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INFLUENCE OF FORMULATION AND OTHER FACTORS ON THE RELEASE OF CHLORPHENIRAMINE MATEATE FROM POLYMER COATED BEADS

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ABSTRACT

Controlled release beads containing chlorpheniramine maleate, coated with Eudragit RL and RS, were prepared using the Wurster process. The effect of membrane thickness, polymer ratio of the coating material, agitation speed and pH of the dissolution medium on drug release were investigated using the USP dissolution basket method. The in vitro release of drug was described adequately by a previously published equation. The release rate constant (K) was dependent on the membrane thickness, the polymer ratio and pH of the dissolution medium. On the other hand, agitation speed used in this study did not have any influence on the release of the drug.

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INTRODUCTION

The main purpose of administering drug in a controlled drug delivery system is to promote the therapeutic benefits while simultaneously minimizing undesirable side effects (1). With controlled drug delivery systems, both unnecessarily high and perhaps toxic concentrations and subtherapeutic levels can be avoided.

For oral administration of drugs, several controlled release drug delivery systems have been developed (2,3). A delivery system frequently used consists of beads that are surrounded by the drug followed by coats of suitable polymers. The type of membrane frequently used in such a system is a nonporous homogeneous polymeric film (4). The drug molecule traverses the membrane by a process of dissolution into the membrane which is then followed by diffusion across the membrane into the surrounding dissolution medium. The major advantage of this system is the ease with which it can be designed to obtain a desirable release rate with high reproducibility (5).

The release of drug from coated beads is shown schematically in Figure 1. The molecules of the crystalline drug lying against the inside wall of the membrane leave their crystals, pass into the polymer membrane by a dissolution process, diffuse through the membrane and pass into the liquid diffusion layers and eventually into the medium surrounding the beads.

THEORY

Drug transport through a polymeric membrane is determined by Fick's first law:

$$J = -\frac{dM}{Adt} = -D_m \frac{dc}{dx} \qquad \text{Eq. 1}$$

where J is the flux, $\frac{dM}{dt}$ is drug release rate, A is the surface area, D_m is

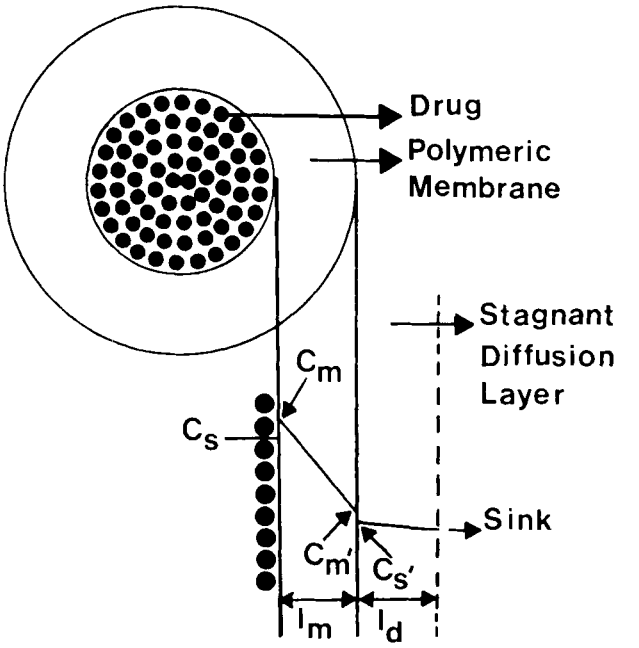

FIGURE 1

Diffusion of Drug from Polymer Coated Bead

drug diffusion coefficient and $\frac{dc}{dx}$ is the concentration gradient within the membrane.

If the drug concentrations in the inner and outer sides of the membrane (Figure 1) are C_m and C_m', respectively and the membrane thickness is equal to l_m, then eq. 1 may be written as:

$$\frac{dM}{dt} = AD_m \frac{(C_m - C_m')}{l_m} \qquad \text{Eq. 2}$$

Eq. 2 assumes that the stagnant diffusion layer surrounding the membrane does not have a significant effect on the total transport process.

The concentration term, $(C_m - C_m')$, in eq. 2 can be replaced by $P(C_s - C_s')$. Where P is the polymer:dissolution fluid partition coefficient and C_s and C_s' are the concentrations of drug in the core and in the surrounding medium at the membrane–medium interface, respectively. Thus eq. 2 may be written as follows:

$$\frac{dM}{dt} = AD_m P \frac{(C_s - C_s')}{l_m} \qquad \text{Eq. 3}$$

If sink conditions are operative in the system, eq. 3 may be written as:

$$\frac{dM}{dt} = \frac{AD_m PC_s}{l_m} \qquad \text{Eq. 4}$$

Eq. 4 suggests that a constant release rate can be obtained if a constant supply of drug in the core is maintained. This will occur as long as an excess amount of solid drug is present in the core and the drug's concentration is maintained above its equilibrium solubility.

The equations considered thus far assume that the drug release is determined solely by the rate of drug diffusion through the polymeric membrane. In practice, however, a stagnant diffusion layer may exist beyond the membrane surface, which will also resist the drug transport.

Flynn et al. (6) and Chien (7) studied the effect of the stagnant diffusion layer on the release of drug from a membrane type system and reported that drug transport through the membrane at a steady state and under sink conditions follows eq. 5.

$$\frac{dM}{dt} = \frac{APD_m D_d C_s}{PD_m l_d + D_d l_m} \qquad \text{Eq. 5}$$

where D_m and D_d are drug diffusion coefficients in the membrane of thickness, l_m, and in the stagnant diffusion layer of thickness, l_d, respectively.

If the membrane resistance to drug diffusion is much greater than the resistance of the stagnant diffusion layer, i.e. $l_m D_d \gg Pl_d D_m$, then eq. 5 can be reduced to eq. 4. On the other hand, if $Pl_d D_m \gg l_m D_d$, eq. 5 becomes

$$\frac{dM}{dt} = \frac{AD_d C_s}{l_d} \qquad \text{Eq. 6}$$

Eq. 6 suggests that the rate determining barrier to diffusional transport is the stagnant diffusion layer. Therefore, the concentration gradient in the diffusion layer, rather than that in the membrane, controls the flux. The importance of the diffusion layer has been reported (4), especially for drugs with low aqueous solubility.

Although a constant activity dosage form exhibits a constant release of drug at a steady-state, it may not do so during the initial period of drug release. For instance, if the system loaded with drug is used immediately, it may be some time before a uniform concentration is established within the membrane (4). Under such a condition, a lag time is observed and the initial release rate will be lower than the steady state rate. In the case of presence of lag time, t_L, a modified equation for a membrane diffusion controlled system can be expressed as follows (8):

$$M_t = \frac{APD_m C_s}{l_m}(t - t_L) \qquad \text{Eq. 7}$$

where M_t is the mass of drug released at time t.

EXPERIMENTAL

Materials

Chlorpheniramine maleate[a], Eudragit RS 100 and Eudragit RL 100[b], non-pareil seeds[c], methocel E5[d], magnesium stearate[e], carbowax 3350, hydrochloric acid, 2-propanol, sodium chloride, sodium hydroxide and acetone[f].

Equipment

Uni-Glatt laboratory unit[g], Hanson dissolution apparatus[h], Spectronic 2000[i], Unitron phase BPH microscope[j].

Preparation of Coated Beads

The fluidized bed coated technique was used for the preparation of coated beads. Non-pareil seeds of mesh 18/20 were used as cores. Chlorpheniramine maleate, with the aid of hydroxypropyl methylcellulose (HPMC), was fixed onto the cores and these cores were subsequently coated with different amounts and ratios of Eudragit RL and RS. Each batch of coated beads was prepared using 100 grams of non-pareil seeds. The compositions of the fixing and coating fluids are given in Tables 1 and 2, respectively.

Polyethylene glycol and magnesium stearate are used as plasticizer and anti-tacking agent, respectively. The optimum conditions used in both fixing and coating processes are summarized in Table 3.

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a Hoffman-Taff, Inc., N.J.
b Rohm Pharm Gmblt, Darmstadt, Germany
c Ingredient Technology Corporation, Pennsauken, N.J.
d Dow Chemical Co., Midland, MI
e Mallinckrodt, Inc., St. Louis, MO
f Fisher Scientific Co., Fair Lawn, N.J.
g Glatt Air Techniques, Inc., Norwood, N.J.
h Hanson Research Co., Northridge, CA
i Bausch and Lomb, Rochester, N.Y.
j Unitron, Phase BPH, Japan

TABLE 1

The Composition of the Fixing Fluid

Ingredients	% W/W
Chlorpheniramine Maleate, USP	10.00
Methocel^{R} E5 Premium	0.30
Polyethylene Glycol 3350, NF	0.10
Alcohol, USP	60.00
Distilled Water	q.s.

TABLE 2

The Composition of the Coating Fluid

Ingredients	% W/W
Eudragit RL and RS	8.00
Polyethylene Glycol 3350, NF	2.00
Magnesium Stearate, NF	8.00
Isopropanol	60.00
Acetone	22.00

TABLE 3

The Optimum Conditions Used in Fixing and Coating Operations

Conditions	Fixing Operation	Coating Operation
Fluidization Pressure (mm water)	200	150
Inlet Temperature (^{o}C)	40-50	30-40
Spray Rate (ml/min)	15	20
Spray Pressure (Atm)	2	2

The following criteria were taken into consideration while selecting optimum conditions: a) nonaggregation of the beads; b) the rapidity of the operation; and c) homogeneity of the coating.

To study the effect of the membrane thickness, separate batches of beads containing drug were coated with 200, 300 and 400 mL of the coating fluid containing Eudragit RL and RS in a ratio of 1:3.

To study the effect of polymer ratio, 300 mL of the coating fluid with Eudragit RL and RS in ratios of 1:1, 1:3 and 1:5 were applied to various batches.

Membrane Thickness Determination

The membrane thickness of the coated beads was determined by a microscopic method. The diameters of the cores were measured after completing the fixing and coating operations. The thickness was determined by obtaining the difference between the diameters and dividing by two.

Dissolution Media

Simulated gastrointestinal fluids (9) of pH 1.2, 4.5 and 7.5, without enzymes, and distilled water were used as dissolution media.

Assay Procedure

Standard Beer's law curves over a concentration range of 5-60 mg/L were prepared for chlorpheniramine maleate in each dissolution medium. The assay of chlorpheniramine maleate was performed spectrophotometrically at the wavelength of the maximum absorption (260.9 - 263.7 nm).

Total Assay

From each batch, 500 mg of coated beads were weighed, ground to fine powder with the use of a glass mortar and pestle and quantitatively transferred into a 500 mL volumetric flask. Distilled water was added to

the flask. The flask was shaken for a period of four hours and then brought to volume. An aliquot of this solution was then filtered and the filtrate was assayed to determine the drug content.

Equilibrium Solubility of the Drug

The equilibrium solubilities of drug in simulated gastrointestinal fluids and distilled water were determined by adding excess of drug into 10 mL of dissolution fluid contained in 20 mL screw capped glass bottles. The bottles were rotated in a water bath at 37.0 ± 0.5°C for a period of 4 hours to ensure the equilibrium condition. Samples were taken and assayed at appropriate time intervals until identical concentrations were obtained on three consecutive occasions.

Release Study

The rotating paddle method as described by the USP XX (7) was used to determine the release of drug. A 500 mg sample of coated beads was added to 500 mL of dissolution medium which was maintained at 37° ± 0.5°C. Agitation speeds of 25, 50 and 100 r.p.m. were used. Five milliliters of dissolution samples were removed at suitable time intervals and replaced with an equal volume of fresh dissolution medium. The samples were filtered through a 0.45 μm filter, diluted if necessary, and assayed for the drug. From absorbance, the cumulative mass of drug released was determined. At the conclusion of each study, residual beads were removed carefully, ground with the use of glass mortar and pestle and quantitatively transferred to a volumetric flask. An aliquot of this solution was filtered and assayed to determine the residual drug content.

Calculations

The percentage of drug released at each sample time was calculated as the ratio of mass of drug released to the total drug content multiplied by

TABLE 4

Membrane Thickness of Coated Beads. Eudragit RL:RS, 1:3

Amount of Coating Fluid mL/100 g of cores	Membrane Thickness[a] (μm)
200	38.1 ± 1.8
300	58.8 ± 2.3
400	81.8 ± 3.8

[a] mean ± SD of one hundred determinations

100. The total drug content was the sum of the cumulative mass of drug released at the last sample time and the residual content. The drug release profile for any formulation was obtained by plotting cumulative percent drug released against $t - t_L$ where t and t_L are the sampling time and lag time, respectively. The release rate constant (K), however, was obtained by using cumulative mass of drug released versus $t - t_L$.

RESULTS AND DISCUSSION

Membrane Thickness Determination

The resulting membrane thicknesses, when 200, 300 and 400 ml of the coating fluids were applied to cores containing drugs, are reported in Table 4. As expected, the increase in the amount of fluid applied resulted in an increase in the membrane thickness.

Total Assay

The mean of the total assay for chlorpheniramine maleate for various batches of the coated beads are reported in Table 5. The results reported

TABLE 5

Total Assay for Chlorpheniramine Maleate in Various Formulations

Amount of Coating Fluid mL/100g of cores	Eudragit RL:RS	Total Assay[a] mg/500mg of coated beads
200	1:3	49.44 ± 0.14
300	1:1	45.82 ± 0.16
300	1:3	45.05 ± 0.18
300	1:5	43.01 ± 0.65
400	1:3	37.17 ± 0.16

[a] mean ± SD of three determinations

indicate the theoretical amount of drug present in 500 mg of the beads. The small standard deviation indicates the uniform distribution of the drug in the beads.

Equilibrium Solubility

The equilibrium solubilities of chlorpheniramine maleate in simulated gastric fluids and distilled water are reported in Table 6. As anticipated, chlorpheniramine maleate, being the salt of a weak base (pKa 9.4), exhibited a lower solubility at pH 7.5. Statistical analysis revealed that at lower pH (1.2 and 4.5) there was no significant difference ($p < 0.05$) in the solubilities.

Influence of Membrane Thickness on Release of Drug

An example of the mean release profiles obtained in the dissolution medium of pH 1.2 is shown in Figure 2. Inspection of the profiles suggests that the data were fitted adequately by equation 7. The computed release rate constant and the reciprocal of the measured membrane thickness for each formulation tested are summarized in Table 7.

TABLE 6

Equilibrium Solubility (C_s) of Chlorpheniramine Maleate at 37°C

Dissolution Medium pH	C_s (g/mL)[a]
1.2	0.520 ± 0.018
4.5	0.555 ± 0.019
6.8[b]	0.547 ± 0.010
7.5	0.463 ± 0.016

[a]mean ± SD of three determinations
[b]pH of distilled water

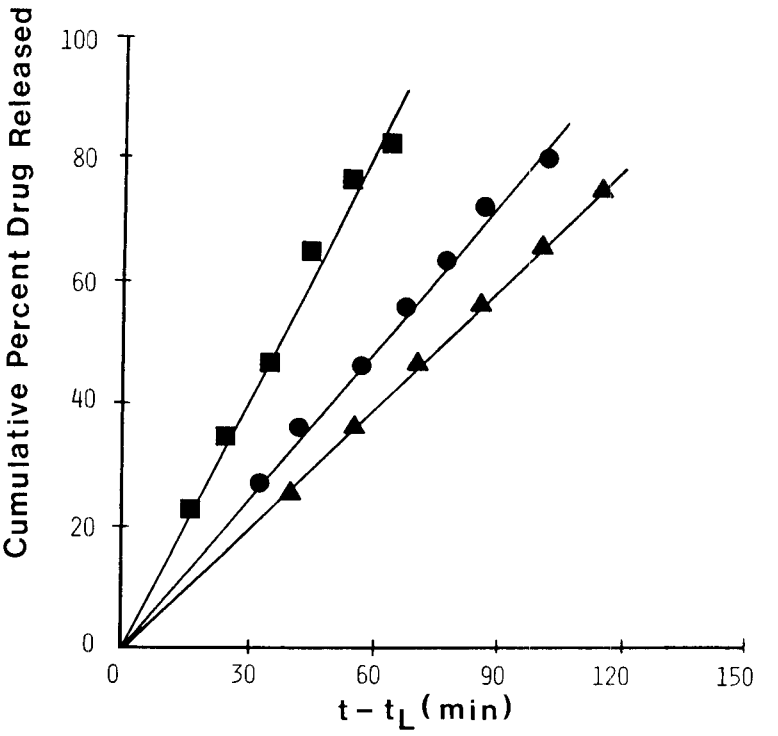

FIGURE 2

Cumulative Percent of Chlorpheniramine Maleate Released from Beads Coated with Eudragit RL:RS in a Ratio of 1:3; Simulated Gastric Fluid of pH 1.2; Agitation Speed, 50 rpm. Key: (■) Membrane Thickness, 38.1 μm; (●) Membrane Thickness, 58.8 μm; (▲) Membrane Thickness, 81.8 μm.

TABLE 7

Computed Release Rate Constant (K) as a Function of Membrane Thickness in Dissolution Media of pH 1.2 and 7.5 and at an Agitation Speed of 50 rpm. Eudragit RL:RS, 1:3

Reciprocal of Membrane Thickness (μm^{-1})	Release Rate Constant, K (mg/min)[a]	
	pH 1.2	pH 7.5
0.026	0.552 ± 0.013	0.503 ± 0.004
0.017	0.365 ± 0.002	0.301 ± 0.004
0.012	0.245 ± 0.005	0.205 ± 0.004

[a] mean ± SD of four determinations

The theoretical dependence of the release rate constant (K) on the membrane thickness is given by equation 7 (8). Accordingly, a plot of the rate constant versus the reciprocal of the membrane thickness (Figure 3) was found to be in agreement with equation 7. In support, there are studies (10,11) reporting a similar inverse relationship for drugs dispersed in the membrane, where ethyl cellulose polymer was used to form a rate controlling membrane.

Influence of Polymer Ratio on Release of Drug

The optimum release profiles obtained for formulations prepared by using various ratios of Eudragit RL:RS are shown in Figure 4. The computed mean values of the release rate constant (K) are summarized in Table 8. The mean value of the release rate constant (K) was plotted against the percent of Eudragit RL in the coating fluid (Figure 5). The plot indicates that an increase in the ratio of RL:RS caused an increase in the release rate constant. The faster release with increasing relative quantity of Eudragit

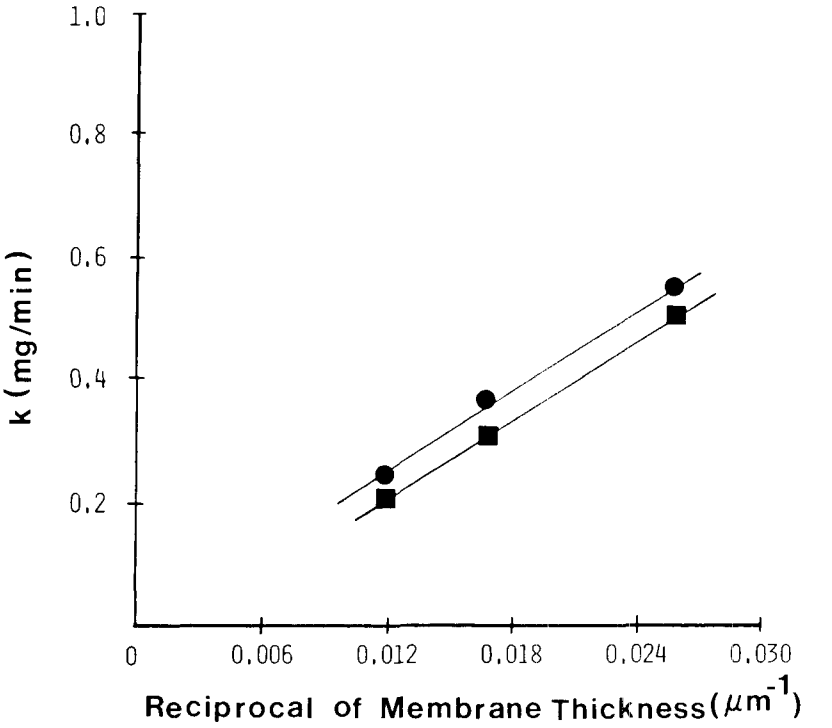

FIGURE 3

The Release Rate Constant (K) Against Reciprocal of Membrane Thickness for Chlorpheniramine Maleate Beads Coated with Eudragit RL:RS in a Ratio of 1:3; Agitation Speed, 50 rpm. Key: (●) Simulated Gastric Fluid of pH 1.2; (■) Simulated Intestinal Fluid of pH 7.5.

RL can be attributed to greater permeability characteristics of the membrane. The plot (Figure 5) also indicates that the relationship between rate constant (K) and percent of Eudragit RL is a linear. The cation content of the membrane, which varies with the type used, can influence the film swelling, film pore size and hence film permeability (12,13).

Influence of Agitation Speed on Drug Release

The optimum release profiles obtained for a formulation at various agitation speeds are shown in Figure 6. The computed mean values of the

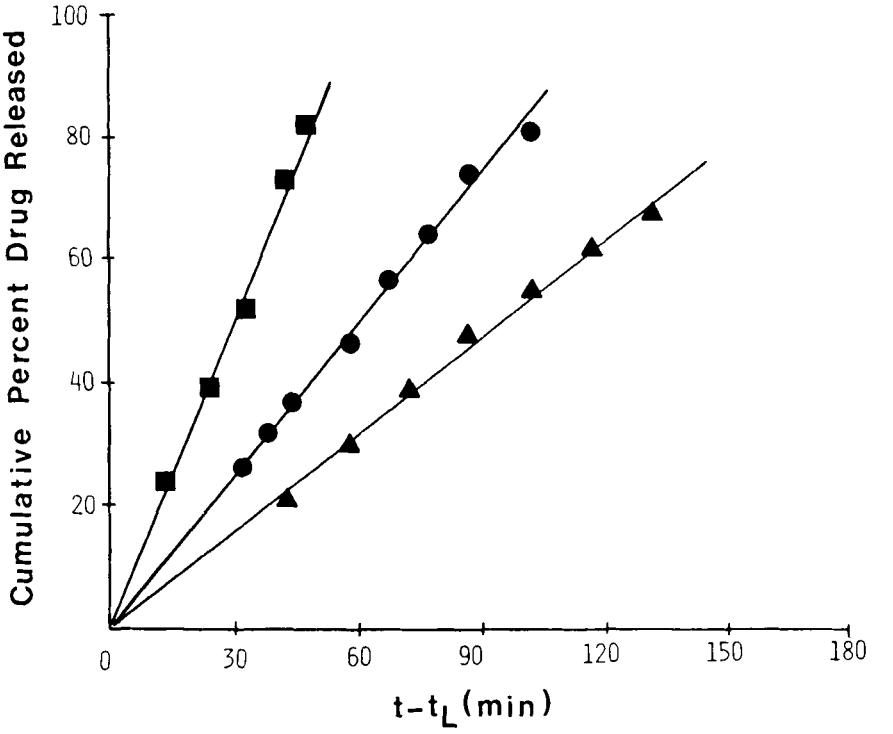

FIGURE 4

Cumulative Percent of Chlorpheniramine Maleate Released from Coated Beads Having Thickness of 58.8 μm; Simulated Gastric Fluid of pH 1.2; Agitation Speed, 50 rpm. Key: (■) Eudragit RL:RS, 1:1; (●) Eudragit RL:RS, 1:3; (▲) Eudragit RL:RS, 1:5.

TABLE 8

Computed Release Rate Constant (K) as a Function of the Polymer Ratio in Dissolution Media of pH 1.2 and 7.5 and at an Agitation Speed of 50 rpm. Membrane thickness, 58.8 μm.

Polymer Ratio RL:RS	Release Rate Constant, K (mg/min)[a] pH 1.2	pH 7.5
1:1	0.634 ± 0.005	0.570 ± 0.007
1:3	0.365 ± 0.002	0.301 ± 0.004
1:5	0.208 ± 0.008	0.156 ± 0.005

[a] mean ± SD of four determinations

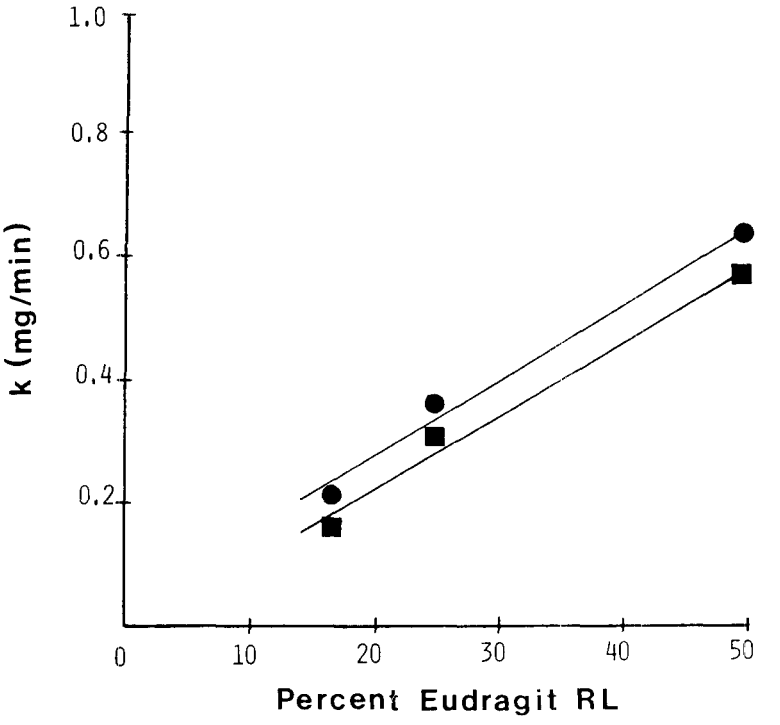

FIGURE 5

The Release Rate Constant (K) Against Percent Eudragit RL Present in the Coating Solution Used to Prepare Chlorphenimarine Maleate Beads Having Membrane Thickness of 58.8 μm; Agitation Speed, 50 rpm. Key: (●) Simulated Gastric Fluid of pH 1.2; (■) Simulated Intestinal Fluid of pH 7.5.

release rate constant (K) are reported in Table 9. From the plots and result of the rate constant, it is clear that agitation speed had no significant ($p < 0.01$) effect on the drug release for the conditions studied. In other studies, Timko and Lordi (14) and Jambhekar and Cobby (15) have reported similar agitation and flow rate independent drug release from coated pellets and nondisintegrating matrix tablets. According to eq. 5, the stagnant diffusion layer should have a significant effect on the release of drugs with low aqueous solubility; however, the results obtained in this study appear to

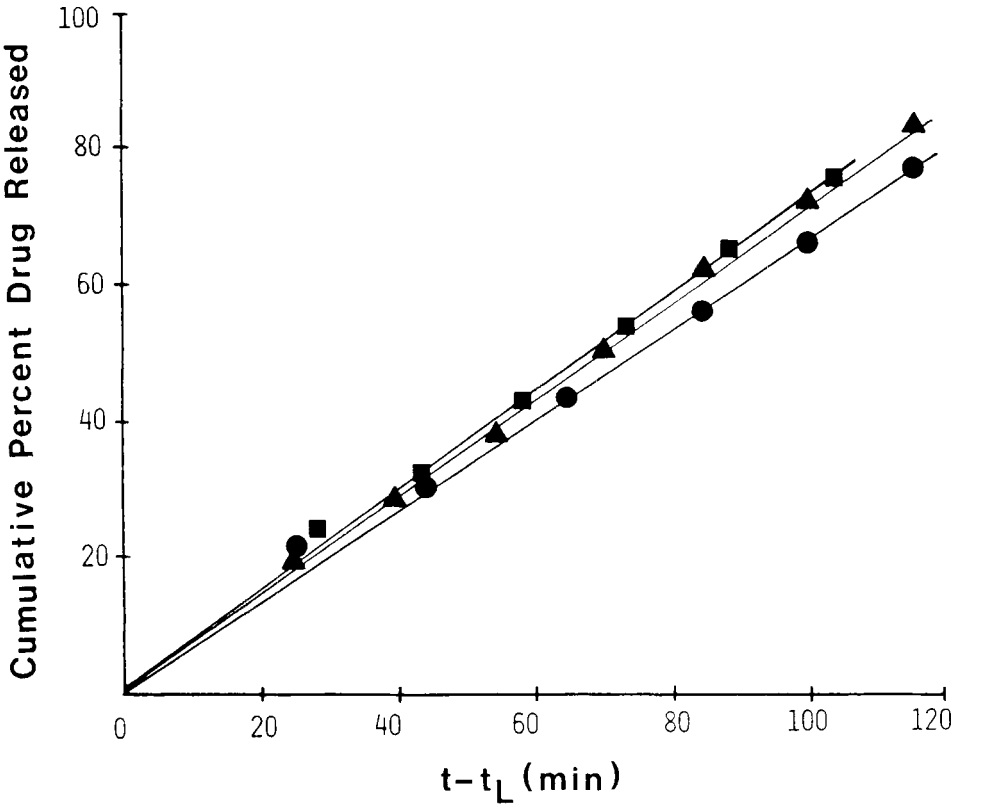

FIGURE 6

Cumulative Percent of Chlorpheniramine Maleate Released from Beads Coated with Eudragit RL:RS in a Ratio of 1:3; Simulated Intestinal Fluid of pH 7.5; Membrane Thickness, 58.8 µm. Key: (■) Agitation Speed, 25 rpm; (▲) Agitation Speed, 50 rpm; (●) Agitation Speed, 100 rpm.

TABLE 9

Computed Release Rate Constant (K) as a Function of Agitation Speed in a Dissolution Medium of pH 7.5. Eudragit RL:RS, 1:3. Membrane Thickness, 58.8 µm

Agitation Speed (rpm)	Release Rate Constant, K[a] (mg/min)
25	0.300 ± 0.004
50	0.301 ± 0.004
100	0.300 ± 0.007

[a] mean ± SD of four determinations

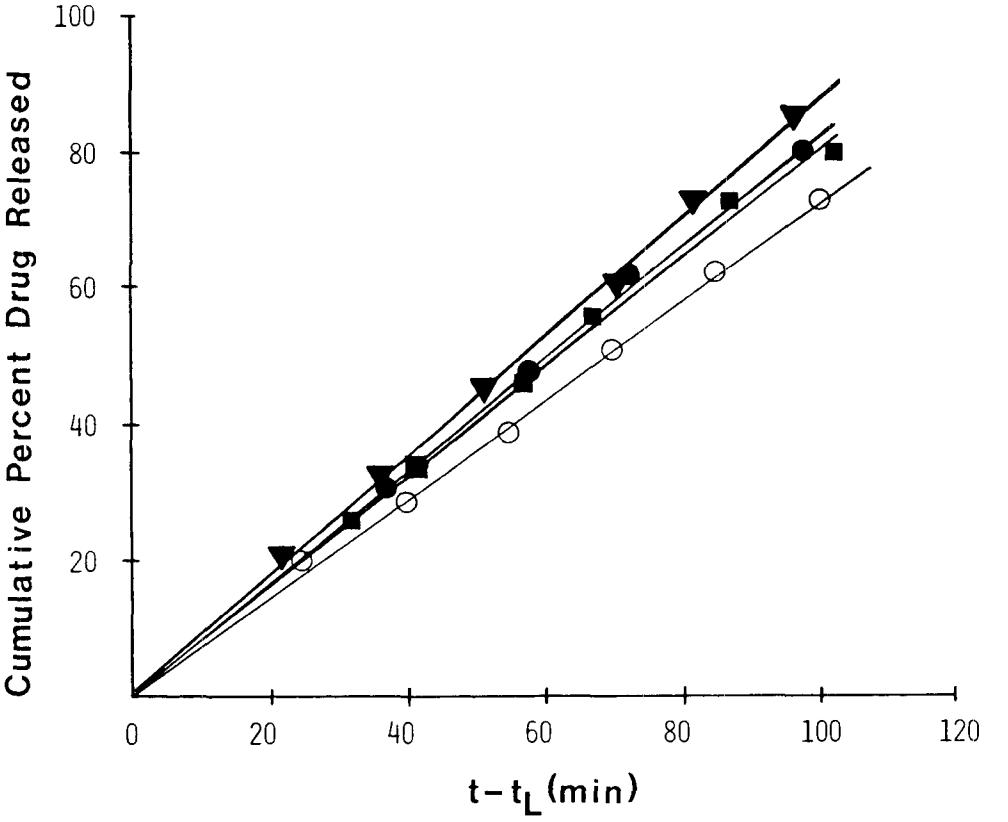

FIGURE 7

Cumulative Percent of Chlorpheniramine Maleate Released from Beads Coated with Eudragit RL:RS in a Ratio of 1:3; Membrane Thickness, 58.8 μm; Agitation speed, 50 rpm. Key: (■) Simulated Gastric Fluid of pH 1.2; (▼) Simulated Gastrointestinal Fluid of pH 4.5; (○) Simulated Intestinal Fluid of pH 7.5; (●) Distilled Water.

indicate that drug transport from coated beads is solely determined by the membrane controlled permeation process, where the effect of the stagnant diffusion layer surrounding the beads is negligible.

Influence of pH on the Release of Drug

An example of the mean profiles obtained in various dissolution media is shown in Figure 7. The computed mean values of the release rate

TABLE 10

Computed Release Rate Constant (K) as a Function of Dissolution Medium pH at an Agitation Speed of 50 rpm Eudragit RL:RS, 1:3. Membrane Thickness, 58.8 μm

Dissolution Medium pH	Release Rate Constant, K[a] (mg/min)
1.2	0.365 ± 0.002
4.5	0.395 ± 0.010
6.8[b]	0.378 ± 0.010
7.5	0.301 ± 0.004

[a] mean ± SD of four determinations

[b] pH of distilled water

constant (K) for the formulations tested are summarized in Table 10. Equation 7 predicts that the drug release from coated beads would depend on the equilibrium solubility (C_s) of the drug. Therefore, for a drug exhibiting pH dependent equilibrium solubility, as observed in this study, it is anticipated that the release of drug would be influenced by the pH of the dissolution media. When the release rate constant (K) was plotted against the equilibrium solubility (Figure 8), a linear relationship was observed. In support of this, there is a study (14) which reports that the release of the drug is influenced by the pH of the dissolution medium when a drug exhibits pH-dependent solubility characteristics. On the other hand, there is also a study (6) in which the release of drug from coated beads was reported to be quite insensitive to pH differences due to pH independent-solubility characteristics of the drug.

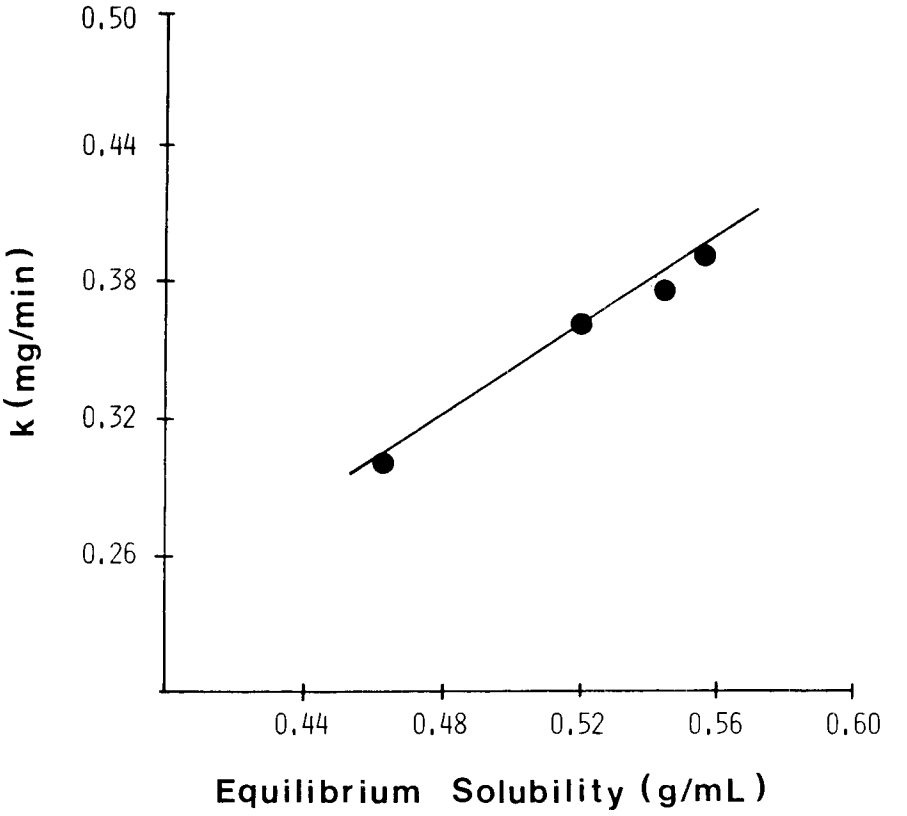

FIGURE 8

The Release Rate Constant (K) Against the Equilibrium Solubility of Chlorpheniramine; Beads Coated with Eudragit RL:RS in a Ratio of 1:3; Membrane Thickness, 58.8 μm; Agitation Speed, 50 rpm.

CONCLUSION

The conclusions based on in vitro dissolution studies clearly show that the fluidized bed technique was found to be very efficient since it offers greater flexibility, a rapid operation process and uniformity of drug and coats on the beads. The results also indicate that the release of the drug can be controlled by formulation factors such as the thickness of the membrane and the type and the concentration of the Eudragit polymer in the

coating fluid. Furthermore, it is clear from the results that the pH of the dissolution media can influence the release of drug only if the drug exhibits pH-dependent solubility characteristics. The results obtained in this study also demonstrate that the transport of the drug from coated beads is determined by a membrane controlled permeation process and the effect of the stagnant diffusion layer surrounding the beads is negligible.

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