates the expansion of the PE chains, turning the complexes (PE-D)_x more hydrophilic than the PE alone.

With regard to PE-D affinity, CB exhibited the highest K_{ip} at low Ld loading, which decreases as the proportion of Ld was increased. This behaviour would be primarily related to the close proximity between carboxylic groups, which would affect the ionic interaction through steric hindrance.

Between the linear PE, EL exhibited a lower K_{ip} than CB that remains almost constant along a wide range of Ld loading. ES having the highest backbone hydrophobicity exhibits the lowest K_{ip} at low loading. However, at higher degrees of neutralisation, K_{ip} is significantly raised. The long distance between ionisable groups, together with the expanding effect of the progressive ionisation, seems to produce a positive effect to raise the ES-Ld affinity.

With regard to the effect of concentration on K_{ip} , Figure 3 shows that $\log K_{ip}$ of (EL-Ld)₅₀ (part (a)) remained essentially constant over 10 times dilution. A similar behaviour was previously observed on a dispersion of (CB-Ld)₇₅ (part (b)) (21) revealing a mass law control of the PE-D interaction.

On the other hand, Me having an amino group of higher basic strength than Ld yields (EL-Me)₅₀ and (ES-Me)₅₀ with higher $\log K_{ip}$ (Table 2), as it was also observed with (CB-Me)₅₀ (21). It is worth to be mentioned that a correlation between $\log K_{ip}$ and pK_a of a set of basic drugs D was also found with the system based on the acid form of carboxymethylcellulose as acid PE (18).

Drug release

Kinetic data of drug release in Franz cells were processed according to Equation (2). Table 3 reports rate coefficients (k) and diffusional exponent (n) values of (EL-D)_x and (ES-D)_x, together with those of (CB-D)_x previously reported (21). In addition, Figure 4 depicts a representative set of kinetic plots.

Drug delivery towards water as the receptor medium was very slow, which is in agreement with the K_{ip} of the three systems. In fact, under such conditions, drug diffusion essentially occurs through free neutral species D since diffusion of DH⁺ is mainly prevented by the electrostatic field of the polyion. With regard to this point, it should be mentioned that the evaluation of pH effects on drug release early performed with (CB-D)_x systems (4, 21, 22) revealed

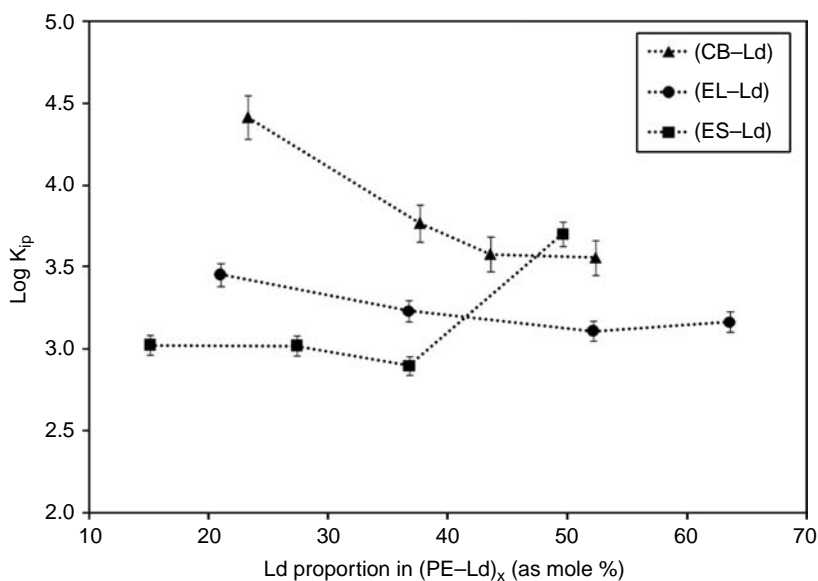


Figure 2. Relationship between affinity constants (K_{ip}) and the proportion of Ld remaining into $(PE-D)_x$ dispersion, after partition equilibrium with the organic solvent.

that the rate is a function of the fraction of drug condensed with the PE rather than a function of the concentration of free neutral species D, as this species is measured under equilibrium conditions. Therefore, the kinetic control is associated with the process of ion-pair dissociation in the microenvironment of the $(PE-D)_x$ macromolecular complex through the exchange H^+/DH^+ .

The average n for the nine kinetic runs was 0.61 with a range of 0.51–0.69. Departure from the value of 0.5 is currently associated to a non-Fickian release mechanism. However, in these systems, such departure would be seen as a consequence of the process of drug dissociation from the complex $(PE-D)_x$ that controls the overall kinetics followed by the Fickian diffusion of D.

Complexes of At and Me, which are bases of higher pK_a than Ld, also exhibit slower release rates, which are quite similar between them. However, complexes of the weaker base Ld exhibit release rates that clearly follow the order $ES > EL > CB$. Such results are in line with the proportion of structural hydrophobic moieties in the PE, nevertheless were not expected from data of K_{ip} of Table 1 and Figure 2, suggesting that, in this case, other factors would also play a significant role in the release process.

As water in the receptor compartment was replaced by 0.9% (0.154 M) NaCl solution, to mimic a biological fluid, an increase in delivery rate was observed in all cases. This behaviour is the consequence of the diffusion of the salt towards the upper compartment, promoting both the cationic exchange with the complex and the further diffusion of DH^+Cl^- together with D. The average of n was 0.66, with a range of 0.57–0.78. Therefore, the exponent n does not exhibit a considerable departure from

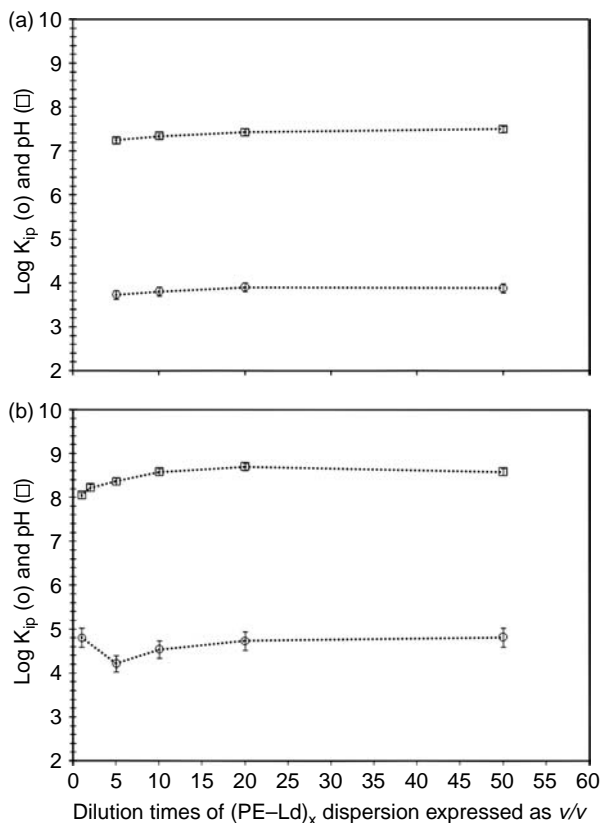


Figure 3. Effect of dilution on affinity constants, K_{ip} (circles) and pH (squares): (a) $(EL-Ld)_{50}$ at 1.0% of Eudragit[®] and (b) $(CB-Ld)_{75}$ at 0.5% of Carbomer.

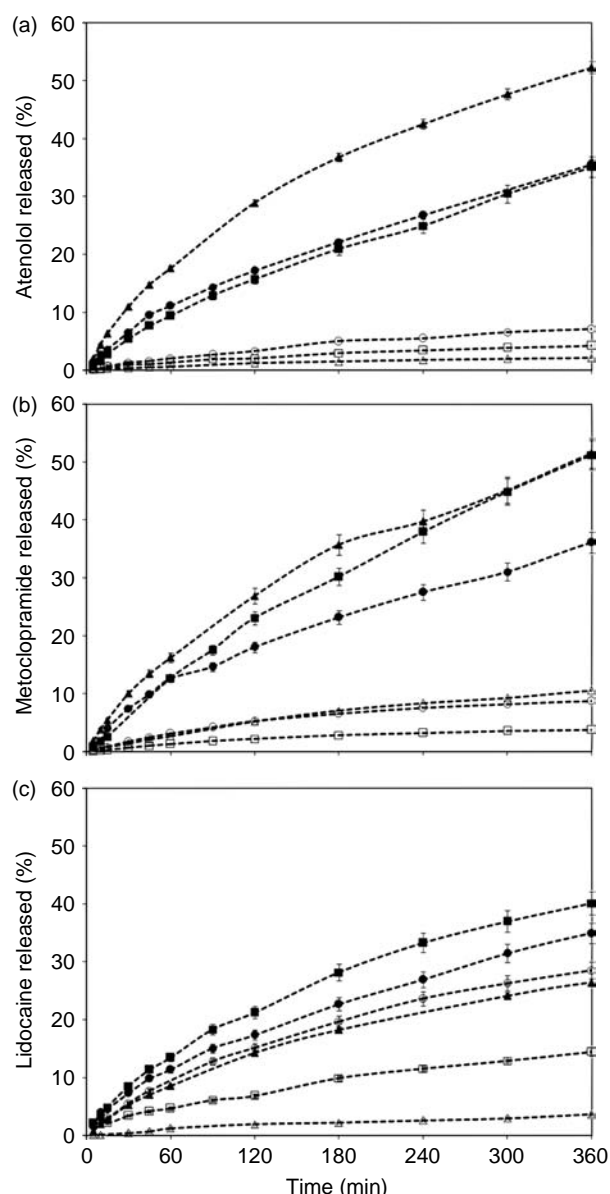


Figure 4. Release profiles of (a) At, (b) Me and (c) Ld from complex dispersions: \blacktriangle (CB-D)₅₀, \blacksquare (EL-D)₅₀ and \bullet (ES-D)₅₀, using water (open symbols) or 0.9% NaCl solution (filled symbols) as the receptor medium.

that observed in water, suggesting that the system keeps the same kinetic control.

The effect of NaCl on release rates is reported in Table 3 as the ratio k_w/k_{NaCl} . Such ratios were proportional to the molar concentration of D in each complex that follows the order CB > EL > ES with the three drugs (Table 3). Therefore, the effect on complexes of the weaker base Ld was similar to those of At and Me. This levelling effect would be associated to the high contribution of the Na⁺ from the receptor medium on the exchange process

(Na⁺/DH⁺) together with the protogenic effect produced by the release of DH⁺, suggesting that the dissociation of RCOO⁻DH⁺ is the main factor that controls drug-releasing rates.

Conclusions

PE-D counterionic condensation of three structurally related acid PE exhibited high affinity constants, log K_{ip} in the interval of 2.9–4.9, with model drugs assayed and remained essentially unchanged on dilution.

Distance between acid pending groups of PE seems to play a significant role. Thus, as Ld loading increases, CB lowers K_{ip} , while ES raises it, and that of EL remains unchanged.

In general, three PE-D systems exhibited a similar release behaviour under the conditions assayed, suggesting that the dissociation of RCOO⁻DH⁺ is the factor that controls releasing rates.

Since dispersions of (EL-D)_x and (ES-D)_x have lower viscosity and similar biocompatibility than those of (CB-D)_x, their concentrations could be raised in order to get systems with higher concentrations of D, which could expand their potential uses as drug carriers.

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