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A NEW APPROACH FOR CONTROLLING THE RELEASE RATE OF PHENIRAMINE AMINOSALICYLATE VIA SOLID DISPERSION IN DIFFERENT TYPES OF EUDRAGIT

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ABSTRACT

Co-precipitates of pheniramine aminosalicylate in different types of Eudragit were prepared. IR spectra indicated the absence of molecular interaction between the drug and Eudragit. The effect of polymer type on the retardation of drug release rate was in the following order: Eudragit S 100 > Eudragit L 100 > Eudragit RSPM or Eudragit RS 100 > Eudragit RLPM or Eudragit RL 100. The concentration of the polymer in the system was a determining factor in controlling the release rate of the drug. As the concentration of the polymer in the system increased, the release rate of the drug decreased.

Co-precipitates of the drug in different ratios of Eudragit blends were also prepared. The release rate of the drug

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decreased by decreasing the concentration of the permeable Eudragit RLPM or Eudragit RSPM in the system.
The rapid release rate of the drug from the physical mixtures excluded their application in controlling drug release.

INTRODUCTION

The solid dispersion technique was originally used to enhance the dissolution rate of poorly soluble drugs (1,2). The purpose of the present study was to apply a solid dispersion technique (solvent method) using different types of Eudragit as inert insoluble carriers to control the release rate of the water soluble and short acting antihistamine pheniramine aminosalicylate with the subsequent prolongation of its duration of action.

EXPERIMENTAL

Materials- Pheniramine aminosalicylate powder (Hoechst AG. Frankfurt.), Eudragit L 100, Eudragit S 100,Eudragit RLPM-powder form, Eudragit RL 100-granule form, Eudragit RSPM-powder form and Eudragit RS 100-granule form, Eudragit types were 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 the Solid Dispersions Under Investigation

Co-precipitates (10%) of pheniramine aminosalicylate in Eudragit: L 100, S 100, RL 100, RS 100, RSPM, and a 5% co-precipitate of the same drug in Eudragit RLPM were

prepared.

In addition, 10% co-precipitates of pheniramine amino-salicylate in mixtures of Eudragit S 100 and RLPM in ratios of 8:1, 2:1, and 1:1 were prepared.

Co-precipitates (10%) of the same drug in mixtures of Eudragit S 100 and RSPM in ratios of 8:1, 1:1, 1:2, 2:7 and 1:8 were also prepared.

Ethyl alcohol was used as the solvent for the drug and polymer except in case of the preparation of co-precipitates containing Eudragit RS 100 or 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.

The solid dispersion obtained was then powdered and a 200-500 μ particle size fraction was collected for each preparation.

The effect of drug/polymer ratio was one of the objectives of this study. This could be effected by varying the concentration of the drug incorporated in the polymer. Accordingly, co-precipitates containing 10, 15 and 20% of the drug in Eudragit L 100 were prepared. Co-precipitates containing 10,15,20 and 30% of the drug in Eudragit S 100 were prepared, and co-precipitates containing 10% and 20% of the drug in Eudragit RSPM were also prepared.

Physical mixtures of the same compositions as those of the solid dispersions were prepared by simple mixing of the powdered drug and Eudragit possessing the same

particle size range.

Qualitative Infrared Spectroscopy - IR spectra by potassium bromide disc method were determined for different polymer-drug systems prepared in this work, using Beckman 4210 Infrared Spectrophotometer.

Determination of Drug Contents in the Co-precipitates-

Samples of 100 mg of the co-precipitates were dissolved in 100 ml ethyl alcohol or acetone in case of co-precipitates containing Eudragit RSPM or Eudragit RS 100. Samples of 10 ml were pipetted, diluted to 100 ml with 0.1N HCl and were analysed spectrophotometrically at λ 268 nm using Unicam SP 1800 U.V. Spectrophotometer. To avoid interference from Eudragit, a blank was used every time. The specific Eudragit (previously treated with solvent as in the preparation of the co-precipitate) was dissolved in 100 ml alcohol or acetone in an amount equivalent to that present in 100 mg of the corresponding co-precipitate. A sample of 10 ml was pipetted, diluted to 100 ml with 0.1N HCl and used as the blank.

Dissolution Studies of the Prepared Co-precipitates

The half change method which simulates the conditions found in the gastrointestinal tract (3) was followed using a rotating bottle device.
A 200-500 μ particle size fraction of the prepared co-precipitates was used for the dissolution study.
Samples of the different dispersions corresponding to

100 mg of the drug were weighed in screw capped bottles. A 50 ml of 0.1N HCl of pH 1.2 previously warmed to 37°C was pipetted in each bottle.

The bottles were capped tightly and rotated at a rate of 40 r.p.m. in a thermostatically controlled water bath at 37°C. After 30 minutes, half of the solution was withdrawn by 25 ml. pipette through a nonabsorbable cotton wool as a filter, kept for analysis and replaced with an equal volume of previously warmed 0.1N HCl. At the end of every successive hour, half of the solution was replaced with an equal volume of previously warmed to 37°C phosphate buffer of pH 7.4.

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.

To avoid any interference of Eudragit, a blank was carried out every time. Different blanks were prepared using the specific Eudragit (previously treated with solvent as in the preparation of the co-precipitate) in an amount equivalent to that present in the corresponding co-precipitate and proceeding exactly as with the dissolution study on the samples.

Three samples from three different batches of the product were used for the dissolution study.

Dissolution rate studies of the physical mixtures were also carried out using three samples for each.

The dissolution of 100 mg of powdered drug was used as a basis for comparison.

RESULTS AND DISCUSSION

Infrared Spectroscopy - The undetected shift of IR bands of the dispersed pheniramine aminosalicylate in the co-precipitates indicated the absence of molecular interaction between the drug and Eudragit.

Effect of Polymer Type on the Release Rate of Pheniramine Aminosalicylate from the Solid Dispersion Systems

From the release rate data presented in Figure 1, the following could be concluded:

a) Within half an hour, 96.7% of the drug content was released from its co-precipitate in Eudragit RL 100, whereas only 79.8% of the drug was released from its co-precipitate in Eudragit RS 100. This may be attributed to the lower permeability of Eudragit RS 100, as it contains lower content of hydrophilic groups. On the other hand, the higher content of hydrophilic groups in Eudragit RL 100 renders it highly permeable (4).

b) A 10% dispersion in Eudragit RSPM (permeable to a low extent) released 77% of its drug content within half an hour. This is nearly the same as the release (79.8%) from the 10% co-precipitate in Eudragit RS 100. This finding is in agreement with the fact that both types of Eudragit are methacrylate polymers of the same structure.

A 96.2% of the drug content was released within half

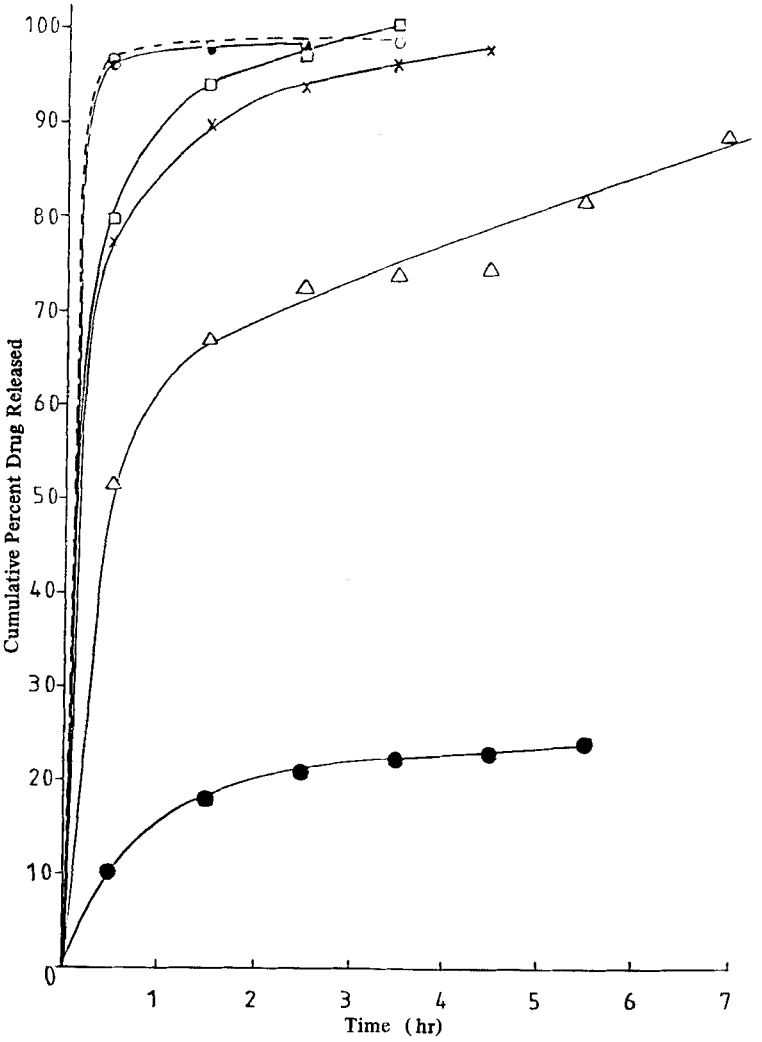

FIGURE 1

Drug release rates from co-precipitates containing 10% of pheniramine aminosalicylate in different types of Eudragit. Key: ● , Eudragit S 100; △ Eudragit L 100; × , Eudragit RSPM; □ , Eudragit RS 100; ---○--- , Eudragit RL 100 and —◐— , co-precipitate containing 5% of the drug in Eudragit RLPM.

an hour from its 5% dispersion in Eudragit RLPM, in spite of its higher polymer content. This may be attributed to the higher permeability of Eudragit RLPM. The Eudragit retard powder masses are insoluble in the pH range of the digestive tract, but they swell in aqueous medium and exhibit a distinct permeability for water and water soluble substances. Their swelling and permeability properties are independent of the pH conditions in the gastrointestinal tract (5). The rapid release of the drug from these permeable polymers, may be attributed to the leaching of the drug by the dissolution fluid which was able to enter the drug-matrix phase through pores to dissolve the drug which was presumed to diffuse from the system along the capillary channels filled with the solvent.

c) The co-precipitate containing 10% drug in Eudragit L 100 released 51.4% of its drug content within half an hour, while only 10.2% of the drug was released from its 10% dispersion in Eudragit S 100. Eudragit L and Eudragit S films are insoluble in acid medium and also water proof (5). The relatively higher rate of drug release from Eudragit L 100, which contains a higher content of methacrylic acid groups (4), may be attributed to the adsorption of some drug on the surface of the polymer and the subsequent release of this drug in the dissolution medium at pH 1.2. At a higher pH value of 6.5 (after 3½ hours) the percentage of the drug that was released from Eudragit L 100

was found to be 74.3%, whereas only 22.3% of the drug was released from Eudragit S 100. The higher methacrylic acid content of Eudragit L 100 and its solubility above pH 6 (5) may explain the higher release rate as compared with Eudragit S 100 which is soluble only above pH 7 due to its lower content of methacrylic acid.

The co-precipitate containing 10% of the drug in Eudragit L 100 was the most favourable system yielding release rate data that were in agreement with the reported (6) in vitro release values for those products exhibiting suitable sustained-action properties when evaluated in vivo by urinary excretion studies(Table 1).

Effect of Polymer Concentration on the Release Rate of the Drug

By comparing the release rates of the drug from its co-precipitates in Eudragit RSPM containing 10 and 20% of the drug, it was found that 77%of the drug content was released from the 10% co-precipitate within half an hour, while 90.7% was released from the 20% co-precipitate.

Figure 2 shows the release rate patterns of the drug from its co-precipitates in Eudragit L 100 containing 10,15 and 20% of the drug corresponding to 90,85 and 80% of polymer content. Within half an hour, 51.4, 63, and 78.4% of the drug content were released from the three systems respectively.

Co-precipitates containing 90,85,80 and 70% of

TABLE 1

Comparison of Reported Release Values with Experimental Results of the Co-precipitate Containing 10% of the Drug in Eudragit L 100.

Time, hr.	Cumulative Percent Release	
	Reported Values	Experimental Values
0.5	32 - 43	49
1.5	-	66
2	39 - 69	69[a]
2.5	-	72.5
3.5	-	74.3
4.5	60 - 90	74.4
5.5	-	82
7	86 - 98	89.4

[a]This value was graphically determined.

Eudragit S 100 released 10.2, 34.5, 71.8 and 76% of the drug within half an hour, (Figure 3).

Tha above release rate data show that by increasing the concentration of the polymer in the co-precipitate, the release rate of the drug decreased. This may be an indication that the percentage of the polymer in the system is a determining factor in the diffusional process within the drug-matrix system.

Release of the Drug from the Co-precipitates in Different Ratios of Eudragit Blends

a) Figure 4 shows the release rate data of the drug from its co-precipitates in mixtures of Eudragit S 100 and

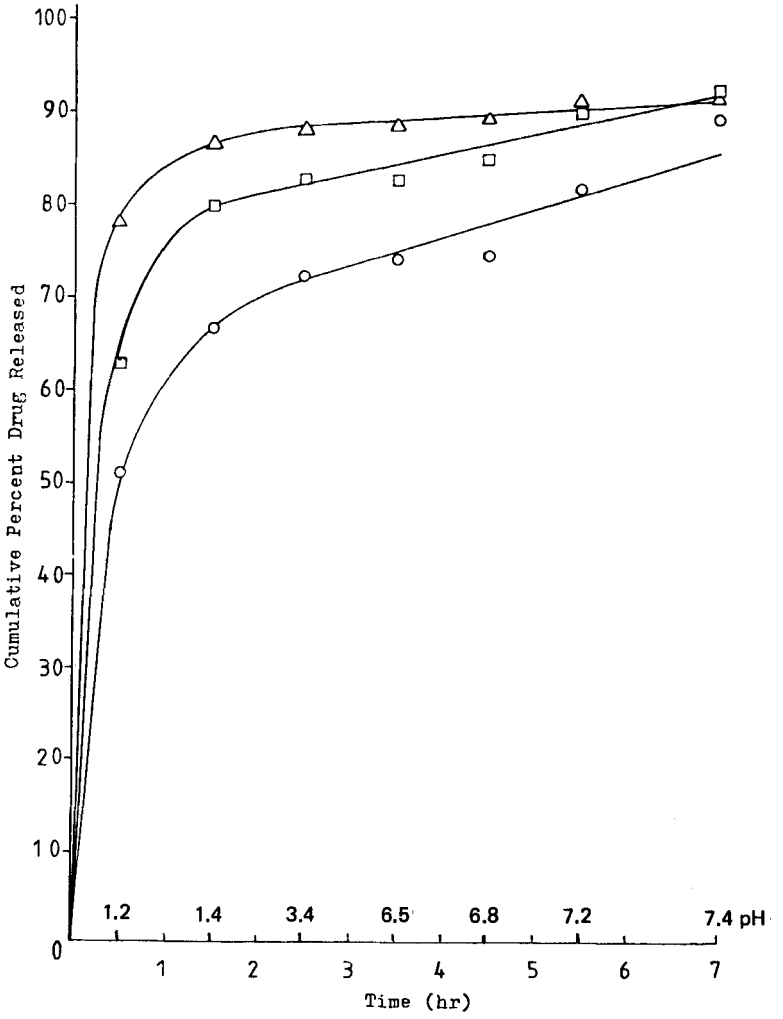

FIGURE 2

Drug release rates from co-precipitates containing different concentrations of the drug in Eudragit L 100. Key: ○ , 10%; □ 15% and △ , 20%.

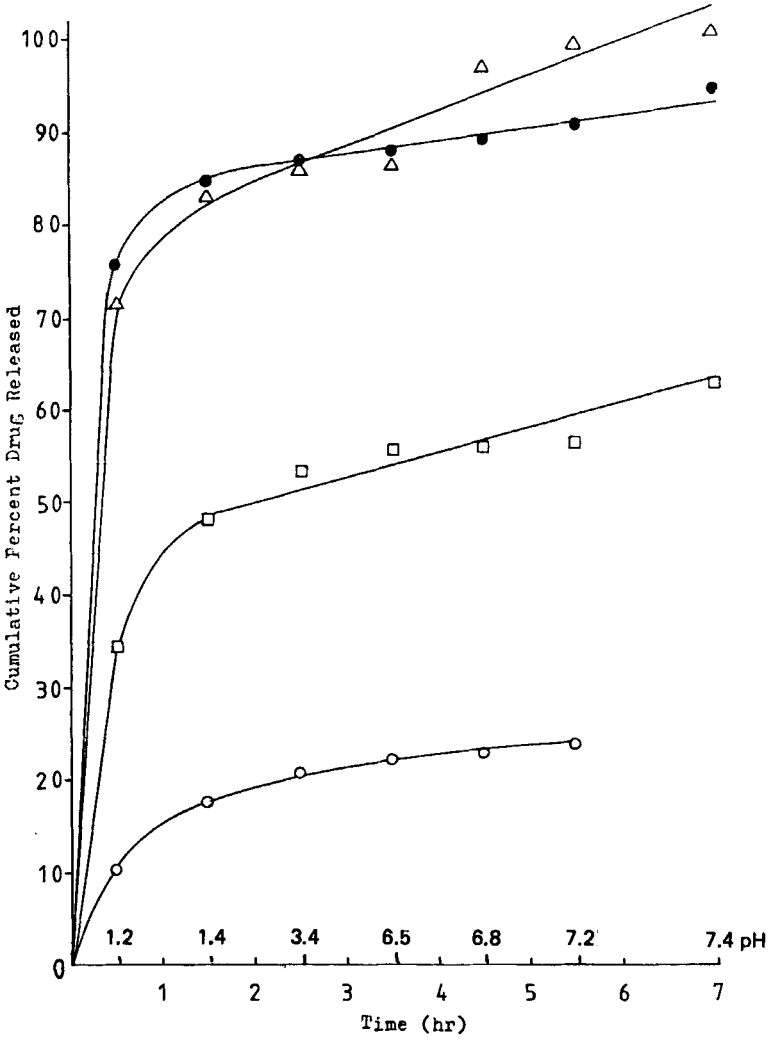

FIGURE 3

Drug release rates from co-precipitates containing different concentrations of the drug in Eudragit S 100. Key: ○ , 10%; □ , 15%; △ , 20% and ● , 30%.

Eudragit RSPM in the following ratios, 8:1, 1:1, 1:2, 2:7 and 1:8 respectively. The drug content in all of these preparations was 10%.

The data revealed the fact that by decreasing the amount of the permeable Eudragit RSPM in the mixture, an evident decrease in the release of the drug was attained.

Within half an hour, 59, 51.9, 39.6, 31.6 and 10.3 of the drug content were released from the mixtures containing 89,78,67,50 and 11% of Eudragit RSPM respectively.

b) Figure 5 shows the release rate data of the drug from its 10% co-precipitates in mixtures of Eudragit S 100 and Eudragit RLPM in the following ratios 8:1, 2:1 and 1:1. It is also evident that the amount of the drug released decreased by decreasing the concentration of the highly permeable Eudragit RLPM in the system.

Within half an hour, 52.6, 39.3 and 16.5% of the drug content were released from the mixtures containing 50, 33 and 11% of Eudragit RLPM respectively.

c) It is interesting to note that 21% more of the drug was released,from the dispersion containing 1:1 Eudragit S 100 and Eudragit RLPM,than from the dispersion containing 1:1 Eudragit S 100 and Eudragit RSPM. This is probably due to the higher permeability of Eudragit RLPM.

d) All physical mixtures showed complete drug release within 30 minutes, a fact that excludes their application in controlling drug release.

Dissolution study of the drug powder showed that 90% of

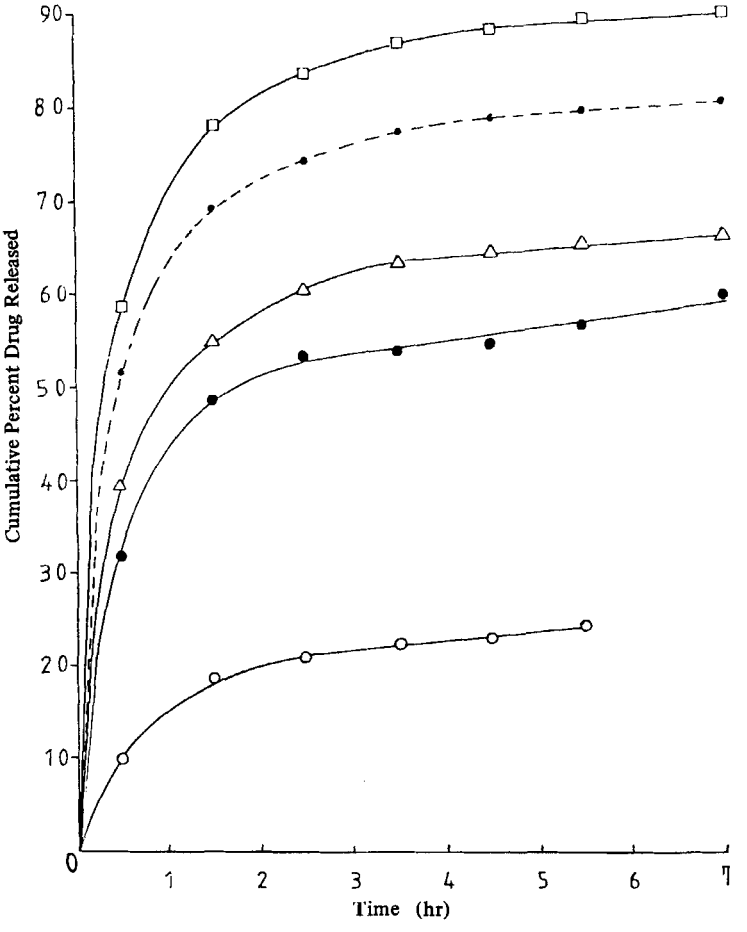

FIGURE 4

Drug release rates from co-precipitates containing 10% of the drug in mixtures of Eudragit S 100 and Eudragit RSPM in different ratios. Key: ○ , 8:1; ● , 1:1; △ , 1:2; --●-- , 2:7 and □ , 1:8.

the drug was released within one minute only.

The Application of A Numerical Method to the Dissolution Data to Replace Analytical data by Calculated Values -

The commonly used half-change procedure is a method to determine the dissolution rate of sustained-release

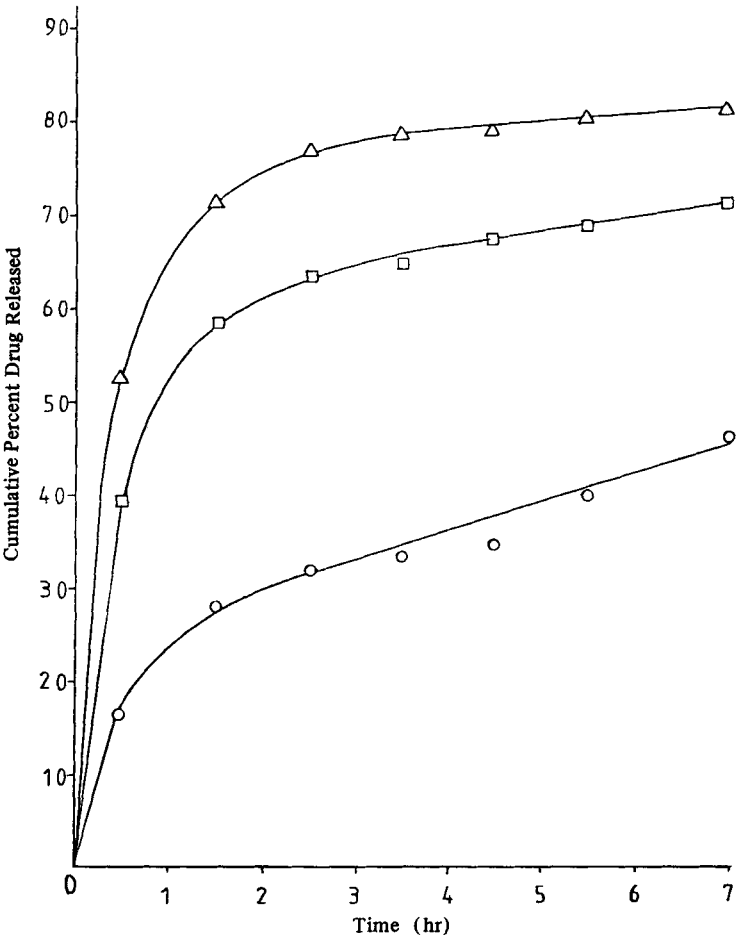

FIGURE 5

Drug release rates from co-precipitates containing 10% of the drug in mixtures of Eudragit S 100 and Eudragit RLPM in different ratios. Key: ○ , 8:1; □ , 2:1 and △ , 1:1.

drugs (3). Every hour a measured volume is taken out of a rotating vessel containing the dosage form and the dissolution medium and the same volume of dissolution medium is added. Within several hours a large number of samples are obtained for the determination. It is impossible to shorten this procedure by changing the

time intervals or by the number of samples, because the proceeding and the way of evaluation are exactly defined. There is no possibility to omit one of these sample preparations but it is not necessary to analyse the whole samples. Only 3 of 7 samples must be analysed and the remaining values can be calculated using a numerical method which can be used to replace analytical data by calculated values in a non linear function. It has been applied to the dissolution rate of d-norpseudoephedrine hydrochloride in Amorphan Depot (7). The function which is most congruous with this curve is described by the following equation.

$$y = a_o + a_1 x + a_2 x^2$$

where y means the extinction of the sample solution and x the number of hours.

a_o, a_1, a_2 are the coefficients of the curvelinear regression.

Table 2 shows experimentally found values in comparison with the calculation that was based merely on 3 values that were determined experimentally at time intervals 0.5, 3.5 and 7 hours. The remaining values proved to be in conformity with the equation.

CONCLUSION

Retardation in the release rate of pheniramine aminosalicylate could be achieved via solid dispersion of the drug in different types of Eudragit. The permeability and the concentration of the polymer were determining

TABLE 2

Total Dissolution Rate

Co-precipitates	Cumulative Percent Release							
	1.5 hrs		2.5 hrs		4.5 hrs		5.5 hrs	
	A*	B**	A*	B**	A*	B**	A*	B**
10% drug in Eudragit L 100	67	61	72	68	74	79	82	84
15% drug in Eudragit L 100	80	71	83	78	85	87	90	90
20% drug in Eudragit L 100	87	83	88	86	89	90	91	91
15% drug in Eudragit S 100	48	43	53	50	56	60	57	62
20% drug in Eudragit S 100	83	77	86	82	97	91	99	95
30% drug in Eudragit S 100	85	81	87	85	89	91	91	93
10% drug in S 100:RSPM 8:1	19	16	21	20	23	24		
10% drug in S 100:RSPM 1:1	48	41	53	48	55	58	57	61
10% drug in S 100:RSPM 1:2	55	50	61	58	65	67	66	68
10% drug in S 100:RSPM 2:7	70	63	74	71	79	81	80	83
10% drug in S 100:RSPM 1:8	78	71	84	80	89	91	90	93
10% drug in S 100: RLPM 8:1	28	23	31	28	35	38	40	42
10% drug in S 100:RLPM 2:1	57	50	63	58	67	69	69	72
10% drug in S 100: RLPM 1:1	71	64	77	72	79	82	80	84

* A: Experimentally found values
** B: Calculated values

factors in controlling the release rate. The rapid release rate of the drug from the physical mixtures excluded their application in controlling drug release.

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