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A Linear Free Energy Relationship Treatment of the Affinity between Carboxymethylcellulose and Basic Drugs

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Abstract: With the purpose of getting information about the factors that determine the affinity between basic drugs (B) and the acid form of carboxymethylcellulose (HCMC), the constant K_{ip} for the equilibrium HCMC + B $\rightleftarrows$ CMC^- BH^+ was measured using a set of nine model B. A linear free energy relationship (LFER) was developed through a multiple correlation of log K_{ip} against (pK_a + log PC), in which the octanol−water partition coefficient (PC) was introduced as an indicator of the hydrophilicity of B. Both magnitudes, pK_a and log PC, contribute to a rise in log K_{ip}. In addition, water uptake and drug delivery were assayed with the product of neutralization of HCMC with atenolol, which was easily wetted, and the drug−HCMC interaction was found essentially reversible.

Keywords: Polyelectrolytes; carboxymethylcellulose; amine drugs; ion pair; LFER

Introduction

Polyelectrolytes (PE) in 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 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.

Therefore, knowledge about the factors that determine the interaction between ionic or ionizable drugs and PE is relevant in the design of pharmaceutical dosage forms.

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(1) Guo, J.-H.; Skinner, G. W.; Harcum, W. W.; Barnum, P. E. Pharmaceutical Applications of Naturally Occurring Water-soluble Polymers. *Pharm. Sci. Technol. Today* **1998**, *1*, 254−260.

(2) Jantzen, G. M.; Robinson, J. R. Ion- Exchange Systems. In *Modern Pharmaceutics*, 3rd ed.; Banker, G. S., Rhodes, C. T., Eds.; Marcel Dekker: New York, 1996; pp 592−593.

(3) Anand, V.; Kandarapu, R.; Garg, S. Ion-Exchange Resins: Carrying Drug Delivery Forward. *Drug Discovery Today* **2001**, *6*, 905−914.

(4) Takka, S.; Rajbhandari, S.; Sakr, A. Effect of Anionic Polymers on the Release of Propranolol Hydrochloride from Matrix Tablets. *Eur. J. Pharm. Biopharm.* **2001**, *52*, 75−82.

(5) Sriwongjanya, M.; Bodmeier, R. Effect of Ion Exchange Resins on the Drug Release from Matrix Tablets. *Eur. J. Pharm. Biopharm.* **1998**, *46*, 321−327.

(6) Schlichting, D. A. Ion Exchange Resin Salts for Oral Therapy I. Carbinoxamine. *J. Pharm. Sci.* **1962**, *51*, 134−136.

(7) Borodkin, S.; Sundberg, D. P. Polycarboxylic Acid Ion-Exchange Resin Adsorbates for Taste Coverage in Chewable Tablets. *J. Pharm. Sci.* **1971**, *60*, 1523−1527.

(8) Vilches, A. P.; Jimenez-Kairuz, A.; Alovero, F.; Olivera, M. E.; Allemandi, D. A.; Manzo, R. H. Release Kinetics and Up-take Studies of Model Fluoroquinolones from Carbomer Hydrogels. *Int. J. Pharm.* **2002**, *246*, 17−24.

(9) Jimenez-Kairuz, A. F.; Allemandi, D. A.; Manzo, R. H. The Improvement of Aqueous Chemical Stability of a Model Basic Drug by Ion Pairing with Acid Groups of Polyelectrolytes. *Int. J. Pharm.* **2004**, *269*, 149−156.

(10) Billany, M. Suspensions and Emulsions. In *Pharmaceutics. The Science of Dosage form design*, 2nd ed.; Aulton, M. E., Ed.; Churchill Livingstone: London, 2002; pp 340−342.

(11) Colestipol. In *Clinical Pharmacology 2000*; Gold Standard Multimedia (http://www.cp.gsm.com, accessed on Feb 3, 2004).

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Although this point has been addressed by many authors (Bishop,[12] Kunin and Myers,[13] Peterson and Gowen,[14] Kennon and Higuchi,[15] Borodkin and Yunker,[16] Sawaya and co-workers[17]), at present a detailed description about the factors governing such interaction is not fully available.

In this context, the aim of this work is to provide a more detailed knowledge about the nature of the factors that determine drug−PE affinity. With such a purpose carboxymethylcellulose of middle viscosity in its acid form (HCMC) was selected as the PE. This macromolecule is insoluble in water and remains in the solid state in contact with solutions of salts (hydrochlorides) of basic drugs. However, after interaction with appropriated counterions (i.e., Na^+, K^+), HCMC behaves as a dispersible PE.

Then, the lowering of drug concentration after equilibration of a drug salt solution in contact with HCMC measures the drug sorption by the PE. Sorption is essentially the consequence of the acid−base reaction between carboxylic groups (R−COOH) of HCMC and the basic group of a protonated drug (BH^+) as depicted in eq 1.

$$R-COOH + BH^+ + Cl^- \rightleftarrows [R-COO^- BH^+] + Cl^- + H^+ \quad (1)$$

Theoretical Background. The constant of the heterogeneous equilibrium 1 has been currently referred as the selectivity coefficient (SC) between the interchanging species according to eq 2,

$$SC = D_{PE}M_S/D_SM_{PE} = [R-COO^- BH^+][H^+]/[R-COOH][BH^+] \quad (2)$$

where $D = BH^+$ and $M = H^+$, and subindices S and PE refer to the fractions of molecules in solution and bound to the PE, respectively.

However, with the purpose of comparing the affinity of drugs having basic groups of different strength it is convenient to use the equilibrium constant for the acid base reaction that yields the ion pair ($[R-COO^- BH^+]$),

$$R-COOH + B \rightleftarrows [R-COO^- BH^+] \quad (3)$$

and

$$K_{ip} = [R-COO^- BH^+]/[R-COOH][B] = SC/K_a \quad (4)$$

where K_{ip}, expressed as 1/molarity (M), is the formation constant for the ion pair, which measures the ability of the basic drug to accept a proton from the R−COOH as well as its capacity to remain electrostatically bound to the PE.

In principle, the extent of the interaction would depend on (a) the accessibility of drug molecules to the acid groups of the PE, (b) the acid−base reaction, and (c) the tendency of the ion pair to dissociate.

Experimental Section

Materials: sodium carboxymethylcellulose (NaCMC) (PA grade, Fluka AG, Buchs SG, Switzerland), atenolol (Atn), diltiazem hydrochloride, diphenhydramine hydrochloride, propranolol hydrochloride, naphazoline hydrochloride, metoclopramide hydrochloride, lidocaine hydrochloride (pharmaceutical grade, Magel S.A., Bs. As, Argentina), procainamide hydrochloride (PA grade, Sigma Chemical Co., St. Louis), ethanol 96° (pharmaceutical grade, Porta, Córdoba, Argentina), sodium chloride (PA grade, Cicarelli, Santa Fe, Argentina), 1000 N hydrochloric acid solution (Merck, Darmstadt, Germany).

Methods

Preparation of HCMC. HCMC was obtained by adding 1 N HCl solution to an aqueous hydrogel of 3.6% NaCMC until pH = 2 and further precipitation with ethanol 96°. The solid was separated by filtration, gently washed with water, filtered, and dried in an oven at 50 °C to constant weight. The product was milled and sieved through 40 and 70 mesh sieves. The equivalents of carboxylic groups per gram of HCMC (1.84×10^{-3}) were assayed by acid base titration.

Equilibrium Measurements. Two series of suspensions of HCMC were prepared in glass-stoppered flasks. In each flask a fixed amount of HCMC (40 mg) and 10 mL of the drug aqueous solution were introduced according to the following scheme:

One series contained solutions with increasing concentration of Atn (base) covering the range 3.75×10^{-4} to 6.02×10^{-3} M.

The other series contained solutions of different drug hydrochlorides at a fixed concentration (4.42×10^{-3} M).

Flasks were placed in a constant temperature bath at 25 °C and mechanically shaken for 24 h.

The pH values of the supernatant were measured at the beginning (pH_i) and end of the experiment (pH_f).

All experiments were performed in triplicate.

Samples of supernatant solutions were appropriately diluted with distilled water and assayed by UV spectrophotometry (Atn, 273 nm; diphenhydramine hydrochloride, 258 nm; diltiazem hydrochloride, 236 nm; lidocaine hydrochloride, 236 nm; metoclopramide hydrochloride, 272.8 nm; naphazoline hydrochloride, 280.6 nm; procaine hydro-

(12) Bishop, J. A. Covalent Adsorption on Base-exchange Resins. *J. Phys. Chem.* **1946**, *50*, 6−12.
(13) Kunin, R.; Myers, R. J. The Anion Exchange Equilibria in an Anion Exchange Resin. *J. Am. Chem. Soc.* **1947**, *69*, 2874−2878.
(14) Peterson, S.; Gowen, E. Equilibria Between Aromatic Acids and Weak Base Anion Exchangers. *Ind. Eng. Chem.* **1953**, *45*, 2584−2586.
(15) Kennon, L.; Higuchi, T. Interaction Studies of Cationic Drugs with Anionic Polyelectrolytes I. Sodium Carboxymethylcellulose. *J. Am. Pharm. Assoc.* **1956**, *45*, 157−160.
(16) Borodkin, S.; Yunker, M. H. Interaction of Amine Drugs with a Polycarboxylic Acid Ion-Exchange Resin. *J. Pharm. Sci.* **1970**, *59*, 481−486.
(17) Sawaya, A.; Benoit, J.-P.; Benita, S. Binding Mechanism of Doxorubicin in Ion-Exchange Albumin Microcapsules. *J. Pharm. Sci.* **1987**, *76*, 475−480.

Table 1. Basic Drugs Selected Together with Their pK_a, MW, and log PC of the Free Bases

drug (hydrochloride)	amine	pK_a[a]	log PC[b]	MW
atenolol	2°	9.6	0.16	302.79
diltiazem	3°	7.7	2.80	450.98
diphenhydramine	3°	9.1	3.27	291.82
lidocaine	3°	7.92	2.26	270.80
metoclopramide	3°	9.3	2.66	336.26
naphazoline	2°	10.9	3.83[c]	246.74
procainamide	3°	9.2	0.88	271.79
procaine	3°	8.8	1.92	272.77
propranolol	2°	9.5	2.98	295.81

[a] Taken from *Foye's Principles of Medicinal Chemistry*, 4th ed.; Lemkes, T. L., Williams, D. A., Eds.; Lea & Febiger: Malvern, PA, 1995; pp 948−959. [b] Taken from *Exploring QSAR, Hydrophobic, Electronic and Steric Constants*; Hansch, C., Leo, A., Hoekman, D., Eds.; ACS Professional Reference Book; American Chemical Society: Washington, DC, 1995. [c] Calculated by CLOGP (version 1.0), Leo, A. (1995 Biobyte Corp.).

chloride, 290.6 nm; procainamid hydrochloride, 278 nm; and propranolol hydrochloride, 289 nm.)

HCMC−Atn Solid Product. This product was prepared by mixing an aqueous suspension of HCMC with the appropriate amount of Atn, to neutralize 50% of the HCMC acid groups. The product was separated and dried in an oven at 50 °C to constant weight.

Uptake Studies. Water sorption (uptake) of HCMC and HCMC−Atn was determined using an apparatus described by Nogami,[18] which was adapted in our lab as described in Llabot et al.[19]

Drug Delivery Measurement. Matrices were prepared by compacting in a hydraulic press 200 mg of HCMC−Atn powder. Delivery kinetics of Atn from the matrix was measured in a USPXXIV dissolution apparatus 1 (Hanson Research, Chatsworth, CA) at 50 rpm, 37 °C using 500 mL of dissolution medium (water, or 0.9% NaCl aqueous solution, or 0.1 N HCl solution). Samples of 5 mL were taken at defined time intervals, and Atn released was spectrophotometrically determined.

Results and Discussion

Table 1 reports the set of nine basic drug hydrochlorides (six tertiary and three secondary amines) used in the study that covers a range of 3.2 pK_a units. The table also contains the octanol−water partition coefficients (log PC) of the free bases of each drug.

Atenolol (Atn) was used as a model to determine the dependence of K_{ip} on the degree of neutralization of HCMC. Figure 1 shows the linear decrease of K_{ip} with the concentration of Atn in the solution. This fact was taken into account to design the experiments with the set of drugs in order that the degree of neutralization produced with the different drugs would be as close as possible.

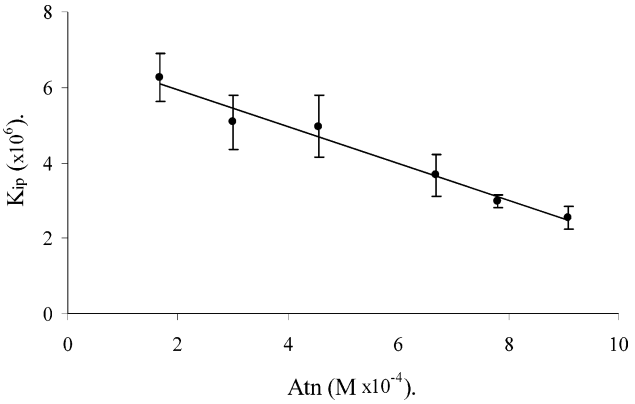

Figure 1. K_{ip} (M^{-1}) versus Atn concentration (M) at equilibrium.

On the other hand, to perform a complementary characterization of the PE−drug complex, dried samples of HCMC 50% neutralized with Atn were compacted to obtain 200 mg matrices which were subjected to water uptake and Atn delivery experiments.

The water uptake studies showed that a HCMC−Atn matrix quickly sorbs water to reach a plateau after having taken about 6 times its weight of water, which is 2-fold higher than the uptake of HCMC. This result indicates a greater interaction with water of HCMC−Atn with respect to HCMC, which is consistent with the ionic nature of the bonds originated by the neutralization.

The Atn delivery measurements showed that release in water is fast, reaching equilibrium quickly after having delivered about 20% of Atn. As water is replaced by either HCl or NaCl solutions, delivery occurs to a greater extent due to the ionic exchange among the ions of the solutions and HCMC−Atn. In summary, the HCMC−Atn complex was easily wetted and the interaction between the drug and the PE was found essentially reversible.

Table 2 reports the results of affinity measurements of the set of drugs. Values of K_{ip} were in the range 10^5-10^8 M^{-1} revealing high HCMC−drug affinity as well as a significant variation among drugs in the extent of the interaction.

HCMC is a linear macromolecule without chemical cross-linking among chains that is easily wetted. On the other hand, there are not important variations in structure or molecular weight among the drugs of the set. Therefore, it seems unlikely that access of drugs to the carboxylic groups of HCMC would be a limiting factor associated with the variations in the extent of the interaction.

Conversely, as expected, the base strength of the reacting groups of the drugs plays a central role in the interaction. In fact, the correlation between log K_{ip} and pK_a (Figure 2) approached a linear relationship with a slope near unity, revealing an important contribution of the basic strength in shifting to the right the heterogeneous equilibrium 3.

(18) Nogami, H.; Nagai, T.; Fukuoka, E.; Sonobe, T. Disintegration of the Aspirin Tablets Containing Potato Starch and Microcrystalline Cellulose in Various Concentrations. *Chem. Pharm. Bull*. **1969**, *17*, 1450−1455.

(19) Llabot, J. M.; Manzo, R. H.; Allemandi, D. A. Double-Layered Mucoadhesive Tablets Containing Nystatin. *AAPS PharmSciTech* **2002**, *3*, article 22, online journal (http://www.aapspharmscitech.org).

Table 2. Affinity Measurements of the Interaction of Different Basic Drugs with HCMC

drug (hydrochloride)	pH_i[a]	pH_f[b]	% COO^- BH^+	SC	K_{ip} (M^{-1})	log K_{ip}
atenolol	4.07	4.02	9.14 ± 0.93	(2.56 ± 0.21) × 10^{-3}	(1.02 ± 0.85) × 10^7	7.01 ± 0.03
diltiazem	5.22	3.81	18.08 ± 0.05	(1.11 ± 0.13) × 10^{-2}	(5.57 ± 0.64) × 10^5	5.75 ± 0.05
diphenhydramine	5.80	3.97	12.95 ± 0.22	(4.60 ± 0.27) × 10^{-3}	(5.80 ± 0.33) × 10^6	6.76 ± 0.02
lidocaine	5.24	4.33	33.17 ± 0.68	(1.22 ± 0.14) × 10^{-2}	(1.02 ± 0.11) × 10^6	6.01 ± 0.05
metoclopramide	6.62	3.75	18.91 ± 0.12	(1.39 ± 0.22) × 10^{-2}	(2.76 ± 0.45) × 10^7	7.44 ± 0.07
naphazoline	5.85	3.87	17.16 ± 0.33	(8.81 ± 0.31) × 10^{-3}	(6.99 ± 0.24) × 10^8	8.84 ± 0.01
procainamide	5.94	4.00	15.32 ± 0.65	(5.54 ± 0.39) × 10^{-3}	(8.78 ± 0.62) × 10^6	6.94 ± 0.03
procaine	5.87	4.02	15.55 ± 0.52	(5.34 ± 0.27) × 10^{-3}	(3.37 ± 0.17) × 10^6	6.53 ± 0.02
propranolol	5.52	3.64	20.39 ± 0.58	(1.99 ± 0.11) × 10^{-2}	(6.30 ± 0.34) × 10^7	7.80 ± 0.02

[a] pH at the beginning of the experiment. [b] pH at equilibrium.

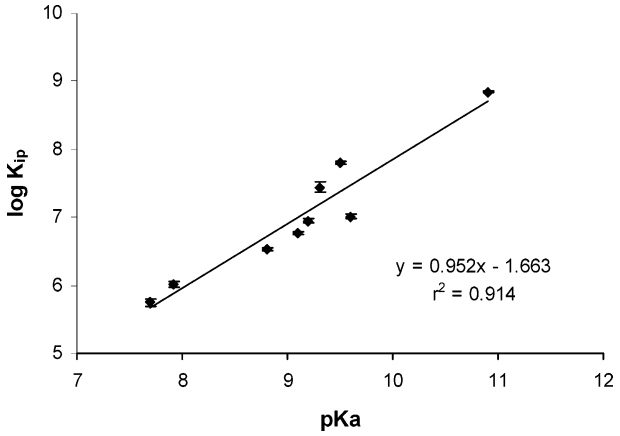

Figure 2. Correlation between log K_{ip} and pK_a for the set of nine drugs.

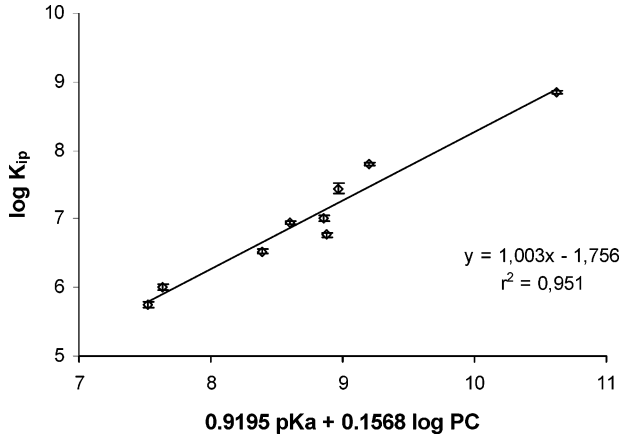

Figure 3. Multiple correlation between log K_{ip}, pK_a, and log PC for the set of nine drugs.

In order to characterize the whole interaction, the ability of the drug to remain attached to the polymer was the third point considered. With regard to this subject it was thought that the hydrophilicity of the drugs would be related to their tendency to dissociate from the ion pair. Ideally, the excess free energy in water of the basic drugs (ΔF^w_{excess}) would be a good indicator of hydrophilicity. However, since such a parameter was not available for the whole set, log PC was used with such a purpose. It was well established that the sensitivity of log PC toward the structural modifications of organic neutral molecules is largely determined by the variation of ΔF^w_{excess} rather than by that of the excess free energy in octanol (ΔF^{oct}_{excess}).[20] Therefore log PC was used as an indicator of the hydrophilic properties of the drugs. The set of drugs exhibits a wide variation of this property (from 0.16 to 3.83), which represents a favorable situation to test if it would be a factor involved in the interaction. In this way, log PC was introduced together with pK_a in a multiple correlation against log K_{ip}. As can be seen in Figure 3, the quality of the linear correlation was improved with regard to that of Figure 2 (r^2 increased from 0.91 to 0.95), suggesting that the hydrophilic character of drugs is also involved in the interaction depicted by equilibrium 3. The insight provided by this correlation is that the higher the water affinity of a molecule, the lower its tendency to remain electrostatically attached to the PE.

In accord with the parameters arising from the multiple correlation, both magnitudes, pK_a and log PC, contribute to a shift of equilibrium 3 to the right, accounting respectively for 85.4% and 14.6% of the whole effect. Therefore, the behavior of the set of basic drugs studied is well described through this LFER[21] among three different equilibria. Last, the correlation does not indicate differences between the behavior of secondary and tertiary amines.

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(20) Chiou, C. T.; Block, J. H. Parameters Affecting the Partition-Coefficient of Organic Compounds in Solvent-Water and Lipid Water Systems. In *Partition Coefficient. Determination and Estimation*, 1st ed.; Dunn, W. J., III, Block, J. H., Pearlman, R. S., Eds.; Pergamon Press: Oxford, 1986; pp 37−60.

(21) Wells, P. R. *Linear Free Energy Relationships.* Academic Press Inc.: London, 1968.