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IN VITRO ADSORPTION-DESORPTION OF PAPAVERINE HYDROCHLORIDE BY MONTMORILLONITE

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ABSTRACT

In an attempt to obtain the basic data necessary in research into the possible use of papaverine in sustained action formulas in the form of complexes with Montmorillonite, the "in vitro" adsorption and desorption of the drug as a function of different factor was studied.

The study of the interaction and adsorption mechanisms was carried out by adsorption isotherms, X-ray diffraction and I.R. spectroscopy.

The adsorption of papaverine by Montmorillonite increases with the rise in pH of the solution, within the pH range studied (2-4) in agreement with the solubility of the compound. According to the isotherms, adsorption

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increases with the concentration of the solution up to 79.16 mEq/100 g (very close to the exchange capacity of the clay). The data fulfill Langmuir's equation, implying a chemical adsorption mechanism.

The results of the X-ray diffraction and I.R. spectroscopy studies confirm the intercalation of the organic cation into the interlayer space of montmorillonite, forming a complex of defined spacing (17.66 Å (Δ = 8.06 Å)). The studies revealed that cation exchange is the mechanism responsible for this interaction.

The "in vitro" desorption studies showed that the amount of papaverine desorbed from the complex depends on the pH of the solution, on its ionic strength, on the presence of free drug and on the elimination rate of the desorbed complex; in all cases, desorption was seen to be very low.

In general, release of the drug follows a single first order kinetic process with a rapid initial desorption of the drug.

INTRODUCTION

Papaverine, a smooth-muscle relaxant, has been primarily used as a peripheral vasodilator. Its therapeutic efficiency is limited by its short plasma half-life and is affected by its very fast and almost complete metabolism. Consequently, frequent dosing is necessary and it is this aspect that leads to the consideration of the possible advantages of a sustained action formulation for maintaining therapeutic concentrations over longer times.

The systems most frequently used to achive such sustained action formulations are those based on the control of the release rate of the drug, and thus of the absorption process, by the use of inert matrices.

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Laminar silicates belong to a group of clay minerals which show the property of being able to form adsorption complexes with organic compounds by intercalation of these molecules into the interlayer space of the clay. The interaction mechanism mainly depends on the molecular size of the organic compound and the structural characteristics of the silicate. Owing to its structure and properties, montmorillonite shows special features in terms of adsorption which permit its use as a support in sustained action formulations.

The development of such formulations requires previous studies on the adsorption of the drug by the silicate, on its interaction mechanism and on its "in vitro" desorption.

The adsorption and interaction mechanism of different drugs with montmorillonite have been the object of several studies reported in the literature. In this sense, experimentation has been carried out on diazepam and different benzodiazepine derivatives (1); clindamycine and tetracycline (2), and several cation and amphoteric drugs (3) by dyalysis and solution methods, among others. Using X-ray diffraction, I.R. spectroscopy and adsorption isotherms,the authors of the present work studied chlorpheniramine maleate (4), propranolol hydrochloride (5) and quinidine sulphate (6). The use of montmorillonite in sustained action formulations has also been described previously by McGinity and Lach (7). for amphetamine sulphate and Vicente Hernandez et at. (8) for sotalol hydrochloride.

The present work studies the adsorption and interaction mechanism of papaverine hydrochloride with montmorillonite as well as the "in vitro" desorption of the drug as a function of different factors with the aim of obtaining preliminary data for the possible "in vivo" use of the clay as a matrix in a sustained action formulation of this drug.

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MATERIALS AND EXPERIMENTAL METHODS

Albagel montmorillonite was used in this study. The < u fraction of the clay was separated by sedimentation. The exchange capacity of the clay is 80 mEq/100g. Na-montmorillonite was prepared by successive treatments of the clay with solutions of sodium acetate followed by several washes with water and ethyl alcohol.

The papaverine hydrochloride was of B.P and U.S.P standards. In the studies on adsorption, 100 mg of sodium montmorillonite equilibrated in an atmosphere of 50 % H_2SO_4, 50 ml in volume, and a temperature of 40 °C were used in all cases. A water bath was used and the suspension was shaken continously.

In the study of the influence of pH on the adsorption of the drug by montmorillonite, 100 mg of Na-montmorillonite were treated with a solution of papaverine hydrochloride (0.2 mEq in 50 ml) adjusted to pH values ranging between 2 and 4 (the solubility range of the compound). The suspension was shaken in a water bath for 30 min. Following this, it was centrifuged and the amount of drug in the supernatant liquid was determined by U.V spectroscopy. (maximum adsorption 250 nm).

To obtain the isotherm, the amounts adsorbed were determined as a function of the concentration, as described above, using the following amounts of papaverine: 0.02; 0.04; 0.06; 0.08; 0.10; 0.15; 0.20; 0.25; 0.30; and 0.35 mEq. pH was 3 and contact time 30 min.

For the study by X-ray diffraction, oriented aggregates were prepared of the samples of Na-montmorillonite and of the montmorillonite-drug complex with and without previous washing in distilled water, adjusted to the pH of the solution employed. X-ray diffractograms were obtained for the complex dried in air and dried under a 0.1 mm

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Hg vacuum. In the latter cases, the aggregates were wrapped in Mylar to prevent rehydration. The corresponding diffractograms were recorded on a Phillips P.W. 1010 apparatus with K Cu radiation and a Nickel filter.

For I.R spectroscopy KBr discs at 0.8 - 1.0 % were used registering the spectra of the samples of Na-montmorillonite, papaverine hydrochloride and of the montmorillonite-papaverine complexes. These were recorded on a Beckman Acculab 6 double beam apparatus.

In the studies on desorption, in all cases, 100 mg of the montmorillonite-papaverine complex were used containing 65.13 10^{-3} mEq of adsorbed drug.

The study of the influence of pH on desorption was carried out by treating 100 mg of the complex with 50 ml of distilled water adjusted to pH values between 2 and 6. The suspensions were shaken in a water bath at 40 °C continously. At intervals of 5, 5, 10, 10, 20 or 30 min. the suspension was centrifuged and the equilibrium concentration was determined. At each interval, 50 % of the supernatant liquid was renewed with the same amount of distilled water adjusted to the corresponding pH value and the suspension was resubjected to shaking.

In order to study the influence of electrolyte on the desorption of the drug the montmorillonite-papaverine complex was treated with NaCl solutions of 80 and 140 mEq/l of NaCl. The method used was the same as that described for the study of the influence of pH. The pH values at which this part of the study was carried out were 4.5 and 6. The replacement of 50% of the supernatant liquid was done with NaCl solutions adjusted to the corresponding pH value. In the study of the influence of $MgCl_2$, the same procedure was used, with a pH value of 4.

With respect to the suty on the influence of free drug in the solution and the elimination rate of the

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desorbed compound, the method followed was the same as that described above for the study of the other factors. In the first case (free drug in the solution) an amount of free drug equal to that adsorbed by 100 mg of complex was added to the solution. In the second case, extractions were carried out successivly every five min. In both cases, the renewals of liquid used 140 mEq/l NaCl solutions adjusted to pH =5.

RESULTS AND DISCUSION

Figure 1 shows the results obtained in the study of the influence of the pH of the solution on the adsorption of papaverine hydrochloride by Na-montmorillonite. The pH interval studied was chosen according to the solubility of the compound, since the drug is not very soluble at pH values close to the pKa of the substance (pKa = 5.9).

Adsorption may be seen to increase with the rise in the pH of the solution and at pH 3.5 and 4 it is greater than the exchange capacity of the clay.

The principal reaction taking place in adsorption must be that of exchange of the Na^+ ions of the montmorillonite by the papaverinium ions in the solution. Adsorption at pH 3.5 and 4 in excess of the echange capacity of the silicate is a phenomenon which has already been described in the adsorption of amine salts by montmorillonite (9,10,11), and is attributed to the additional adsorption of molecules by Van der Waals forces. The molecules may be found adsorbed as an amine salt or as a neutral amine.

Bearing in mind the pKa of papaverine it seems probable that the molecules adsorbed in excess are adsorbed in the form of the amine hydrochloride.This additional

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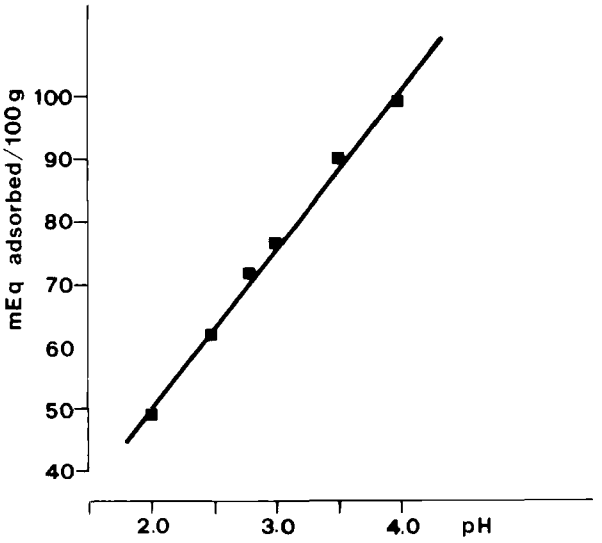

FIGURE 1.- Influence of pH on the adsorption of papaverine hydrochloride by montmorillonite.

adsorption by Van der Waals forces was confirmed by X-ray diffraction, as will be described below.

At very low pH values, there must be considerable competition between the H^+ ions and the papaverinium ions, preventing the total substitution of the Na^+ ions by the organic cation.

The study of the influence of contact time on adsorption shows that the reaction is rapid and that there is no additional adsorption after 15 min of treatment.

The adsorption isotherm of papaverine hydrochloride by montmorillonite is shown in figure 2a, where the equilibrium concentration is plotted as a function of the amount adsorbed. This amount is seen to increase with the concentration of the solution until an adsorption of 79.16 mEq/100 g is reached, very close to the exchange capacity of the clay, on the limit of the con-

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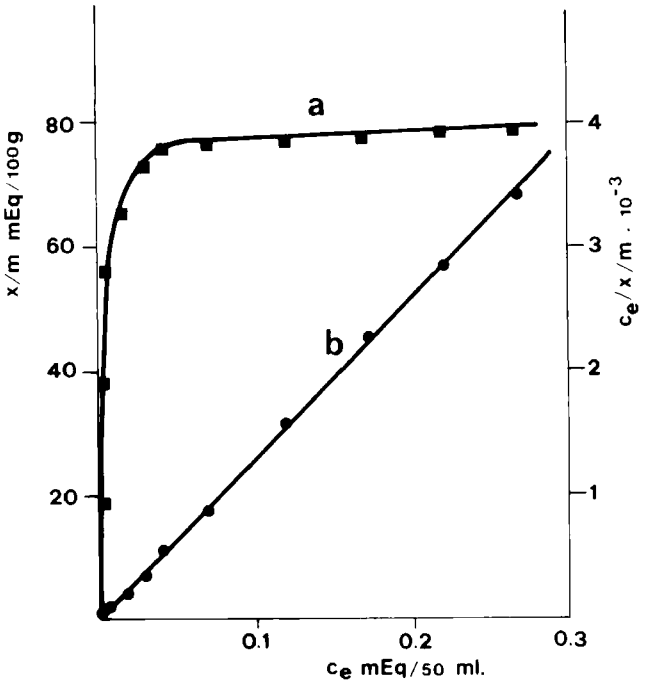

FIGURE 2.- Adsorption isotherm of papaverine hydrochloride by Na-montmorillonite a) amount adsorbed for 100 g of clay (x / ml as a function of the equilibrium concentration (Ce), b) Langmuir plot for the adosrption isotherm.

centration employed. If the adsorption data are plotted according to Langmuir's equation a straight line is obtained (figure 2b). According to Giles (12), the agreement of these data with this equation suggests a chemical adsorption mechanism.

In order to confirm the adsorption of the papaverinium ions into the interlayer space of montmorillonite and to suggest the possible disposition of the organic cations in the interlayer X-ray diffractograms were made of Na-montmorillonite and of the same substance tre

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ated with drug solutions at different concentrations and pH values (table I and II).

The increase observed in the d_{001} basal spacing of the silicate with the amount adsorbed indicates that intercalation of the papaverinium ions into the interlayer space of the clay takes place. The size of this increase depends on the pH and the concentration of the solution.

The increase in pH is thus reflected by an increase in the d_{001} spacing of the silicate. The increment in spacing with respect to the value of 9.6 Å of dehydrated montmorillonite varies from 6.75 Å at pH=2 to 9.80 A at pH=4, in unwashed samples. If the samples treated with solutions at pH 2 and 3 are washed repeatedly with water and vacuum dried their basal spacing remains unaltered; however, if the samples treated with solutions at pH 3.5 or 4 are subjected to the same treatment their basal spacings are shifted to 17.66 Å. This ease in desorption of the molecules adsorbed in excess of the exchange capactity of the clay at these pH values confirms their physical adsorption by Van der Waals forces.

The d_{001} basal spacing of the samples treated with solutions at different concentrations but with the same pH increase with the concentration of the solution from 14.72 Å (amount adsorbed = 18.86 mEq/100 g) to 17.66 Å. The spacings are not modified on washing the samples with distilled water nor by vacuum drying. This shows that no physical adsorption should be taking place and that no molecules are being retained weakly by Van der Waals forces; furthermore, the organic cations are strongly retained in the interlayer space. The low values of basal spacing should correspond to interstratified phases due to partial replacement of inorganic cations by organic cations.

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TABLE I

d_{oo1} basal spacing of Na-montmorillonite treated with solutions of papaverine hydrocloride at different pH.

pH	AMOUNT OF ORGANIC COMPOUND		WASHED SAMPLES			
			Dried in air		Vacuum Dried	
	Added (mEq)	Adsorbed (mEq/100g)	d_{oo1} Å	Δ Å	d_{oo1} Å	Δ Å
2.0	0.200	49.00	16.35	6.75	16.35	6.75
2.5	0.200	62.00	16.98	7.38	16.98	7.38
2.8	0.200	73.50	16.98	7.38	16.98	7.38
3.0	0.200	77.34	17.66	8.06	17.66	8.06
3.5	0.200	90.37	18.39	8.79	17.66	8.06
4.0	0.200	99.00	19.19	9.59	17.66	8.06

Figure 3 shows the I.R spectra of Na-montmorillonite (A), papaverine hydrochloride (B) and Na-montmorillonite treated with solutions of papaverine hydrochloride at different concentrations and at the same pH (pH =3) (C,D and E).

Detailed study of the spectra reveals that organic compound exists in the interlayer space of montmorillonite; this may be seen from the presence of principal absorption bands corresponding to papaverine in the spectra of the complexes washed several times with distilled water (figure 3, C-D-E). The intensity of the bands increases with the rise in concentration of the solution, indicating that the amount of organic cation pre

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TABLE II

d_{001} basal spacing of Na-montmorillonite treated with solution of papaverine hydrochloride at different concentrations, pH=3.

AMOUNT OF ORGANIC COMPOUND		WASHED SAMPLES			
		Dried in air		Vacuum Dried	
Added (mEq)	Adsorbed (mEq/100 g)	d_{001} Å	ΔÅ	d_{001} Å	ΔÅ
0.020	18.865	14.72	5.12	14.72	5.12
0.040	39.030	15.77	6.17	15.77	6.17
0.060	57.585	16.05	6.45	16.05	6.45
0.080	65.155	16.98	7.38	16.98	7.38
0.100	72.890	16.98	7.38	16.98	7.38
0.120	76.290	16.98	7.38	16.98	7.38
0.150	77.880	16.98	7.38	16.98	7.38
0.200	77.340	17.66	8.06	17.66	8.06
0.250	76.820	17.66	8.06	17.66	8.06
0.300	78.590	17.66	8.06	17.66	8.06
0.350	79.160	17.66	8.06	17.66	8.06

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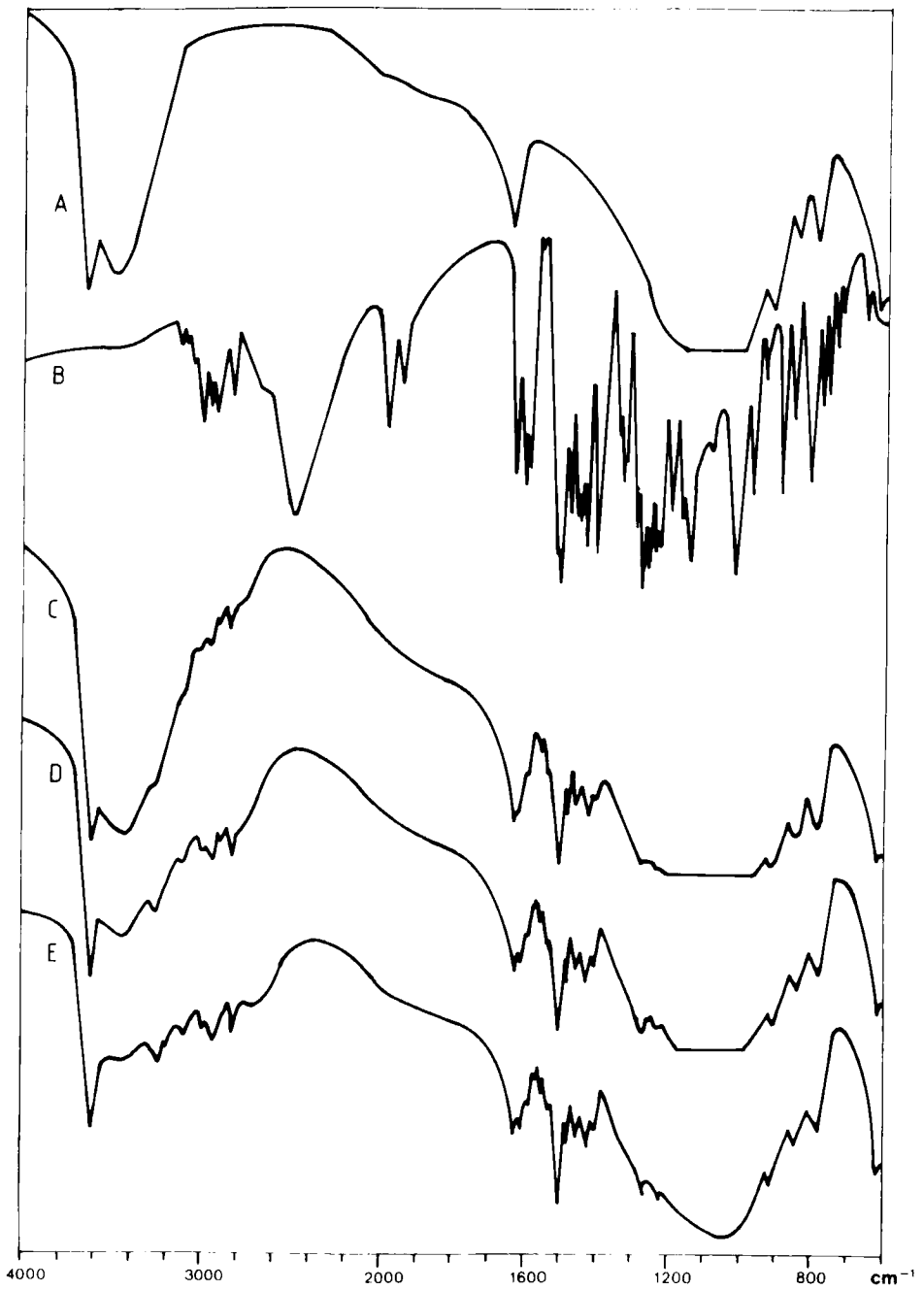

FIGURE 3.- I.R. spectra of A) Na-montmorillonite; B) papaverine hydrochloride, C), D) and E) Na-montmorillonite treated with papaverine hydrochloride at different concentrations, pH=3 (0.04 mEq/50 ml, 0.10 mEq/50 ml, 0.25 mEq/50 ml).

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sent in the interlayer space increases parallel to the rise in the amount adsorbed. Thus a decrease may be observed in the intensity of the stretching and bending vibration bands of the water associated to the exchange sites of montmorillonite (at 3430 and 1620 cm^{-1}) on increasing the concentration of the solution, since such water is progressively displaced from the interlayer space of the silicate by the organic cations.

The stretching bands of the NH^+ group, which appear in the spectrum of papaverine hydrochloride at 1940 and 1980 cm^{-1} and as a wide unstructured band with a slight maximum at 2500 cm^{-1} (corresponding to the $C=NH^+$ group), are shifted in the spectra of the complexes towards regions between 2800-3000 cm^{-1} and 3100-3300 cm^{-1}, respectively. Such shifts reveal that interaction must between the NH^+ groups and the negative surface of the oxygen atoms of the silicate.

In order to discern the possible arrangement of the organic cations in the interlayer space of the clay its molecular dimensions were calculated from the angles and bonding distances (13,14) and with the help of scale atomic models. Also taken into account was the fact that the molecule should adopt an orientation with the NH^+ group towards the negative surface of the oxygen atoms of montmorillonite.

The flat surface of the molecule (108.10 $\mathring{A}^2$) is greater than the available surface for a monovalent exchange cation (80 $\mathring{A}$). A flat arrangement, if we consider that adsorption, is close to the exchange capacity of the clay, requires the formation of a two-layer complex. This would account for the increase in spacing observed (8.06 A) since the thickness of each layer, assuming a flat arrangement for each of them, is approximately 4 $\mathring{A}$.

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"In vitro" desorption

As a previous step to the "in vivo" application of papaverine as a complex with montmorillonite, studies were carried out on the "in vitro" desorption of the drug. The aim of such research was to obtain information on the release rate and the amount released as time progressed as a function of various factors.

The amount of drug released over a given period increased with a decrease in the pH of the solution. Thus in the first 5 min, the amount released varied from 6.09 mEq/100 g at pH=6 to 12.55 mEq/100 g at pH =2. The phenomenon which must be taking place is that of exchange of the papaverinium ions by the H^+ ions of the solution, this displacement becoming greater as the pH value falls or as the concentration of H^+ ions in the solution increases (figure 4-A).

In order to make an approximate study, for comparative purposes, of the kinetic release process of the drug, the experimental data were fitted to a first order process. The amounts of drug remaining in the interlayer space and the logs of such amounts (log (a-x)) were plotted as a function of time for each of the factors studied. In all cases the equations of the regression straight lines were calculated, together with the linear correlation coefficients and the release rate constants (table III).

In the study on the influence of pH it may be seen (figure 5) that the release follows a first order kinetic process with a rapid initial desorption of the drug. The release constants (table III) are very low and their values are very close to each other, indicating that the determining factor in desorption must be the amount released in the first 5 min which, as reported above, becomes greater as pH falls. This study

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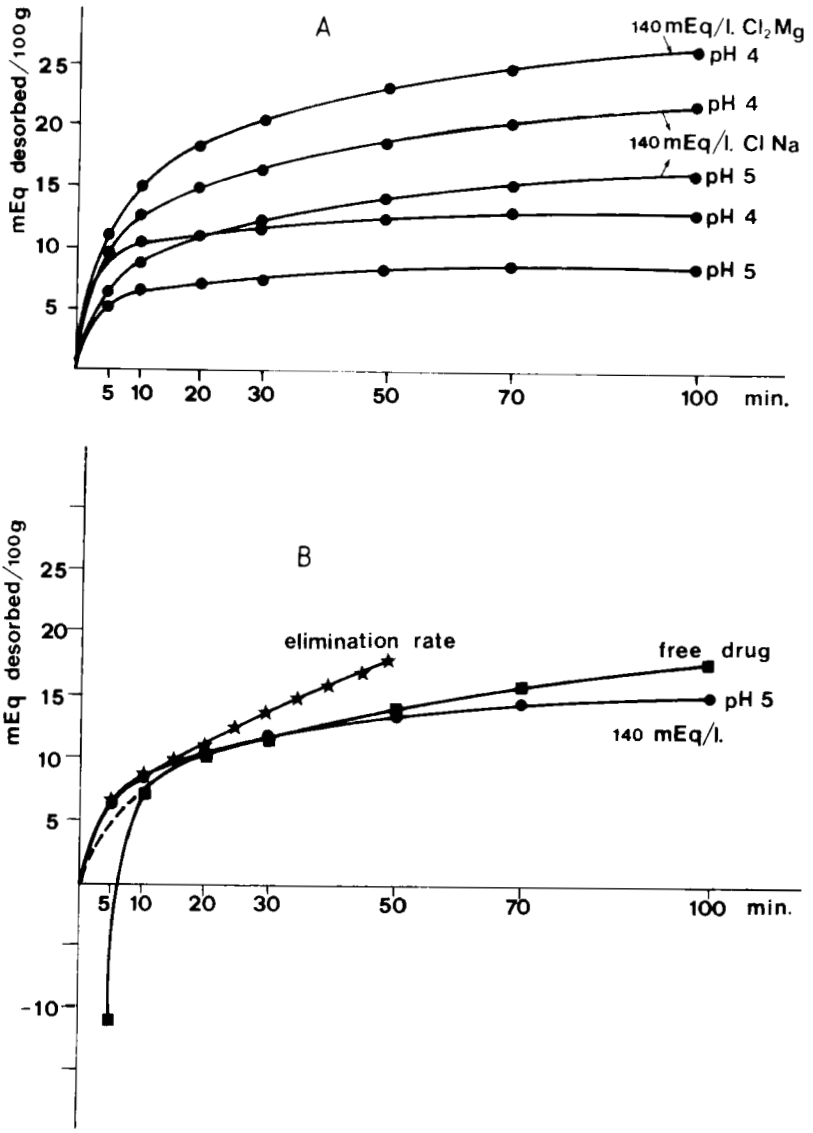

FIGURE 4.- Influence on the desorption of papaverine of: A) pH and ionic concentration; B) presence of free drug in the solution and of the elimination rate of the desorbed compound. Cumulative amounts as a function of time.

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TABLE III

Release rate constants as a function of the system.

SISTEMA	$K_1 10^4 min^{-1}$	$k 10^4 min^{-1}$	$K_2 10^4 min$
pH = 2		9	
pH = 3		9	
pH = 4		9	
pH = 5		5	
pH = 6		5	
pH = 4; 80 mEq/l ClNa	184		14
pH = 5; 80 mEq/l ClNa		14	
pH = 6; 80 mEq/l ClNa		9	
pH = 4; 140 mEq/l ClNa	207		18
pH = 5; 140 mEq/l ClNa		18	
pH = 6; 140 mEq/l ClNa		16	
pH = 5; 140 mEq/l ClNa free drug		21	
pH = 4; 140 mEq/l ClNa elimination rate 5 min.		62	
pH = 5; 140 mEq/l ClNa elimination rate 5 min.		46	

shows that the desorption of papaverine takes place to a very limited extent as a function of this factor.

According to the above, a further study was carried out on the influence of the presence of electrolyte in the solution using NaCl concentrations and pH

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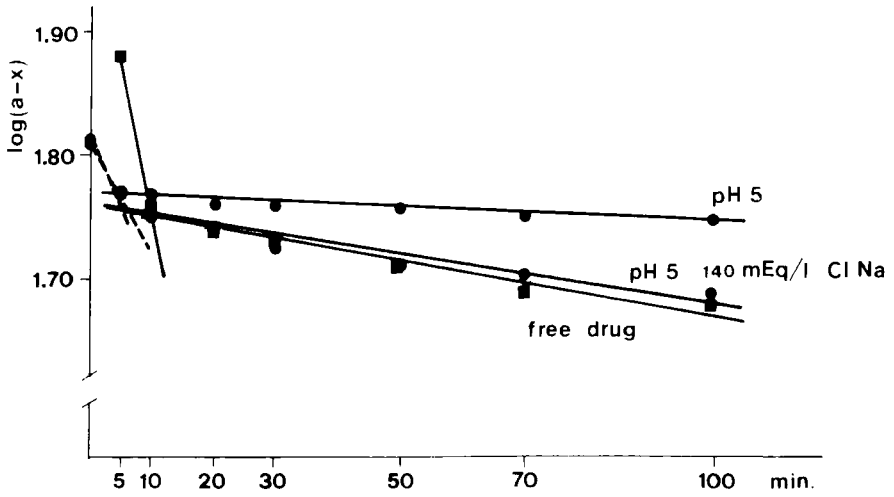

FIGURE 5.- Desorption kinetic of papaverine as a function of different factors (a : amount of papaverine in the interlayer space at time 0; x : amount of papaverine released at time t.

values close to those of the G.I tract (80 - 140 mEq/l and pH 4.5 and 6).

Figure 4 a shows the results obtained and includes, for comparison, those obtained in the same conditions but without the presence of electrolyte. It may be seen that the amount of drug released increases in the presence of NaCl. Thus at 100 min the amounts desorbed increase from 8.79 mEq/100 g at pH=5 to 16.36 mEq/100 g in a solution at the same pH but with 140 mEq/l of NaCl. For the same concentration of electrolyte the amounts released increase with the fall in the pH of the solution.

At pH 5 and 6, in the presence of electrolyte the release of the drug follows a single first order kinetic process, as in the study of pH, with a rapid initial desorption phase of the drug (figure 5). At pH=4, the ex-

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perimental points obtained may be fitted to two intersecting straight lines, showing that release takes place in two stages, both of first order but with different release constants (table III). In other words, the rate of the process varies as time progresses. The K_2 rate constant increases for the same pH value when there is electrolyte in the solution. At pH=4, the value of the K_1 rate constant also increases as a function of electrolyte concentration.

The faster desorption of the drug in the presence of NaCl is due to the greater displacement power of the Na^+ ion, compared with the H^+ ion, for the papaverinium cations.

Such results point to the importance that the presence of ions in the solution has on the process, even though the amount desorbed is low for the purposes proposed. It was therefore decided to study the influence of different concentrations of $MgCl_2$ in the solution (figure 4A) in similar conditions to the previous studies. The amounts of desorbed drug in these conditions may be seen to be slightly greater than when there is NaCl in the solution. Thus in the first 5 min, the amount desorbed was 10.62 mEq/100 g at pH=4 in the presence of 80 mEq/l of $MgCl_2$, compared with 9.65 mEq/100 g desorbed in the same conditions but with NaCl.

The kinetic process takes place in two first order stages, each with different release constants (table III). It may be seen that there is an increment in the K_1 and K_2 rate constants when there is $MgCl_2$ in the solution compared with the values obtained in the same conditions but in the presence of NaCl. This must be due to the greater polarizing power of the Mg^{2+} ion compared with the behaviour shown by the Na^+ ion for the drug cations.

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In certain circunstances, in order to achieve efficiency in a sustained action formulation it may be necessary to use a dosage schedule in which the drug is partially administered in the free form and partly in the adsorbed form. Experiments were therefore carried out to study the influence of free papaverine in the solution on the desorption of the drug. The results obtained are plotted in figure 4B and include, for comparison, those obtained in the same conditions but without free drug. It may be seen that, initially, additional adsorption of the drug takes place, the amount of papaverine adsorbed being 11.26 mEq/100 g. After 10 min, desorption of the drug begins, the amount released being very similar to those obtained in the same conditions but without free drug in the solution. In the studies on the adsorption of the drug it was shown that in certain conditions, the drug was adsorbed in amounts greater than the exchange capacity of the silicate. Bearing in mind that $77.93 \cdot 10^{-3}$ mEq were adsorbed in the formation of the complex used in the desorption experiments, it may be inferred that the complex formed still showed the ability to adsorb more organic cations.

From the start of desorption (figure 5) the release of the drug follows a single first order kinetic process (table III). From a comparison of the results obtained with those corresponding to desorption in the same conditions but without free drug it may be deduced that in the presence of free papaverine the desorption rate during the first 10 min decreases, while later it is practically equal.

Such finding indicate that a dosing in which part of the drug is administered in the free form and the other part in adsorbed form, would contribute considerably to achieving a sustained action formulation since

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initially only the free drug (and then not all of it) would be available after which the drug being desorbed would become available; this could be of great interest in "in vivo" application.

The rate at wich the compound is absorbed by the organism must influence the release of the drug from the complex to a considerable extent. The variations in this absorption rate may be simulated "in vitro" by varying the times of renewal of the solution. Thus an increase in absorption is equal to a decrease in the renewal times of the solution. The results obtained after carrying out extractions followed by renewals from the solution every 5 min are plotted in figure 4B; also included, again for comparative purposes, is the desorption of the drug from the complex in the same conditions (140 mEq/l of NaCl, pH=5) but with less frequent extractions and renewals. The amount of drug released at a given time is seen to increase with the rise in the elimination rate of the cations desorbed from the solution.Thus the amount desorbed at pH 5 after 50 min was 17.77 mEq/100 g compared with 13.59 mEq/100 g desorbed in the same conditions but with less frequent extractions and renewals. Also at pH=4, the desorbed amouts were 23.32 mEq/100 g and 18.43 mEq/100 g respectively.

The release kinetics process may be adjusted to a single first order process with a rapid initial desorption of the drug. It may be seen (table III) that there is a noteworthy increase in the rate constants as a consequence of the more frequent elimination of cations from the solution. This points to the fact that the increase in the elimination rates is one of the most important factors in the control of the desorption of papaverine adsorbed by montmorillonite.

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From the "in vitro" desorption studies it may be deduced that the papaverinium cations must show great affinity for the clay. Two main facts are apparent: on one hand, a very low desorption under the influence of the various factors studied and on the other, an additional adsorption in the presence of very low concentrations of free drug in the solution. With due care, such factors should permit the regulation of the release rate of the drug in such a way that the complex may be used "in vivo", in the foreseeable future.

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