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IN VITRO ADSORPTION OF PROPRANOLOL HYDROCHLORIDE BY VARIOUS ANTACIDS

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ABSTRACT

The purpose of this study was to investigate by in vitro methods whether an interaction takes place between propranolol hydrochloride and adsorbents when antacids are taken concomitantly with the beta-blocker or when excipients having adsorbent properties are present in formulations of the drug products containing propranolol hydrochloride.

Specific surface areas of magnesium trisilicate, magnesium oxide, magnesium hydroxide, dihydroxy aluminum sodium carbonate, magnesium carbonate and kaolin were calculated from nitrogen adsorption isotherms using single point method and it was found that magnesium trisilicate has the largest specific surface area.

The adsorption of propranolol hydrochloride to these adsorbents was investigated by in vitro methods. The adsorption iso-

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therms were drawn and the adsorptive capacities of the adsorbents were calculated from the slopes. It was found that magnesium trisilicate, magnesium hydroxide and dihydroxy aluminum sodium carbonate possess the highest adsorptive capacities while kaolin and magnesium carbonate possess the lowest.

The results of the adsorption studies indicate that the concomitant use of propranolol hydrochloride and the above mentioned adsorbents could affect the bioavailability of the beta-blocker adversely.

INTRODUCTION

In modern therapeutics, concomitant administration of two or more drugs has become a common practice. However, as numerous dosage forms contain ingredients having adsorbent properties, it must be considered that such simultaneous administration may lead to adverse or advantageous interactions between otherwise noninteracting drugs. The adsorption effects of antacids and adsorbents on drugs have been extensively reported (1-5).

The purpose of this study was to investigate by in vitro methods whether an interaction takes place between propranolol hydrochloride and antacids or excipients having adsorbent properties.

EXPERIMENTAL

Materials:

Magnesium oxide light (Merck), magnesium hydroxide (Merck), magnesium carbonate (Tan Chem. Co.), magnesium trisilicate (BDH), aluminum hydroxide (Merck), kaolin (Givoudan-Lavirotte) and propranolol hydrochloride (Doğu Pharm. Co.).

All antacid powders and propranolol hydrochloride were used without further purification as they were pharmaceutical grade.

Preparation of adsorbents for study:

The antacid powders were heated at 120°C for 24 hours and the dried material was sieved (Endecott Ltd.) Since most of the particles cumulated between 63-180 µm, this fraction was used in the adsorption experiments. Adsorbents were stored in air-tight bottles.

Adsorption experiments

Samples of antacid powder were weighed accurately (magnesium trisilicate 0.1g; other adsorbents 1g) and transferred to screw-capped tubes. A standard aqueous solution of propranolol hydrochloride (20 ml) was added to each tube to give final concentrations of 0.0148-0.148 mg ml^{-1}. The tubes were placed in a mechanical shaker with a thermostated water bath at 37±0.1°C (Gerhard L 88-1) and agitated at 50 cpm for an hour, which was adequate to attain equilibrium. At the end of this period the content of each tube was centrifuged at 5000 rpm (magnesium trisilicate and magnesium carbonate, 15.000 rpm) for 10 minutes. The supernatant solutions were filtered through Whatman No 42 filter paper and analyzed(Bausch and Lomb 700) for residual propranolol hydrochloride concentration.

Assay:

Propranolol hydrochloride was assayed spectrophotometrically at 289 nm. In order to delete the effect of particles that could not be separated by filtration from the supernatant, appropriate blank corrections were made.

Also at the end of the adsorption experiment supernatants were checked for degradation of propranolol hydrochloride by thin layer chromatography on Silica gel G (0.2mm thick, activated by heating at 110°C for 45 minutes) using a solvent system of ethyl acetate-methanol-ammonia (40:5:5, v/v).

The standard curve of the drug exhibiting the best distribution was illustrated by the least square method. The intercept and slope of the line were determined from the regression equation, and in order to estimate the accuracy of the results correlation and determination coefficients were also calculated.

RESULTS AND DISCUSSION

Propranolol hydrochloride was found to be adsorbed by the adsorbents tested to a significant extent.

Since our purpose was to investigate if there is an interaction between propranolol hydrochloride and the antacids, the adsorptive capacities of the adsorbents had to be determined and the adsorption isotherms had to be drawn. In order to determine the type of the adsorption isotherm, the experimental data applied both Freundlich and Langmuir equations. According to the following form of the Freundlich equation,

$$\log \frac{x}{m} = \log K + N \log C$$

the observed values of $\frac{x}{m}$ (mg adsorbed drug per g adsorbent) were plotted on a log-log scale against C (mg drug per 100 ml, remaining in solution after equilibrium had been reached). In the equation K and N are constants. K is a rough measure of the relative adsorptive capacity for a given drug, while N gives a general idea of the affinity of the adsorbate for the adsorbent.
For the Langmuir adsorption isotherm, $\frac{C}{x/m}$ was plotted against C, according to the linear form of the Langmuir equation.

$$\frac{C}{x/m} = \frac{1}{ab} \quad \frac{C}{b}$$

Constant "a" is related to the forces involved in binding the adsorbate molecules to the surface of the adsorbent and constant "b" is the maximum amount of drug which can be adsorbed per gram of adsorbent. The slopes of the lines were taken as a measure of the degree of adsorption.

The adsorption of propranolol hydrochloride on magnesium oxide obeyed the Langmuir adsorption isotherm at low concentrations, and the Freundlich adsoption isotherm at concentrations between

2.958 mg.100 ml^{-1} and 14.79 mg. 100 ml^{-1}. The slope of the Langmuir adsorption isotherm for magnesium oxide was found 0.52 (Fig.3). This indicates that magnesium oxide has a high adsorptive capacity for propranolol hydrochloride.

The adsorption of the drug on the various antacids in most cases obeyed the Freundlich adsorption isotherm (Fig.2 and table 1). Results indicated that magnesium trisilicate had the highest adsorptive capacity for propranolol hydrochloride. Magnesium hydroxide, dihydroxy aluminum sodium carbonate and aluminum hydroxide had intermediate, while kaolin and magnesium carbonate had the least adsorptive capacity.

The high adsorptive capacity of magnesium trisilicate for propranolol hydrochloride is due to the large specific surface area it possesses and the interaction between the negatively charged silicate anion and the positively charged propranolol molecule. The pK_a value of propranolol hydrochloride is 9.45. During the adsorption studies the pH of the magnesium trisilicate and propranolol hydrochloride suspension was found to be 9.45. At this pH propranolol hydrochloride is 50% ionized so an electrostatic interaction will take place between silicate anion and propranolol.

The interaction between magnesium hydroxide magnesium carbonate, aluminum hydroxide, dihydroxy aluminum sodium carbonate and propranolol hydrochloride does not correlate with the specific surface areas of the adsorbents. Hydrogen bond formation between the electron-accepting hydrogen atom of hydroxyl groups in contact with the negative oxygen on the antacid surface, is probably one of the major factor for the uptake of the drug by these adsorbents. The extent of the electrical forces between the sorbent surface and the sorbate molecules differs from one antacid to another.

The high adsorptive capacity of magnesium oxide may also be related to the hydrogen bond formation. There may also have been a pH effect. The pH value of the solution was 10. As the pK_a value of the propranolol hydrochloride is 9.45, at this pH the ionization and solubility of the drug is very low. Decreased solubility of

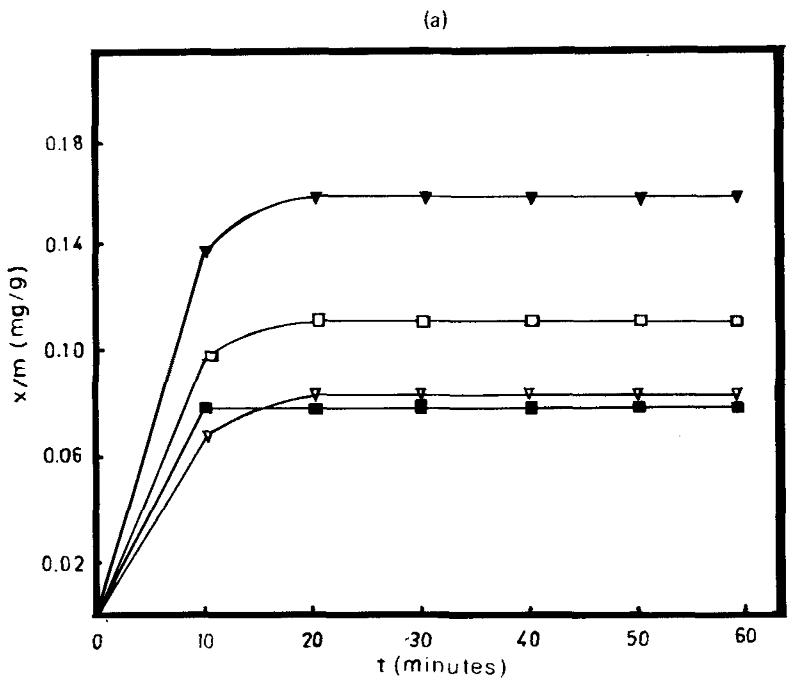

FIGURE 1a

Adsorption-rate studies of propranolol hydrochloride with: ▼—▼ dihydroxy aluminum sodium carbonate, ▽—▽ aluminum hydroxide, ■—■ magnesium carbonate, □—□ magnesium hydroxide.

propranolol due to the pH of the solution, could also explain high adsorptive capacity of magnesium oxide.

The molecular structure of kaolin, $Al_4Si_4O_{10}(OH)_8$ is composed of two basic units and is well documented. It has been pointed out that the kaolin lamella has two distinct areas for adsorption, i.e. the kaolin edge surface and the larger cleavage plane surface (6). As seen in Fig.2a kaolin did not adsorb propranolol hydrochloride to an appreciable extent. Although kaolin has a high adsorptive potential, its limiting adsorptive capacities are generally low.

(b)

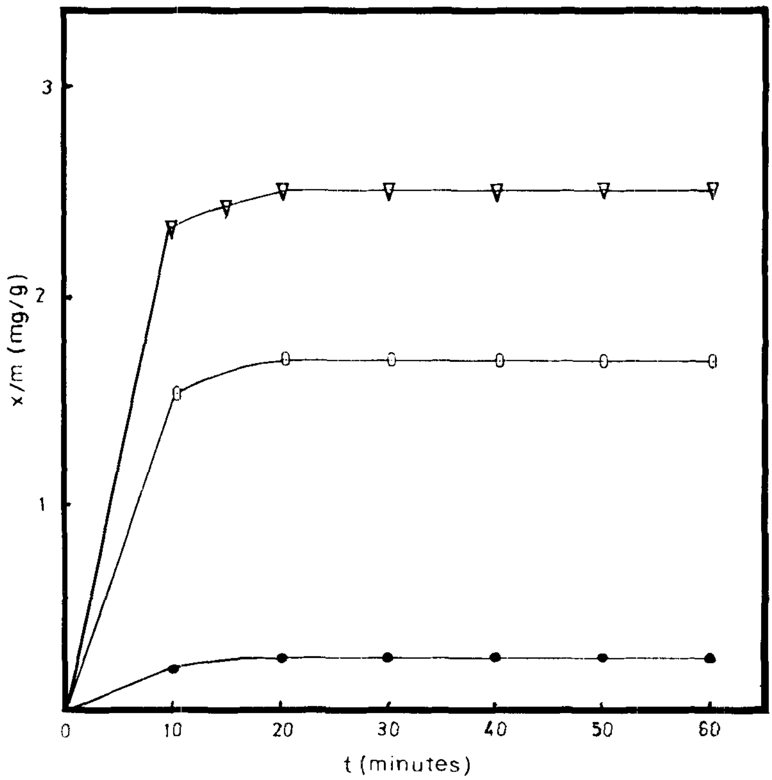

FIGURE 1b

Adsorption-rate studies of propranolol hydrochloride with: ●——● magnesium oxide, O——O kaolin, ▽——▽ magnesium trisilicate.

This is probably due to "face-edge flocculation" which reduces the number of sites available for adsorption(7).Moreover,the pH of the solution is about 4.90 at which value propranolol will be mainly protonated. This will prevent hydrophobic interaction with nonpolar-sites in kaolin.

Specific surface area is one of the most important parameters that effects the amount adsorbed; the extent of adsoption is

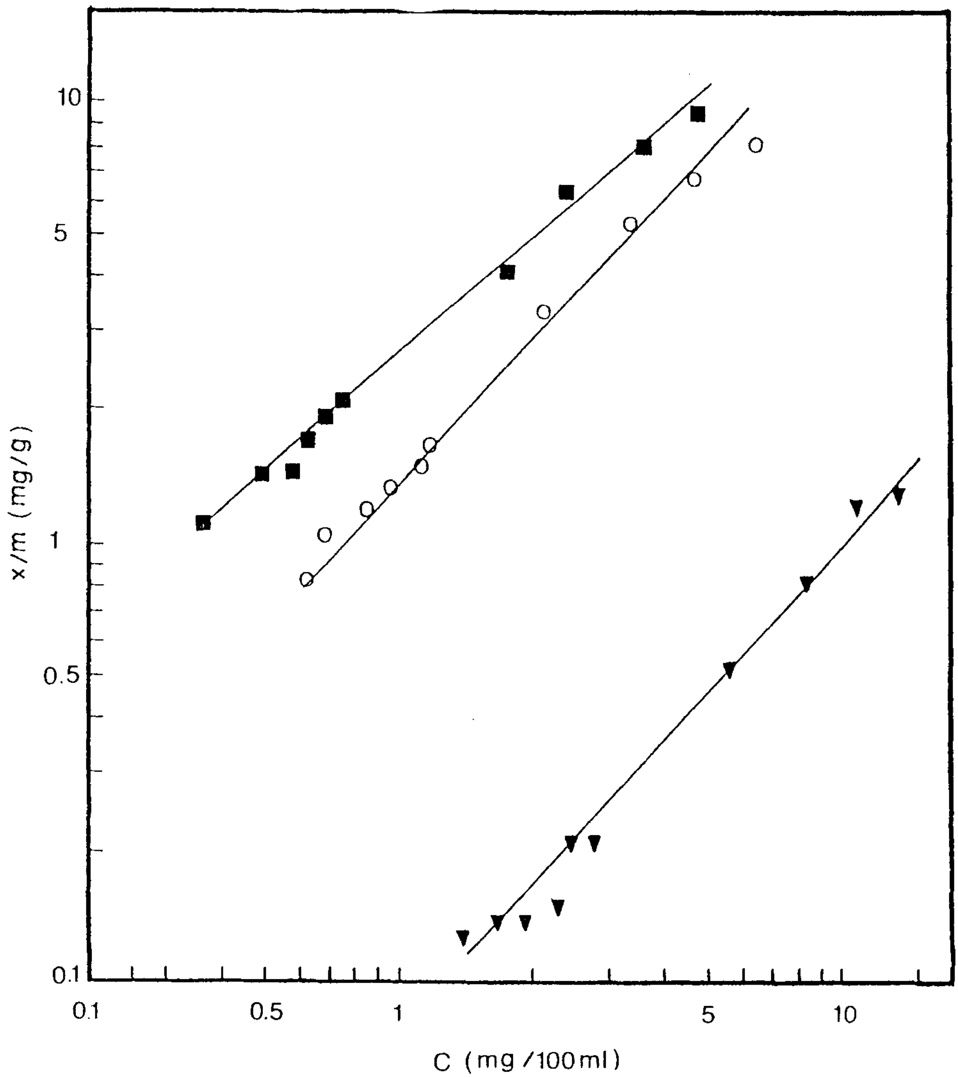

FIGURE 2 (a)

Freundlich adsorption isotherms for propranolol hydrochloride on various adsorbents, ▼——▼ dihidroxy aluminum sodium carbonate, ■——■ magnesium trisilicate, O——O kaolin.

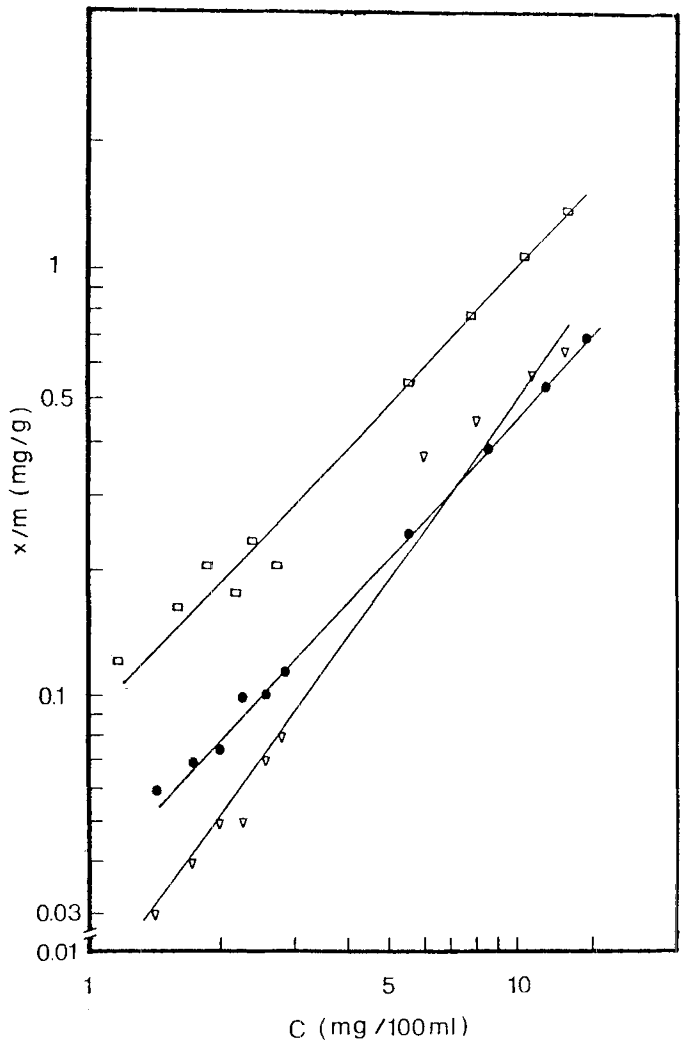

FIGURE 2 (b)

Freundlich adsorption isotherms for propranolol hydrochloride on various adsorbents, ●——● aluminum hydroxide, ▽——▽ magnesium hydroxide, □——□ magnesium carbonate.

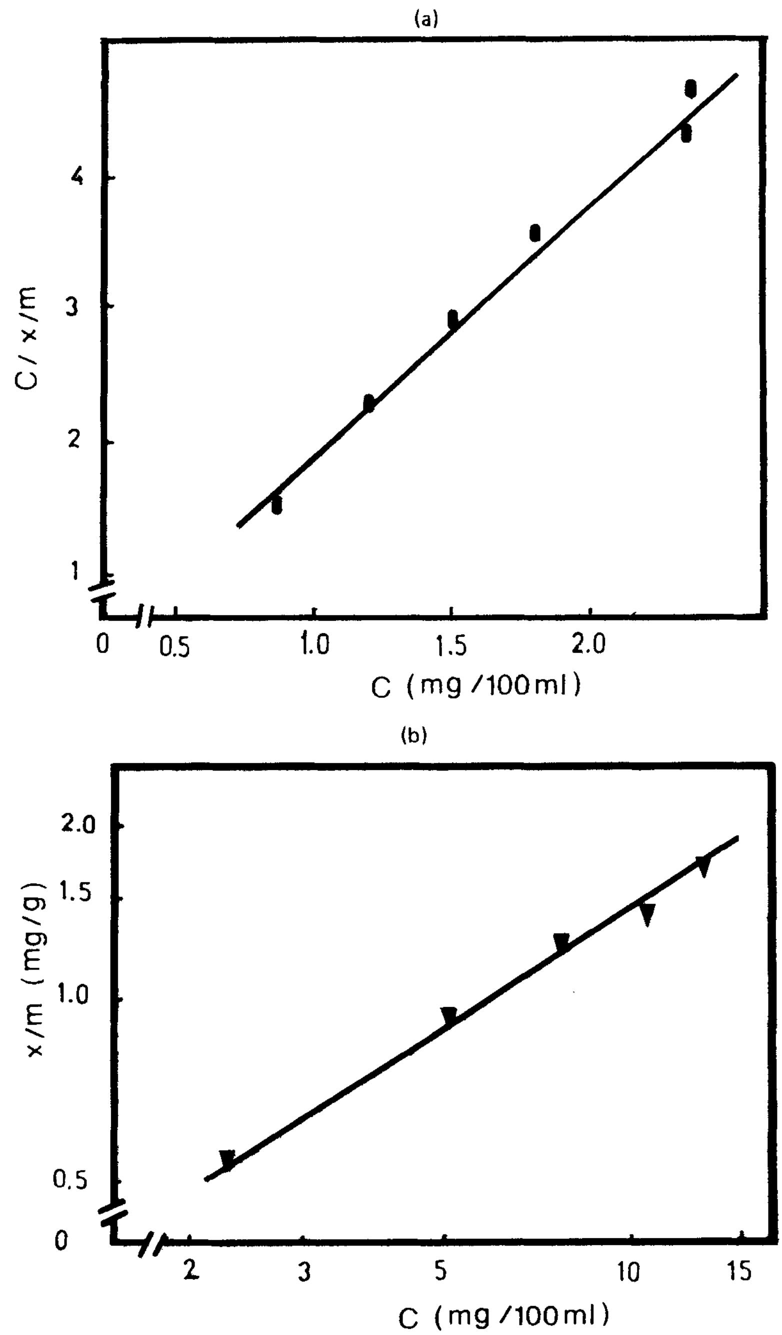

FIGURE 3: a) Languir adsorption isotherm for propranolol hydrochloride on magnesium oxide. b) Freundlich adsorption isotherm for propranolol hydrochloride on magnesium oxide.

TABLE 1

The evaluation of the adsorption data of propranolol hydrochloride

Adsorbent	Determination coefficients (r^2)		y = mx + n	Adsorption capacity	pH	
	Langmuir	Freundlich			I[x]	II[xx]
Aluminum hydroxide	0.698	0.997	y=1.10x−1.42	1.10	7.88	8.35
Dihydroxy aluminum sodium carbonate	0.263	0.976	y=1.14x−1.15	1.14	9.65	9.68
Magnesium trisilicate	0.740	0.993	y=0.89x+0.42	0.89[xxx]	9.62	9.45
Magnesium hydroxide	0.619	0.965	y=1.55x−1.81	1.55	9.88	9.80
Magnesium carbonate	0.163	0.979	y=0.99x−1.03	0.99	9.82	9.90
Kaolin	0.200	0.985	y=0.97x+0.13	0.97	5.05	4.90
Magnesium oxide	0.996	0.751	y=1.94x−0.12	0.52	10.06	10.02

x Initial pH
xx Final pH
xxx Magnesium trisilicate weighed 0.1 g; other adsorbents 1 g.

TABLE 2

Specific surface areas and adsorption capacities of adsorbents

Adsorbent	Specific Surface area (m^2/g)	Adsorption Capacity
Aluminum hydroxide	42.95	1.10
Dihydroxy aluminum Sodium carbonate	69.14	1.14
Magnesium trisilicate	451.77	0.89
Magnesium hydroxide	30.81	1.55
Magnesium carbonate	41.70	0.99
Kaolin	51.97	0.97
Magnesium oxide	70.93	0.52

directly proportional to the specific surface area of the adsorbent (8,9). In order to determine the relationship between the adsorptive capacities and specific surface areas of the adsorbents, specific surface areas were calculated from the nitrogen adsorption isotherms using BET method. The values found for the surface areas of the adsorbents are given in Table 2. As seen in table 2 we couldn't find a direct correlation between these two parameters(10) This might be due to the large size of propranolol hydrochloride molecules which hinders penetration into the small pores of the adsorbents which are accessible to gas molecules. Besides in water the surface areas of most of the antacids change due to swelling, and adsorption from solution is a complex phenomenon, as it includes solute-solvent and solvent-adsorbent as well as solute-adsorbent interactions.

CONCLUSION

The co-administration of antacids tested with propranolol hydrochloride could result in decreased availability of the potent drug for absorption. Since the adsorption capacity of kaolin was found low for propranolol hydrochloride, it can be used in the solid dosage forms of propranolol hydrochloride as an excipient. But if the concentration of kaolin is more than 10 % of the dosage form there might be a significant interaction between kaolin and propranolol hydrochloride. The above findings should be correlated with results of in vivo experiments.

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