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PREPARATION AND IN-VITRO EVALUATION OF PROLONGED RELEASE TABLETS OF PHENIRAMINE AMINOSALICYLATE.

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ABSTRACT

Prolonged release tablets of pheniramine aminosalicylate were prepared from co-precipitates of the drug in different types of Eudragit. The hardness of the tablet had a pronounced effect on the release rate of the drug. Tablets (500 mg, hardness 13 kg) and 375 mg tablets (hardness 6.5 kg) prepared from the co-precipitates containing 15% of the drug in Eudragit L 100, and 20% of the drug in Eudragit S 100 respectively, showed release rate patterns that were in agreement with Lang primary requirements for drug release from sustained release tablets.

Tablets (500 mg) prepared from the co-precipitates containing 15% of the drug in Eudragit L 100 or Eudragit

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S 100 and 375 mg tablets containing 20% of the drug in Eudragit S 100 showed release rate patterns that were best described by Higuchi equation, indicating that a diffusion controlled mechanism was mainly operative.

INTRODUCTION

The aim of the present study was to investigate the application of the solid dispersion technique in the preparation of prolonged release tablets of pheniramine aminosalicylate using different types of Eudragit. The usual dose of pheniramine aminosalicylate is 25 to 50 mg thrice daily, but sustained release preparations are commonly used for administration twice daily (1).
One of the objectives of this study was to compare the prolonged-action tablets prepared in this work with the sustained release "Avil retard" tablets (Hoechst Orient, Cairo) containing 75 mg of pheniramine maleate.

EXPERIMENTAL

Materials - Pheniramine aminosalicylate powder (Hoechst AG. Frankfurt), Avil retard tablets produced by Hoechst Orient S.A.A., Cairo, under licence of Hoechst AG. Frankfurt, Germany.
Eudragit L 100, Eudragit S 100, Eudragit RLPM and Eudragit RSPM, provided by Röhm Pharma GMBH, Darmstadt, West Germany.
Ethyl alcohol, acetone A.R., 0.1N HCl A.R. and Sørensen phosphate buffer pH 7.4.

Preparation of Tablets - Co-precipitates of the following compositions were used in the preparation of tablets: 15% drug in Eudragit L 100, 15% drug in Eudragit S 100, 20% drug in Eudragit S 100, 10% drug in Eudragit RSPM, 10% drug in a mixture of one part of Eudragit S 100 and 8 parts of Eudragit RSPM and 10% drug in a 1:1 mixture of Eudragit S 100 and Eudragit RLPM.

Ethyl alcohol was used as the solvent for the drug and polymer except in case of the preparation of co-precipitates containing Eudragit RSPM, acetone was used as the solvent. Removal of the solvent was effected by evaporation on an electric bath. Complete drying of the product was attained by desiccation for 3-5 days.

A 200-500 μ particle size fraction of the above powdered products was compressed to constant weight tablets (500 mg)using Erweka single punch tablet machine. All the tablets were compressed at constant pressure using flat-faced beveled edge punches. The punches and die were lubricated with 1% suspension of magnesium stearate in carbon tetrachloride.

For reason of comparison with "Avil retard" tablets (Hoechst Orient), 375 mg tablets were prepared using the solid dispersion product containing 20% of pheniramine aminosalicylate in Eudragit S 100, following the same procedure and using the same machine. A 20% physical mixture of the drug in Eudragit S 100 was subjected to tabletting under the same conditions.

The compressibility of the granules obtained from the pulverized solid dispersions and physical mixture

was quite sufficient to ensure their direct compression without any additives.

Tablet thickness was measured with a micrometer. The tablet hardness was also determined using the Stokes-Monsanto tester.

Study of the Effect of Tabletting on In-Vitro Drug Release Rate - The half change method which simulates the conditions found in the gastrointestinal tract (2) was followed using a rotating bottle device and three tablets prepared from each co-precipitate.
At each time interval, the samples which were withdrawn were analysed, for drug content, spectrophotometrically at 268 nm after suitable dilution with 0.1N HCl, using Unicam SP 1800 U.V. Spectrophotometer. To avoid any interference of Eudragit, a blank was carried out every time. Different blanks were prepared using the specific Eudragit in an amount equivalent to that present in the specific tablet. This Eudragit was previously treated with solvent as in the preparation of the co-precipitate and compressed into a tablet and proceeded exactly as with the dissolution study on the tablet containing the drug.

RESULTS AND DISCUSSION

Quality Control of the Prepared Tablets - Physical characteristics of the tablets are presented in Table 1. Tablets (500 mg) prepared from the solid dispersions containing 15% drug in Eudragit L 100, 15 and 20% drug

TABLE 1

Physical Characteristics of Tablets Prepared from Co-precipitates of Pheniramine Aminosalicylate in Different Eudragit Types.

Tablet Contents	Weight of Tablet (mg)	Drug Equivalent (mg)	Hard-ness (kg)	Diame-ter (mm)	Thickness (mm)
1- 15% drug in Eudragit L 100	500	75	13.0	12	4.27
2- 15% drug in Eudragit S 100	500	75	13.0	12	4.40
3- 20% drug in Eudragit S 100	500	100	13.0	12	4.40
4- 20% drug in Eudragit S 100	375	75	6.5	12	3.90
5- 10% drug in a mixture of Eudragit S 100 & Eudragit RSPM in a ratio of 1:8	500	50	4.0	12	4.51
6- 10% drug in Eudragit RSPM	500	50	4.0	12	4.65
7- 10% drug in a mixture of Eudragit S 100 & Eudragit RLPM 1:1	500	50	2.5	12	4.27
8- Avil retard tablet produced by Hoechst Orient S.A.A. Cairo	425	75 mg of Pheniramine maleate	6.5		

in Eudragit S 100 showed a hardness of 13 kg. Whereas the hardness, of 375 mg tablets prepared from the solid dispersion containing 20% drug in Eudragit S 100, was found to be 6.5 kg i.e. the same hardness as that of Avil retard tablets (Hoechst Orient).

Tablets (500 mg) prepared from 10% drug solid dispersion in a mixture of 1:8 Eudragit S 100: Eudragit RSPM and tablets prepared from 10% drug solid dispersion in Eudragit RSPM showed a hardness of 4 kg. This decrease in hardness may be attributed to the low compressibility of Eudragit RSPM.

Tablets prepared from 10% drug dispersion in a mixture of 1:1 Eudragit S 100: Eudragit RLPM showed a hardness of only 2.5 kg due to the lower compressibility of Eudragit RLPM as it is more porous.

In-Vitro Release Rate of the Drug From the Prepared Tablets:

"Drug release rate" is an important functional characteristic of all solid pharmaceutical preparations. For sustained release preparations, Lang (3) suggested a conventional set of requirements based essentially on the in-vitro rotating bottle method described by Vora and coworkers (4) with minor modifications. The conditions of primary and secondary requirements for release from tablets suggested by Lang depend on the conception that the effective plasma concentration should be achieved within the possibly shortest time, thereafter only the maintenance of this concentration is needed.

Figure 1 shows the release rate patterns of the tablets. From the release rate data the following could be concluded.

a) The release rate pattern from 500 mg tablets prepared from the solid dispersion containing 15% of pheniramine aminosalicylate in Eudragit L 100, and showed a hardness of 13 kg, was found to be in agreement with the primary requirements for drug release from sustained release tablets as stated by Lang (Table 2).

b) The rate of drug release from a 375 mg tablet, prepared from the solid dispersion containing 20% of the drug in Eudragit S 100, was compared with that from "Avil retard" tablet (Hoechst Orient). Both tablets have the same hardness of 6.5 kg and contain the equivalent of 75 mg of the drug per tablet. It was interesting to find that the release rate from the tablet prepared in this work confirmed with Lang primary requirements while the release rate from "Avil retard" tablet confirmed with these requirements till the end of the fifth hour (Table 2 and Figure 2). After 7 hours, the extent of release from Avil tablet was only 67.47%, whereas Lang stated (3) that after 6.5 hours, 70-90% of the drug content must be released. This finding proved the efficiency of the tablet prepared in this work.

c) Tablets (375 mg) prepared from the physical mixture of 20% of the drug in Eudragit S 100 showed a 100% drug release within 1½ hours, whereas the tablets prepared

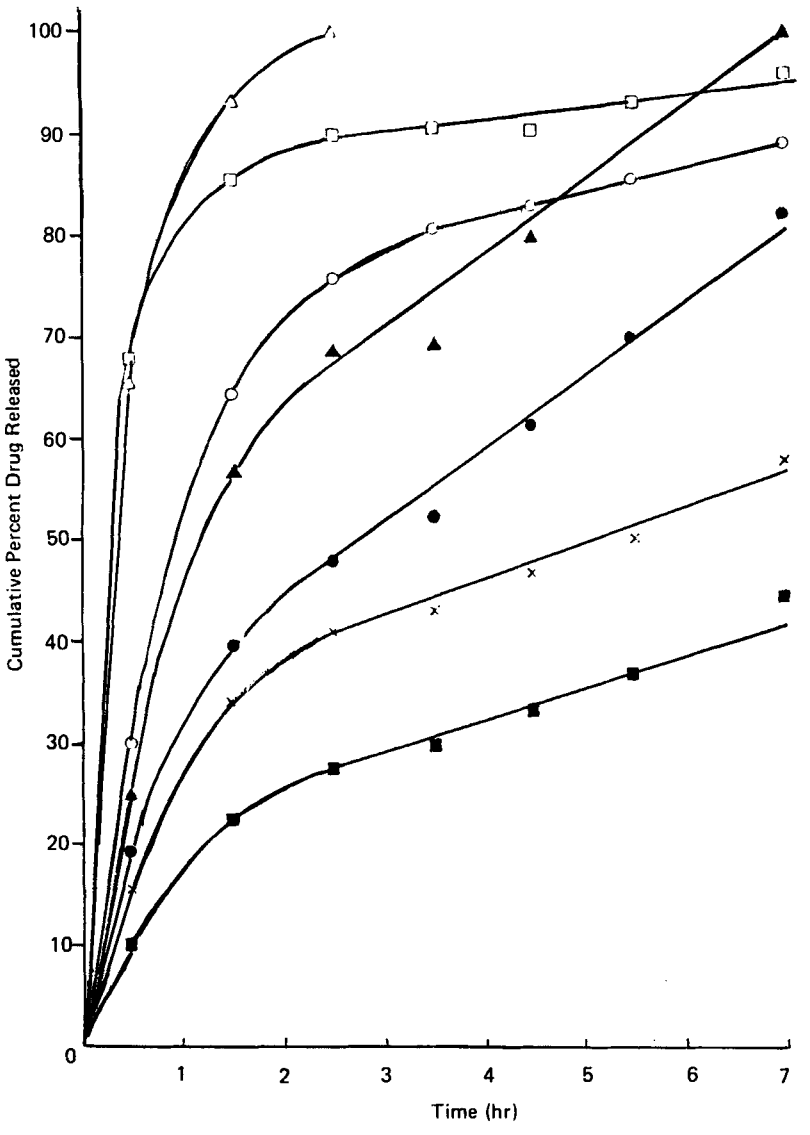

FIGURE 1

Drug release rates from 500 mg tablets prepared from solid dispersion systems containing the drug in different types of Eudragit. Key: ■ , 15% of the drug in Eudragit S 100; × , 20% of the drug in Eudragit S 100; ● , 15% of the drug in Eudragit L 100; ▲ , 20% of the drug in Eudragit S 100 (375 mg tablet); ○ , 10% of the drug in a mixture of Eudragit S 100 and Eudragit RSPM in a ratio of 1:8; □ , 10% of the drug in a mixture of Eudragit S 100 and Eudragit RLPM in a ratio of 1:1 and △ , 10% of the drug in Eudragit RSPM.

TABLE 2

Comparison of the Reported Lang Primary Requirements for the Release of Drugs from Sustained-Release Tablets with the Experimental Results.

Time (hr.)	Cumulative Percent Release			
	Reported values	Experimental values		
		Tablet (1)[a]	Tablet (2)[b]	Tablet (3)[c]
Up to the end of the 1st hour	25 - 50	19.2	20.11	24.96
Up to the end of the 2nd hour	40 - 60	39.62	38.72	56.71
After 3.5 hours from the start	52 - 72	52.42	52.37	69.09
After 5 hours from the start	60 - 80	70.02[d]	61.22[d]	93.25[d]
After 6.5 hours from the start	70 - 90	82.39[e]	67.47[e]	100[e]
After 8 hours from the start	Not less than 80% must be dissolved from the active ingredient			

a. Tablet containing 15% of the drug in Eudragit L 100.

b. Avil retard tablet (Hoechst Orient).

c. 375 mg tablet containing 20% drug in Eudragit S 100.

d. Samples were withdrawn after 5.5 hrs.

e. Samples were withdrawn after 7 hrs.

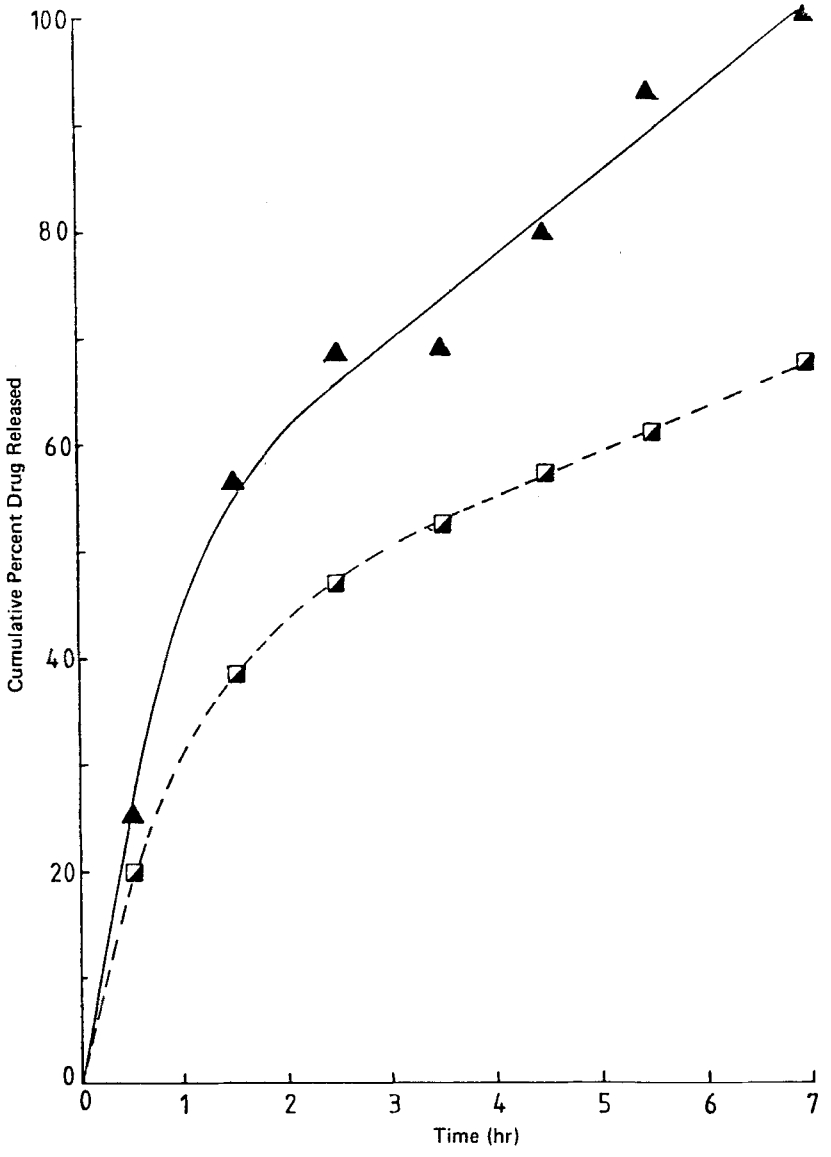

FIGURE 2

Drug release rates from: –◪–, Avil retard tablets (Hoechst Orient) and ▲, 375 mg tablets containing 20% of the drug in Eudragit S 100.

from the corresponding solid dispersion showed only a 56.71% drug release during this time interval, followed by continuous and uniform release until 100% release was achieved within 7 hours. This is an indication that the solid dispersion technique adopted in this work is more efficient than the physical mixture in the formulation of sustained release tablets.

d) Hardness of the tablet seemed to exert an important effect on the release rate of the drug. The extent of drug release from 375 mg tablets containing 20% of the drug in Eudragit S 100 (hardness, 6.5 kg) was 100% within 7 hours. Whereas 500 mg tablets containing 20% of the drug in Eudragit S 100 (hardness, 13 kg)released only 57.8% of the drug content within 7 hours(Figure 1). The release from the later tablets did not even fulfill the Lang secondary requirements (3).

It could, therefore, be concluded that the release rate from the tablets having the lower hardness (6.5 kg) was higher than that from the other tablets (13 kg).

Kinetics of Pheniramine Aminosalicylate Release from Tablets Prepared from the Solid Dispersion Systems -

It was assumed that drug release may be either first order or a diffusion controlled process (5).
From the release rate data of pheniramine aminosalicylate, the logarithm of the percent of drug remaining in the tablet was plotted as a function of time as predicted by first-order release.

$$\log W = \log W_o - \frac{K}{2.303} t \qquad \text{Eq. 1}$$

where, W is the amount of drug left in tablet.

W_o is the initial amount of drug in tablet.

K is the first-order release rate constant.

t is the time.

Figures 3-5 illustrate the release profiles of the drug when plotted in this way.

A linear relationship, (Figure 3), indicating a first order release, was obtained up to the end of 1½ hours for the

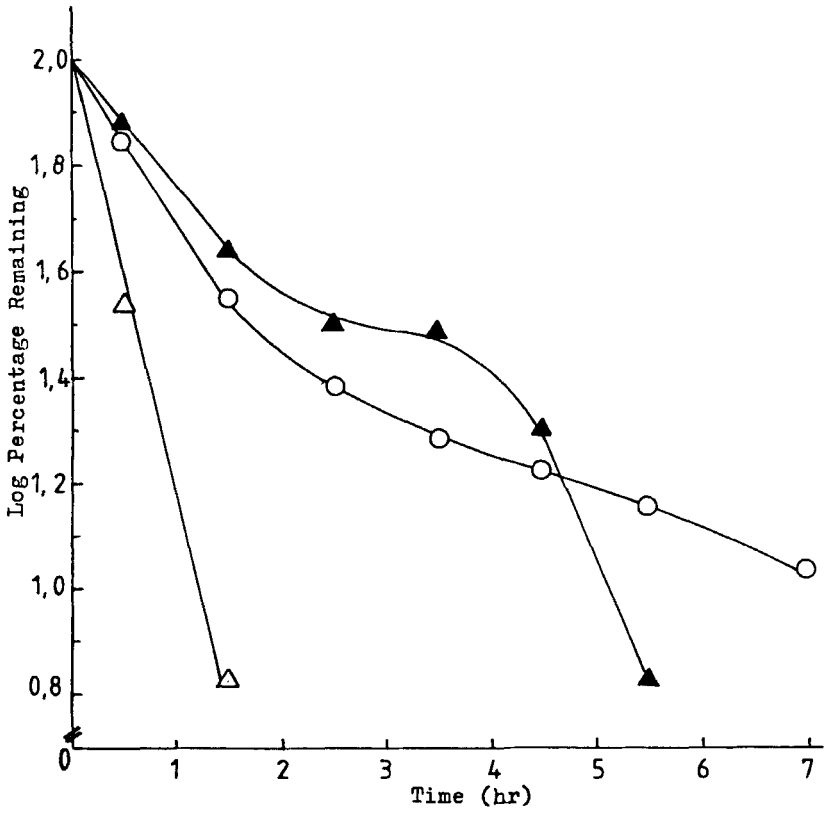

FIGURE 3

Release profiles of the drug from tablets when plotted according to first-order kinetics. Key: △, 10% of the drug in Eudragit RSPM; ○, 10% of the drug in a mixture of Eudragit S 100 and Eudragit RSPM in a ratio of 1:8 and ▲, 20% of the drug in Eudragit S 100 (375 mg tablet).

release of 93.17 and 64.3% of the drug content from 500 mg tablets containing 10% of the drug in Eudragit RSPM and in a mixture of Eudragit S 100 and Eudragit RSPM at a ratio of 1:8 respectively. The corresponding first order release rate constants were found to be 1.88 and 0.71 hr^{-1}. This rapid initial release was achieved by the leaching effect of the permeating fluid. Discontinuity of the linearity of the release rate curve of the later tablet indicates that thereafter another mechanism is operative, probably diffusion of the drug through the matrix and out into the dissolution fluid.

Deviation from the first-order behaviour was shown for the release of the drug from the following tablets: 375 mg tablets containing 20% of the drug in Eudragit S 100 (Figure 3). "Avil retard" tablets (Hoechst Orient),500 mg tablets containing 15% of the drug in Eudragit L 100 (Figure 4) and 500 mg tablets containing 15 and 20% of the drug in Eudragit S 100 (Figure 5).
The plots are actually sigmoidal in nature indicating a diffusion controlled process.

In order to obtain a constant blood level for some desired period of time from a sustained-release dosage form, Nelson (6) has stated that a constant (zero-order) rate of release from a dosage form is desired. Some authors (7,8) have shown that some sustained-release preparations released drugs by apparent zero-order process. Rowland and Beckett (9) have further claimed that first order release from a dosage form cannot give the "idealized" blood concentration-time curve. Unfortunately, experience

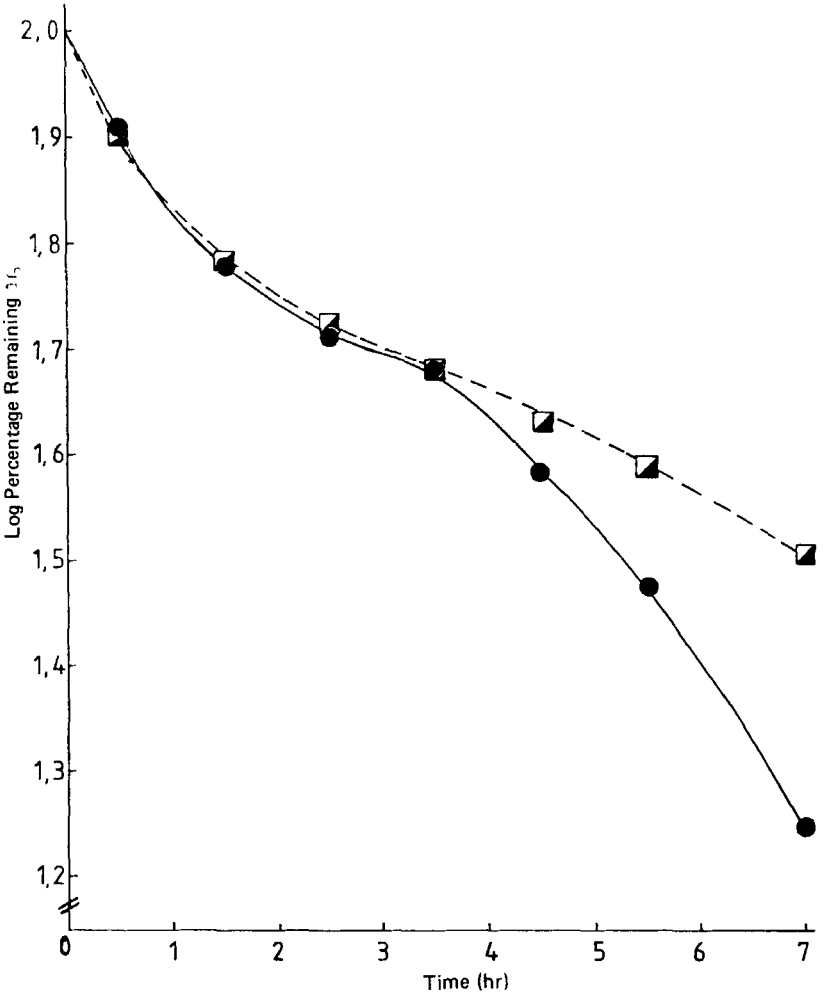

FIGURE 4

Release profiles of the drug from tablets when plotted according to first-order kinetics. Key: ● , 15% of the drug in Eudragit L 100 and –◪– , Avil retard tablets (Hoechst Orient).

suggests that the majority of sustained-release formulation techniques produce formulations that release drug at roughly a first-order rather than zero-order rate.

Systems containing solid drugs randomly dispersed in solid matrices have been widely studied and utilized as bases for dosage forms which provide more or less conti-

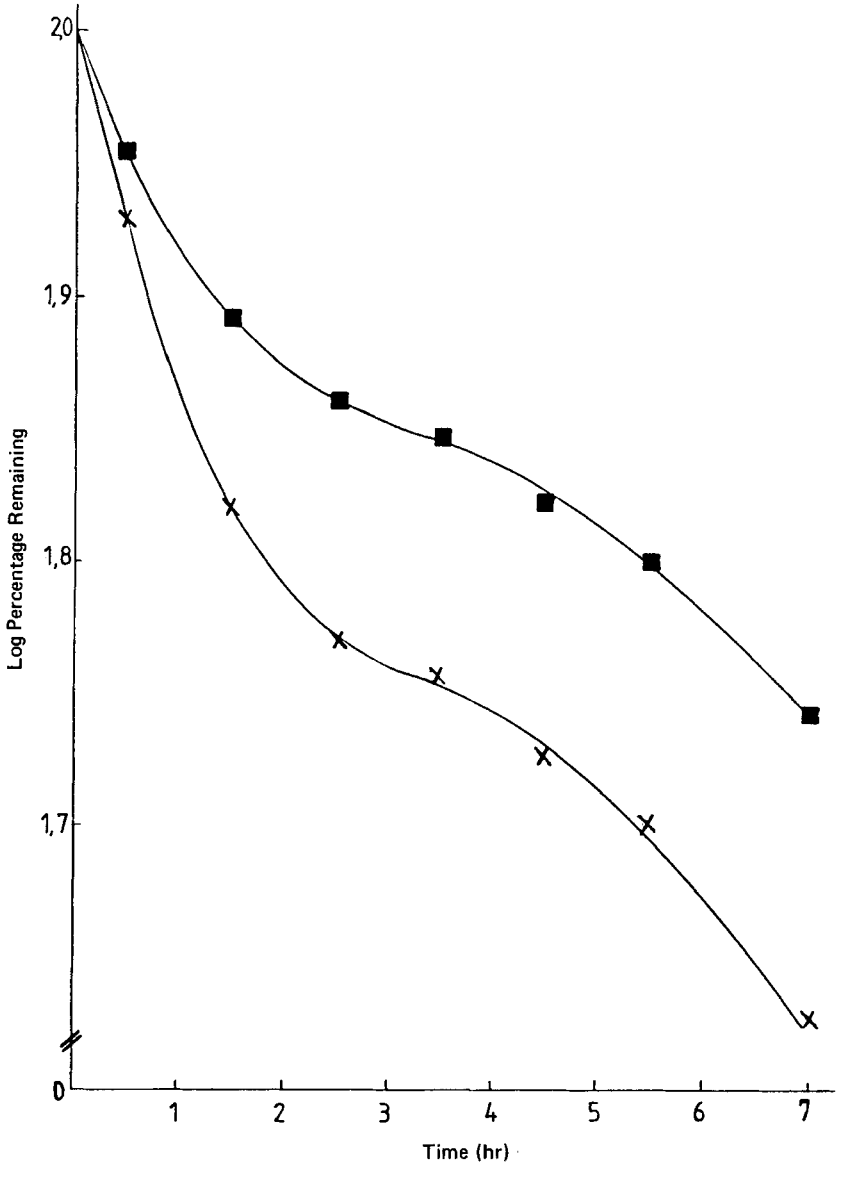

FIGURE 5

Release profiles of the drug from tablets when plotted according to first-order kinetics. Key: X , 20% and ■ , 15% of the drug in Eudragit S 100.

nuous release of medicaments over relatively long periods. Higuchi (10) tried to relate the rate of release of drugs from such systems to the pertinent physical constants based on simple laws of diffusion.

Mathematical relations have been obtained for cases (a) where the drug particles are dispersed in a homogeneous, uniform matrix which acts as the diffusional medium, and (b) where the drug particles are incorporated in an essentially granular matrix and released by the leaching action of the penetrating solvent.

For the leaching type release mechanism occurring through diffusion movement utilizing intergranular openings, Higuchi equation (11), $Q = \sqrt{Dt\ (2A - C_s)\ C_s}$ Eq. 2 for the release from a planar system having a homogeneous matrix must be modified (10) for the effective volume, where diffusion can occur and the effective diffusional path. It can readily be seen for this system that.

$$Q = \sqrt{\frac{D\epsilon}{\gamma}(2A - \epsilon C_s)\ C_s t} \qquad \text{Eq. 3}$$

where Q = the amount of drug released after time t per unit exposed area.

D = the diffusion coefficient i.e. the diffusitivity of the drug in the permeating fluid.

γ = the tortuosity factor of the matrix. It is introduced to correct for the lengthened diffusional path caused by the necessary lateral excursions.

A = the total amount of drug present in the matrix per unit volume, expressed as gm/ml.

C_s = the solubility of the drug in the permeating fluid (release medium).

ϵ = the porosity of the matrix, refers to the volume fraction that is permeated by the solvent and available for diffusion in the already leached portion of the matrix.

Although equations 2 and 3 are for different mechanisms, they both describe drug release as being linear with the square root of time $Q = Kt^{1/2}$ Eq. 4

Where for the homogeneous matrix system: $K = \left[D(2A-C_s)C_s\right]^{1/2}$

and for the granular matrix system: $K = \left[\frac{D\epsilon}{\tau}(2A - \epsilon C_s)C_s\right]^{1/2}$

The validity of the relationships has been confirmed experimentally by a number of workers using various systems (5,12-23). The relationship, suggested by Higuchi (10) for the release of drug from a planar system having an insoluble granular matrix was studied extensively by Desai et al (12,13,18,19) and Singh et al (20,21) using polyethylene and polyvinyl chloride as plastic matrices. Farhadieh et al (14,15) showed that the release profiles of drug from tablets containing a methyl acrylate-methyl methacrylate copolymer matrix are best described by the linear square root of time dependence, indicating that a diffusion-controlled mechanism is operative (13).

An attempt was made, to determine whether the release of pheniramine aminosalicylate from the prepared tablets could be described by the diffusion equation proposed by Higuchi (10). According to this equation, for a diffusion-controlled mechanism for release, a plot of the amount of drug released versus the square root of time should be linear $Q = Kt^{1/2}$ (Eq. 4). Figure 6 illustrates the linear

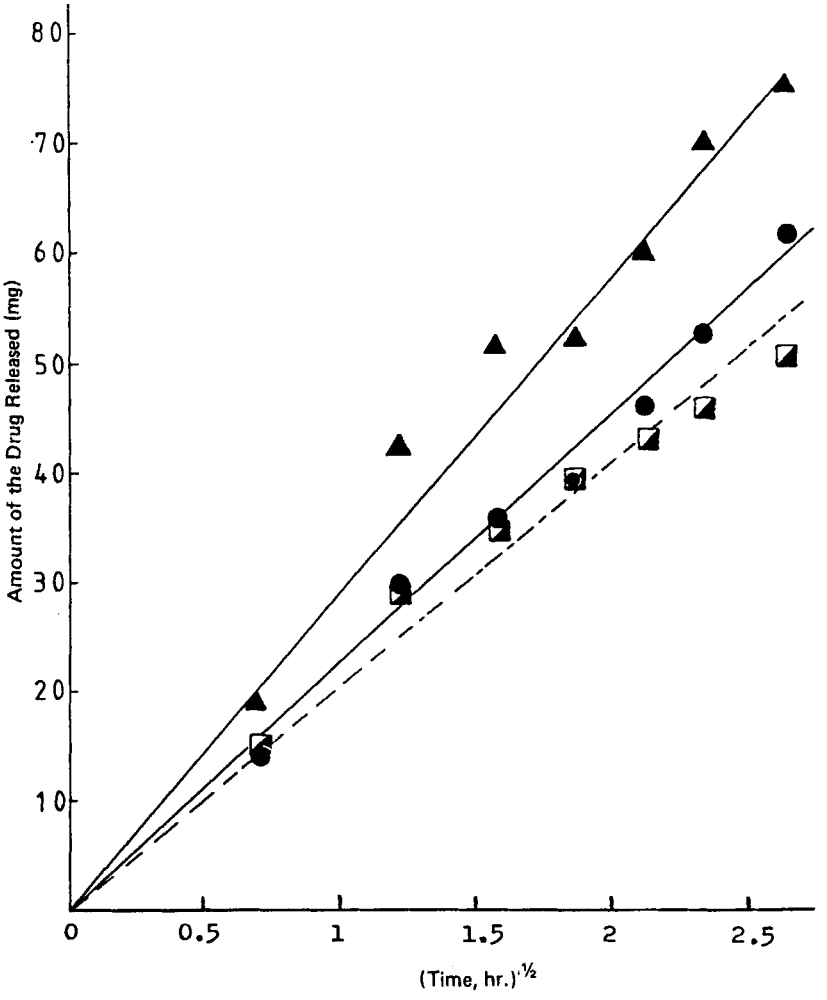

FIGURE 6

Drug release from tablets as a function of the square root of time (according to Higuchi equation*). Key: – ◪ – , Avil retard tablets (Hoechst Orient); ● , 500 mg tablets containing 15% of the drug in Eudragit L 100 and ▲ , 375 mg tablets containing 20% of the drug in Eudragit S 100.

* $Q = Kt^{1/2}$

relationship obtained for the release of the drug from the whole tablet in case of the following tablets; 375 mg tablets containing 20% of the drug in Eudragit S 100, 500 mg tablets containing 15% of the drug in Eudragit L 100 and "Avil retard" tablets (Hoechst Orient).

The effect of varying the drug concentration on the release rate was investigated utilizing 500 mg tablets prepared from the solid dispersions containing 15 and 20% of the drug in Eudragit S 100. Plots of the amount of drug released versus the square root of time show a linear relationship as shown in Figure 7. The slopes of the lines are equal to 12.3 and 19.7 respectively, i.e. nearly proportional to the concentration of the drug in the tablet as predicted by Higuchi equation (10) Eq. 3. This confirms that the mechanism of release is mainly diffusion. Assuming that increasing the amount of drug in tablet would also increase the porosity by the same factor, but would not affect the other variables, it is evident from Eq. 3 that the slope also should increase by the same factor, slight deviation may indicate that the other factors in the equation are changing with the amount of the drug or that porosity was not proportional to A (the total amount of the drug present in the matrix per unit volume).

Curves in Figure 8 show deviation from linearity, when the amount of the drug released was plotted versus the square root of time for the tablets containing 10% of the drug in Eudragit RSPM, 10% of the drug in a mixture of 1:1 Eudragit S 100 and Eudragit RLPM and 10% of the drug in a

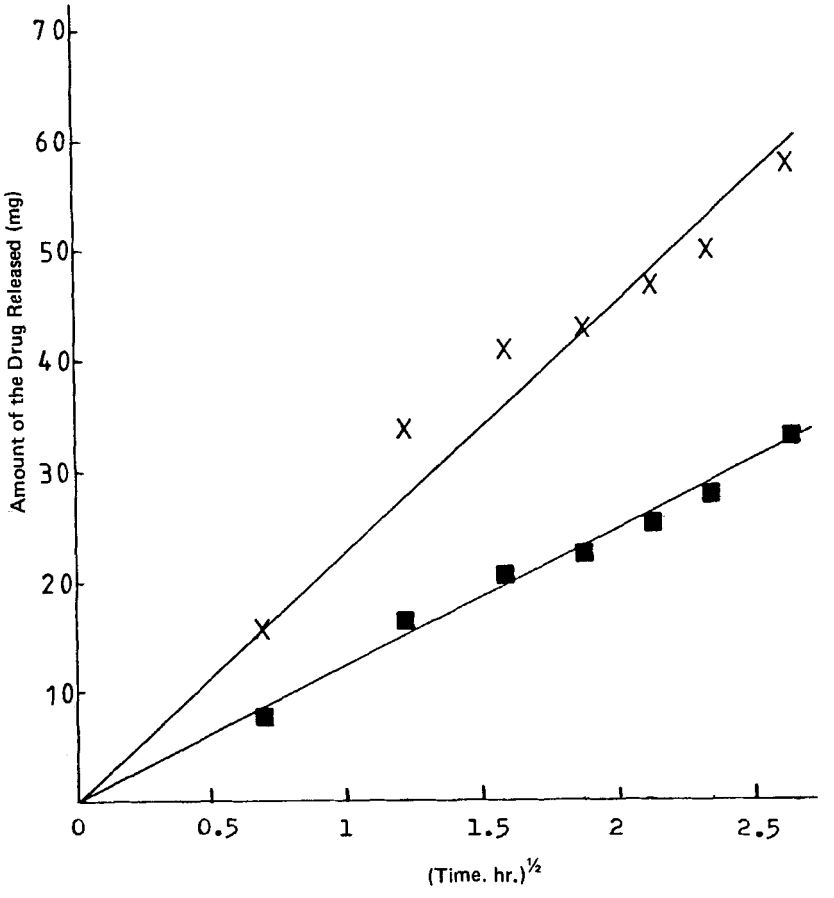

FIGURE 7

Drug release from 500 mg tablets as a function of the square root of time (according to Higuchi equation)*. Key: ■ , 15% and X , 20% of the drug in Eudragit S 100.

* $Q = Kt^{½}$

mixture of Eudragit S 100 and Eudragit RSPM at a ratio of 1:8. These tablets disintegrated before completion of drug release.

A more stringent test was developed (5) to distinguish between the two mechanisms of drug release namely: first order and diffusion.

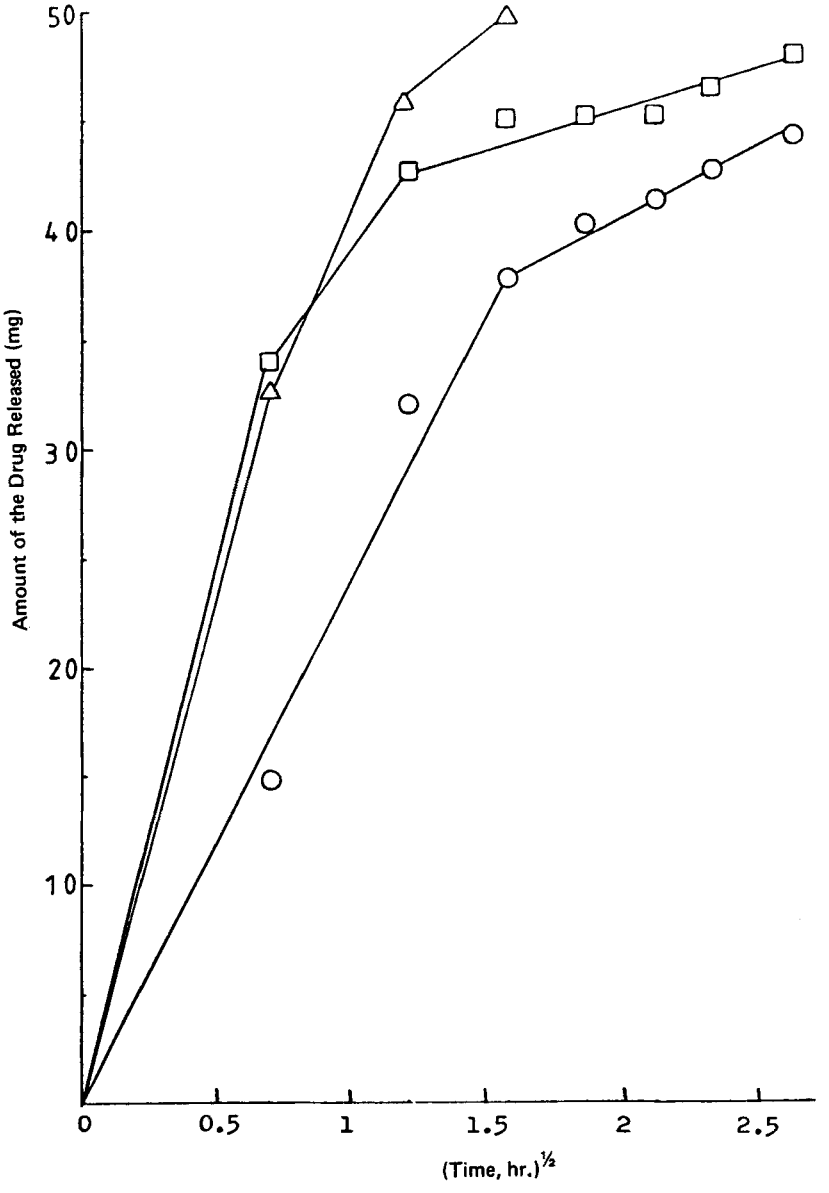

FIGURE 8

Drug release from 500 mg tablets as a function of the square root of time (according to Higuchi equation). Key: Tablets containing 10% of the drug in: ○ ,a mixture of Eudragit S 100 and Eudragit RSPM in a ratio of 1:8; □ , a mixture of Eudragit S 100 and Eudragit RLPM in a ratio of 1:1 and △ , Eudragit RSPM.

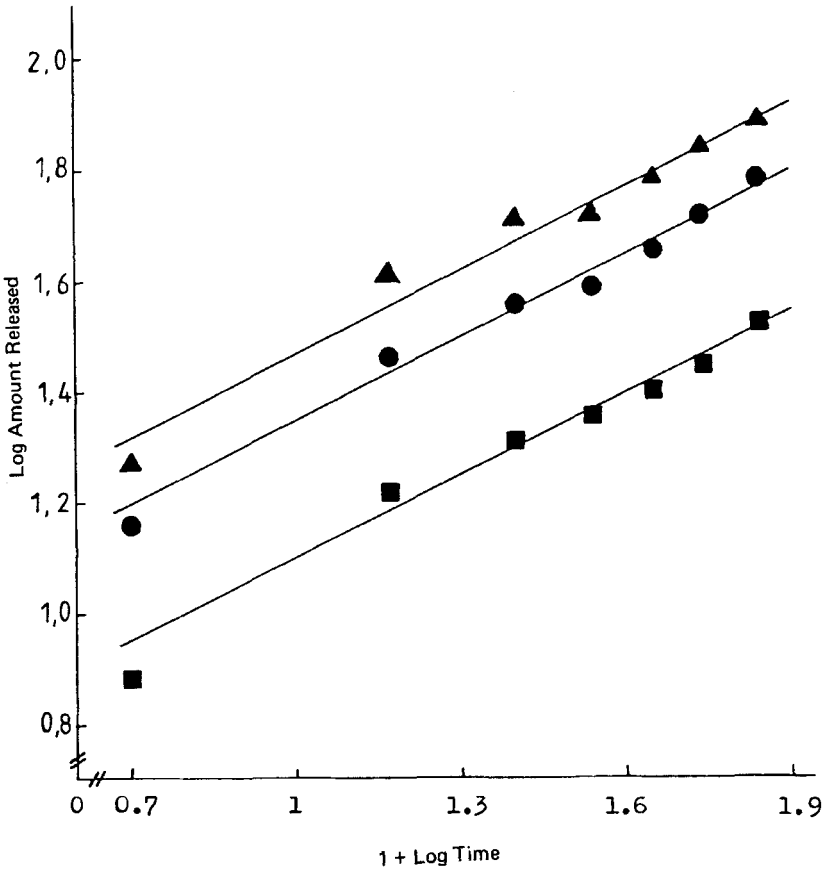

FIGURE 9

Plot of the log of the amount of drug released from tablets against the log of time. Key: 500 mg tablets containing 15% of the drug in ■ , Eudragit S 100 and ● ,Eudragit L 100. ▲ , 375 mg tablets containing 20% of the drug in Eudragit S 100.

By taking logs of Equation 4 $Q = Kt^{1/2}$

$$\log Q = \log K + \tfrac{1}{2} \log t \qquad \text{Eq. 5}$$

This predicts that a plot of log Q versus log t must not only give a straight line, but must have a slope of 0.5 indicating that the diffusion-controlled mechanism is operative and that a first-order release is incorrect. This was found to be true* and is illustrated in Figure 9

* The slopes were calculated by the least square method.

for 500 mg tablets containing 15% of the drug in Eudragit L 100 or Eudragit S 100 and for 375 mg tablets containing 20% of the drug in Eudragit S 100. This confirms that the mechanism of release from these tablets is diffusion controlled, as was previously shown by their sigmoidal first order plots.

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