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An in vitro study of the interaction between mebeverine hydrochloride and magnesium trisilicate powder

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Summary

The in vitro uptake of mebeverine hydrochloride onto magnesium trisilicate powder has been investigated. Adsorption data were obtained at temperatures 25, 37 and 50°C, with respect to changes in pH values from 0.8 to 7.73 and the presence of electrolytes. The calculated data were in accordance with Langmuir isotherms. The Langmuir constants and the thermodynamic functions were determined for the reaction. The results showed that adsorption was endothermic. Only partial elution of adsorbed drug occurred in different elution media. Dissolution of the tablets or capsules was adversely affected. The antacid efficacy of magnesium trisilicate was evaluated alone and in the presence of the pure drug or its dosage forms. It was shown that the acid reactivity of the antacid was affected and suppressed to a great extent.

Introduction

Irritable bowel syndrome (IBS) may be associated with gastric and duodenal ulcers and inflammation of the digestive tract. Antacids are, therefore, the most widely recommended coadministered drugs with that used for IBS, namely mebeverine hydrochloride which is a musculotropic antispasmodic with a direct action on the smooth muscle of the gastrointestinal tract. Many workers have studied, by various in vitro techniques, the interaction of antacids with drugs, such as anticholinergics (Khalil and Moustafa, 1973), antiepileptics (Naggar and Khalil, 1978), antispasmodics (Thoma and Lieb, 1985), antihypertensives (Babhair, 1988), antirheumatics (Naggar et al., 1976), antidiabetics (Naggar and Khalil, 1980), anticoagulants (Khalil et al., 1984) and antibiotics (Khalil et al., 1976). Among the antacids tested, magnesium trisilicate appeared to possess the highest adsorptive capacity (Naggar, 1981).

The purpose of this study was to assess mebeverine-magnesium trisilicate interactions by means of an adsorption-elution test in different media, at different temperatures, pH values, and in the presence of mono and divalent electrolytes; and by dissolution of its tablets and capsules. Moreover, the drug-antacid interaction was also

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evaluated by the in vitro determination of the effect of mebeverine hydrochloride powder and its dosage forms on the acid reactivity of magnesium trisilicate.

Materials and Methods

Materials

Mebeverine hydrochloride (HCl) pure powder, and its dosage forms, sugar coated tablets 135 mg, sustained release capsules 200 mg, and suspension (each ml contains 10 mg mebeverine pamoate), were obtained from Duphar B.V. (Weesp, The Netherlands). Magnesium trisilicate, pharmaceutical grade, surface area 3.25 $m^2 g^{-1}$ (determined by nitrogen adsorption technique) was obtained from Evans PLC (U.K.). The electrolytes used were of AR quality. All other reagents were of pure grade, and were used as supplied.

Methods

Adsorption experiments

General method for adsorption experiments: A solution of the drug (20 ml) of known concentration in 0.1 M HCl was added to 100 ml stoppered conical flasks containing 10 g of magnesium trisilicate powder. The flasks were shaken in a thermostatically controlled water bath (Karl Kolb type D.6.72, F.R.G.) at the desired temperature $\pm 0.5°C$, at a speed of 80 rpm for the required equilibration time (90 min). A control was also prepared to check for any change in drug stability which was confirmed by thin-layer chromatography technique.

The suspensions were filtered, appropriately diluted and the drug content was then determined at 263 nm using a Pye Unicam SP 8800 spectrophotometer (Cambridge, U.K.). The blank experiments for the antacid powder showed no interference at that wavelength. Three replicates were made, and the results were averaged.

The effects of temperature (25, 37 and 50°C), pH (0.8–7.73) and mono- and divalent electrolytes (sodium chloride and magnesium chloride) on the extent of adsorption were investigated.

Desorption experiments

The extent of elution of the adsorbed mebeverine HCl was determined in 20 ml of deionised distilled water (pH 6.1), 0.01 M HCl (pH 2.1), 0.1 M HCl (pH 1.2), 0.1 M NaCl (pH 6.8) and 0.1 M $MgCl_2$ (pH 5.8) at 80 rpm and 37°C.

Dissolution studies

In vitro release studies of both 135 mg tablets and 200 mg sustained release capsules of mebeverine HCl were performed using the USP dissolution apparatus (Erweka, type DT6, Frankfurt, F.R.G) at 100 rpm. The dissolution medium for tablets was 1 l of 0.1 M HCl, with or without different concentrations of magnesium trisilicate powder at 37°C. Aliquots were withdrawn periodically over 2 h, appropriately diluted and measured spectrophotometrically at 263 nm. For the sustained release capsules, the test was performed in 1 l of 0.1 M HCl for 2 h and the dissolution medium was then adjusted with a known amount of NaOH to pH 6.7. Samples were withdrawn over a period of 24 h, and assayed for its drug content.

Evaluation of the acid reactivity of magnesium trisilicate powder

Determination of the acid absorption power of magnesium trisilicate powder. The experiment was run according to acid absorption test BP (1988) for the powder alone and in the presence of mebeverine hydrochloride powder or its dosage forms.

Determination of the rate of neutralisation of magnesium trisilicate powder. Procedure A: 2 g of antacid powder with or without mebeverine hydrochloride or its dosage forms was added to a 150 ml beaker containing 50 ml of 0.1 M HCl maintained in the water-bath at $37°C \pm 0.5°C$. Stirring was effected by an overhead stirrer (Janke and Kunkel, GmbH, type RW 10 R, F.R.G.) at 310 rpm. The rate of acid neutralisation was followed by monitoring the pH changes of the mixture with respect to time, readings were taken at intervals for 1 h.

Evaluation of the buffering capacity of magnesium trisilicate powder. Procedure B: 2 g of antacid powder with or without mebeverine hydrochloride or its dosage forms was introduced

into a 500 ml beaker containing 50 ml of 0.1 M HCl under the same conditions as for procedure A. Immediately after adding the dose, additional 0.1 M HCl was introduced into the mixture at a constant flow rate of 2 ml min^{-1} via a peristaltic pump (Sage Instruments, model 375 A, U.S.A.) and the pH changes were measured with respect to time until the pH returned to a baseline of 2.0.

Procedures A and B were carried out in accordance with the specifications reported by Desai et al. (1963) with some modifications.

All the experiments were run in triplicates, and the results were averaged.

Results and Discussion

The adsorption data (Table 1) fitted a Langmuir plot in its linear form. The results obtained indicate an endothermic reaction. This was shown by the calculated monolayer capacities a as 122.10, 132.70 and 198.40 mg g^{-1} at 25, 37 and 50°C, respectively.

Since b is the equilibrium constant of adsorption, the following equations are derived:

$$\Delta F^{\circ} = -RT \ln b$$

$$\Delta H = \mathrm{d}(\Delta F^{\circ}/T)/\ \mathrm{d}(1/T)$$

$$\Delta S = (\Delta H - \Delta F^{\circ})/T$$

Table 2 shows that the enthalpy value of this endothermic reaction ($\Delta H = 5.80$ kcal mol^{-1}) is accompanied, therefore, by a positive charge. This could be explained as an entropy-driven reaction

TABLE 1

The effect of temperature on the Langmuir constants a and b for the adsorption of mebeverine HCl onto magnesium trisilicate (5.0% w/v) at pH 6.7

Temperature (°C)	Regression analysis		Langmuir constants	
	Slope ($1/a$)	Intercept ($1/ab$)	a (mg g^{-1})	b (l g^{-1})
25	0.0082	0.0549	122.10	14.90
37	0.0075	0.0290	132.70	25.98
50	0.0050	0.0719	198.40	7.01

TABLE 2

Thermodynamic functions ΔF°, ΔH, and ΔS for the adsorption of mebeverine HCl onto magnesium trisilicate (5.0% w/v)

Temperature (°C)	ΔF° (kcal mol^{-1})	ΔS (kcal deg^{-1} mol^{-1})
25	−5.240	0.03704
37	−5.793	0.03738
50	−5.194	0.03404
ΔH (kcal mol^{-1})	5.80	

as the absolute value of $T\Delta S > \Delta H$. This is in agreement with Nogami et al. (1968) who reported an endothermic adsorption reaction of tryptophan onto carbon black. The enthalpy value would suggest a physical form of adsorption of the Van der Waals type.

The systems in the temperature range studied have positive entropy values. Therefore, a marked change in the amount of disorder would be expected; consequently, there was an increase of 76.3 mg g^{-1} in the monolayer capacity of the adsorbent when the temperature was increased from 25 to 50°C. This increase in the entropy resulted in a negative free energy.

Since the structure of mebeverine base indicates the presence of lipophilic groups, the endothermic reaction may possibly be due to the hydrophobic bonding of the drug with the orderly iceberg structure of the water molecules, originally surrounding both the drug and the active sites, being disrupted and showing an increased randomness (Nogami et al., 1968). Moreover, the negative free energy could also be attributed to the deflocculated state of the system at higher temperatures.

The effect of pH on the adsorption (Table 3) shows that the extent of drug adsorption onto the adsorbent was pH-dependent within the pH range 0.8–7.73. The decrease in adsorption at low pH may be due to dissolution of a proportion of magnesium oxide component of the molecule of magnesium trisilicate (El Masry and Khalil, 1974) which causes a reduction in the active sites available for adsorption. On the other hand, as pH increases, the dissolution decreases and more active sites will be available for adsorption. Also, the resulting decrease in adsorption, may be attri-

TABLE 3

Effect of pH on the adsorption of mebeverine HCl (0.33% w/v) onto magnesium trisilicate (5.0% w/v) at 37 °C

pH	x/m (mg g^{-1})
0.8	57.20
1.01	58.71
2.0	59.15
3.14	60.69
4.0	61.50
5.0	62.40
6.77	64.13
6.90	64.89
7.37	65.90
7.73	66.18

buted to the fact that, at low pH, hydronium ions and the protonated amine may compete for anionic sites on the adsorbent surface, or for positions on the electrical double layer existing around the adsorbent particles. Since mebeverine is a weak base, it therefore exists predominantly as the cation below its pK_a (10.7). The results are inconsistent with those of Ridout (1968), who reported similar results for atropine sulphate adsorption onto kaolin.

In addition, the adsorption may increase at higher pH values due to low solubility of the non-protonated forms of the drug (Lundeliu's rule). Moreover, the effect of pH on the adsorption of mebeverine HCl could be related to its effect on the flocculation of the system.

TABLE 4

The effect of electrolytes, 0.1 M NaCl, or $MgCl_2$, on the Langmuir constants a and b for the adsorption of mebeverine HCl onto magnesium trisilicate (5.0% w/v) at 37 °C and pH 6.7

Langmuir constants	Without electrolytes	With NaCl	With $MgCl_2$
a (mg g^{-1})	132.70	120.48	103.20
b (l g^{-1})	25.98	8.46	9.14

The effect of mono- and divalent electrolytes on the extent of adsorption (Table 4) shows suppression in adsorption in the presence of 0.1 M NaCl or $MgCl_2$. This is either due to competition of the positively charged cations with mebeverine base for the active sites available for adsorption, and/or due to the effect of electrolytes on the flocculation of the system, hence, the addition of electrolytes will cause partial neutralisation of the negative charges on the adsorbent. Another possible explanation is further supported by the pronounced reduction of adsorption caused by the

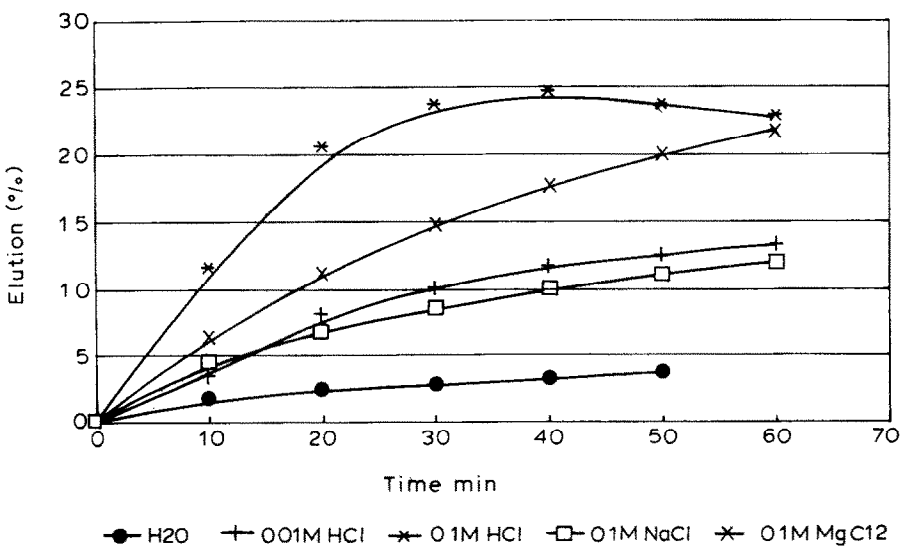

Fig. 1. Desorption of mebeverine HCl in 0.1 M HCl from magnesium trisilicate (5.0% w/v) at 37 °C, by various eluents.

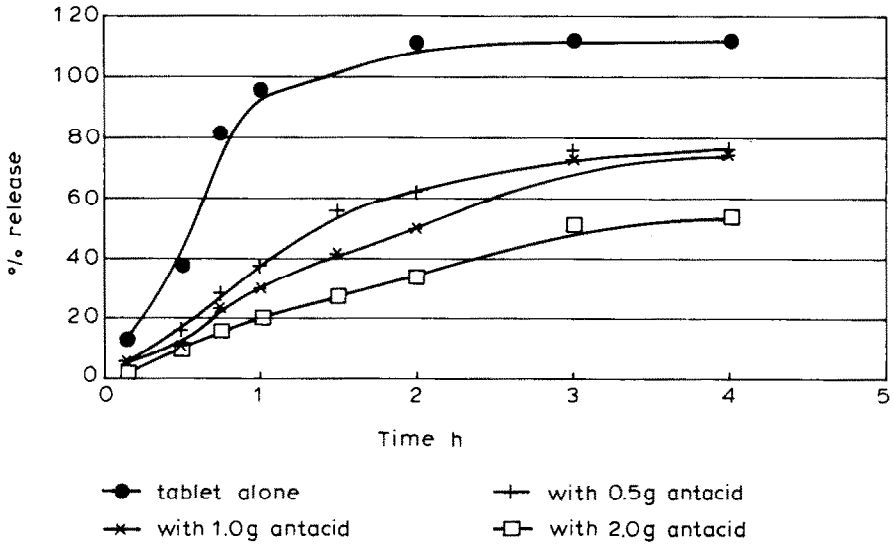

Fig. 2. The effect of magnesium trisilicate powder on the dissolution profile of mebeverine HCl from duspatalin tablets 135 mg.

divalent magnesium ions over sodium ions. These results confirm the data reported on the methantheline bromide-magnesium trisilicate system (Blaug and Gross, 1965).

The effect of different media on the desorption of mebeverine HCl (Fig. 1) shows that elution is pH-dependent. Based on the previous explanation, that the adsorption at different pH values involved a competitive mechanism, the desorption could be treated in the same manner. At low pH, the hydronium ions are expected to compete with the protonated mebeverine for the anionic sites on the adsorbent, therefore, more drug will be displaced and desorbed. The results are in agreement with El-Masry and Khalil (1974) who reported that elution of adsorbed atropine and hyoscine

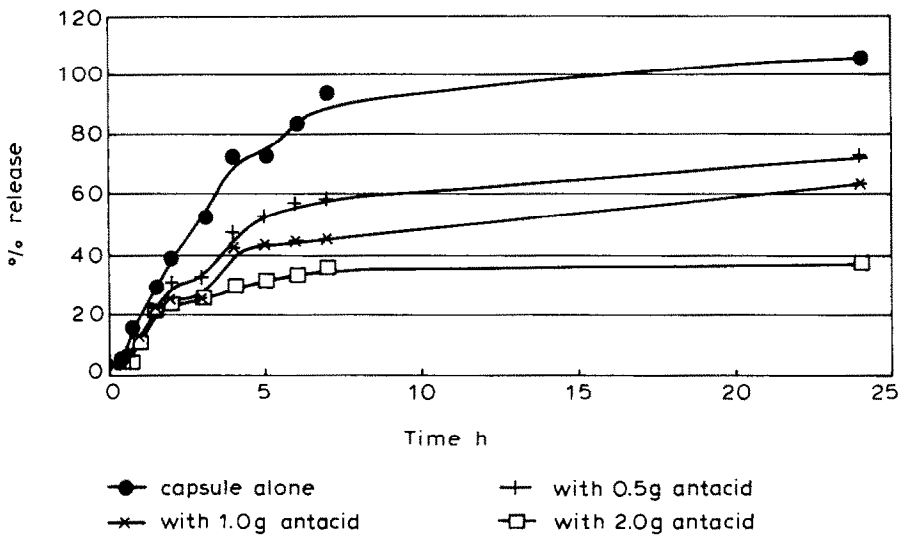

Fig. 3. The effect of magnesium trisilicate powder on the dissolution of mebeverine HCl from duspatalin sustained release capsules 200 mg.

from magnesium trisilicate was pH-dependent. Fig. 1 also shows that magnesium ions are more efficient than sodium ions in displacing the drug from the adsorbent. This confirms the results reported by McGinity and Hill (1975) for the adsorption of neomycin from negatively charged clays.

Since mebeverine is a weak base and its elution at higher pHs is impaired by solubility or competitive mechanism, there may be a problem arising in vivo as the drug is not so easily desorbed.

The effect of different amounts of magnesium trisilicate on the dissolution rate of mebeverine HCl tablets or sustained release capsules (Figs 2 and 3) shows that the presence of magnesium trisilicate had an adverse effect on the rate of dissolution of the drug and the effect is concentration-dependent. This adverse effect may be attributed to adsorption. As the concentration of the antacid increased, the surface area increased, thus, the active sites available for adsorption increased, and consequently, the percentage release of the drug from tablets or capsules decreased. This adverse effect may also be attributed to the effect of pH on adsorption.

The results (Table 5) denote a decrease in the acid absorption power of the antacid in the presence of mebeverine HCl as pure powder or its dosage forms.

TABLE 5

The effect of concomitant presence of mebeverine HCl with magnesium trisilicate on its acid absorption power

Dosage form	0.1 M NaOH consumed (ml)	0.1 M HCl (ml) absorbed/g antacid	% decrease in acid absorption power
Magnesium trisilicate powder	14.3	114	–
Mebeverine HCl powder	16.6	68	40.4
Mebeverine HCl tablet	16.2	76	33.3
Mebeverine HCl capsule	17.0	60	47.4
Mebeverine pamoate suspension	16.3	74	35.1

Standard error (S.E.) varied between 0.02–0.035.

TABLE 6

Rate of neutralisation of magnesium trisilicate alone and in the presence of mebeverine HCl powder or its dosage forms at 37 °C (Procedure A)

Time (min)	pH changes				
	Antacid 2 g alone	Antacid powder 2 g with mebeverine HCl			
		Powder	Tablet	Capsule	Suspension [a]
0	1.20	1.20	1.20	1.20	1.20
1	1.75	1.25	1.75	1.60	1.80
2	3.26	1.38	1.88	1.65	2.38
3	4.60	1.51	2.02	1.83	2.79
4	5.33	1.64	2.18	1.91	3.11
5	5.62	1.80	2.36	2.04	3.35
6	5.82	1.99	2.63	2.31	3.54
7	5.99	2.23	3.03	2.70	3.70
8	6.10	2.62	3.77	3.80	3.81
9	6.16	3.50	4.63	4.35	3.94
10	6.24	4.22	5.13	4.95	4.01
15	6.50	5.69	5.92	5.94	4.41
20	6.66	6.06	6.18	6.16	4.78
25	6.74	6.20	6.30	6.28	5.18
30	6.82	6.30	6.37	6.38	5.60
35	6.87	6.36	6.43	6.41	5.79
40	6.91	6.43	6.48	6.44	5.91
45	6.99	6.47	6.51	6.47	5.99
50	7.01	6.50	6.54	6.49	6.05
55	7.01	6.52	6.54	6.50	6.09
60	7.01	6.54	6.54	6.50	6.14

S.E. varied between 0.003 and 0.029.
[a] Mebeverine pamoate suspension in all experiments.

The rate of neutralisation of antacid 2 g alone and in the presence of the drug as pure powder or its dosage forms (Table 6) shows that magnesium trisilicate 2 g is an ideal antacid since pH 3.26 was attained after 2 min, while in the presence of pure drug or its dosage forms, there was a delay in onset of action.

Table 7 shows that, antacid alone raised the pH to 3.9 after 3 min, and kept the pH buffered for 55 min, whereas, in the presence of the pure powder, tablet and capsule, the antacid failed to raise the pH to 3.0 and its buffering capacity was suppressed to a great extent. On the other hand, in the presence of the suspension, pH 3.03 was reached after 10 min and sustained for only 15 min. It could be suggested that the results obtained from

TABLE 7

Evaluation of the buffering capacity of magnesium trisilicate alone, and in the presence of mebeverine HCl powder or its dosage forms, at 37°C (Procedure B)

Time (min)	pH changes				
	Antacid 2 g alone	Antacid powder 2 g with mebeverine HCl			
		Powder	Tablet	Capsule	Suspension
0	1.20	1.20	1.20	1.20	1.20
1	1.76	1.29	1.37	1.65	2.00
2	2.20	1.37	1.42	1.74	2.20
3	3.90	1.44	1.61	1.91	2.39
4	5.08	1.53	1.82	2.17	2.56
5	5.29	1.94	2.00	2.18	2.72
6	5.31	1.99	2.14	2.27	2.79
7	5.31	2.07	2.26	2.33	2.87
8	5.22	2.13	2.34	2.37	2.93
9	5.14	2.17	2.40	2.39	2.94
10	4.96	2.19	2.44	2.40	3.03
15	4.60	2.27	2.51	2.38	3.15
20	4.40	2.23	2.42	2.23	3.09
25	4.24	2.21	2.40	2.06	3.02
30	4.09	2.13	2.07	2.00	2.97
35	3.90	2.00	2.00		2.89
40	3.70				2.80
45	3.48				2.72
50	3.29				2.64
55	3.00				2.50
60	2.80				2.35
65	2.55				2.25
70	2.45				2.19
75	2.41				2.14
80	2.33				2.11
85	2.15				2.00
90	2.12				
95	2.00				
[a]	240	120	120	110	220

[a] ml of acid absorbed to return pH to 2.0.
S.E. varied between 0.004 and 0.03.

the evaluation of the acid reactivity of the antacid in the presence of the pure drug or its dosage forms, are due to adsorption of the drug on the antacid particles, consequently, the surface area available for acid absorption was reduced.

In conclusion, the results of this study showed that, not only mebeverine HCl was adsorbed onto magnesium trisilicate powder in vitro, but, moreover, the acid reactivity of the antacid was suppressed in the presence of the pure drug or its dosage forms. These results should be evaluated by further in vivo investigation.

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