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SOME FACTORS INFLUENCING THE RELEASE OF DRUG FROM NONDISINTEGRATING SLOW RELEASE TABLETS

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ABSTRACT

The purpose of this study was to investigate some factors that control the drug release from nondisintegrating cylindrical slow release tablets using sodium salicylate as a model drug. The in vitro release of sodium salicylate was described adequately by a previously published cubic equation. It was found that the release of the drug from a nondisintegrating tablet is controlled by the factors such as porosity (ε) of the tablet and the mass of drug present (A) per unit tablet volume. On the other hand, pH of the dissolution fluid had no influence on the release of sodium salicylate.

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INTRODUCTION

Several methods have been suggested for sustaining drug release over a long period of time (1,2). A physical barrier of some kind is used in the majority of sustained released dosage forms to decrease the rate of drug release to the absorption site. One type of slow release tablet can be prepared by compressing a mixture of polymer and drug (3).

The release of drug from a nondisintegrating tablet has been described by many kinetic theories, some of which apply specifically to slow release matrix tablets. Higuchi (4,5) was the first to derive an expression for the amount of drug released through a unit surface. Dissolution fluid penetrates the matrix and dissolves the drug, which then diffuses out of the tablet.

Any factor in the formulation which influences the penetration of the matrix by the dissolution fluid or the diffusion of the drug out of the matrix will have an effect on the rate of drug release. This begins with the composition of the matrix and includes other factors such as drug solubility, external agitation, mass of drug and porosity of the matrix (6-9).

One objective of this study was to examine, by the use of an appropriate equation, the *in vitro* release characteristics for a drug incorporated in a cylindrical plastic matrix tablet when all surfaces of the tablet are exposed to the dissolution fluid. The second objective was to study the effect of some fundamental parameters such as the initial mass of drug present (A) per unit volume of the tablet and the porosity of the matrix (ε) on the release of the drug from the nondisintegrating cylindrical plastic matrix tablet.

EXPERIMENTAL

Materials

Sodium Salicylate[a], polyvinyl chloride and polyethylene[b], hydrochloric acid and chloroform[c].

Equipment

Carver press[d], flow cell dissolution apparatus (13), spectrophotometer[e], centrifuge[f], pH meter[g] and peristaltic pump[h].

Dissolution Fluids

Three dissolution fluids were prepared: a) 0.1M HCl having a pH of 1.25 ± 0.05 (mean ± SD of 12 batches); b) 0.1M sodium citrate: HCl buffer (10) having a pH of 3.05 ± 0.05 (mean ± SD of 12 batches); c) 0.1M phosphate buffer (11) having a pH of 7.40 ± 0.05 (mean ± SD of 16 batches). The fluids will be referred to as the pH 1.2 fluid, the pH 3.0 fluid and the pH 7.4 fluid, respectively.

Manufacture of Tablets

Sodium salicylate tablets were manufactured as described previously (3); the matrix to drug ratios were 3:2, 4:1, 9:1 and 19:1. The weight and thickness of each tablet were measured and tablets were stored in amber plastic bottles.

Tablet Parameters

The porosity of the tablet matrix (ε) and the mass of drug present per unit tablet volume (A) were determined for each tablet in accordance with published methods (12).

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a. Fisher Scientific Company, Fairlawn, NJ 07410
b. Polysciences, Inc., Warrington, PA 18976
c. Eastman Kodak Company, Rochester, NY 14650
d. Fred S. Carver, Inc., Summit, NJ
e. Beckman Instrument, Inc., Fullerton, CA 92634
f. Dynac Centrifuge, Clay Adams, Division of Becton Dickinson and Co., Parsippany, NJ 07054
g. Orion Research, Inc., Cambridge, MA
h. Cole Parmer Instrument Co., Chicago, IL 60648

Assay

Standard Beer's law curves over a concentration range of 25-100 mg/L were prepared for sodium salicylate in each dissolution fluid by the procedure described by Jambhekar and Cobby (3).

In Vitro Release of Drug from Tablets

Dissolution Test Apparatus. The flow-through cell apparatus was reported by Cobby et al (13). A dissolution fluid rate of 50 mL/min was chosen.

Procedure. The procedure described by Jambhekar and Cobby (3) was used to conduct the release studies.

Calculations. The fraction of drug released at each sample time (f_t) was calculated as the ratio of the mass of drug released to the total drug content of the tablet. The latter is the sum of the cumulative mass of drug released at the last sample time plus the residual content. The fraction of drug released (f_t) was fitted to a cubic equation using the nonlinear regression computer program NONLIN (14):

$$f_t = (q+2)K_r(t^{1/2}-t_o^{1/2}) - (2q+1)[K_r(t^{1/2}-t_o^{1/2}]^2 + q[K_r(t^{1/2}-t_o^{1/2})]^3 \qquad \text{Eq. 1}$$

where q is the measured ratio of tablet diameter to thickness and K_r and t_o are the computer determined rate constant and lag time, respectively. This equation is a modification of that proposed by Cobby et al (15) and takes into account the apparent delay in the appearance of the drug in the dissolution fluid reservoir. The initial estimate of the release rate constant (K_r) was obtained by using an equation proposed by Cobby et al (15):

$$K_r = \frac{1}{qT^{1/2}} \qquad \text{Eq. 2}$$

where T is the estimated time at which complete release (f_t = 1.0) will occur.

RESULTS AND DISCUSSION

Initial Tablet Parameters

The mean porosity of the tablet matrix (ε) and the mass of drug present (A) per unit tablet volume for each formulation are shown in Table 1. Inspection of the table indicates that, as the ratio of matrix:drug increases, the porosity of the tablet matrix (ε) and the mass of drug present (A) per unit volume both decrease.

In Vitro Release of Drug from Tablets

An example of the mean profiles obtained for a matrix:drug ratio of 9:1 in a dissolution fluid of pH 7.4 is shown in Figure 1. Inspection of the profiles suggests that the data were fitted adequately by the cubic equation (Eq. 1). The computed mean values of the release rate constant (K_r) and of the root lag time ($t_o^{1/2}$) for the formulations tested are summarized in Table 2.

The observed release rate constant (K_r) was plotted (Figure 2) against the porosity. In addition, the observed release rate constant was also plotted (Figure 3) against the mass of drug present per unit tablet volume. As can be seen from the example, the observed value of rate constant (K_r) decreases as either the mass of drug present per unit tablet volume or the initial porosity of the tablet matrix decrease. Higuchi (5) showed theoretically that drug release from a planar surface tablet of granular matrix is dependent on fundamental parameters such as porosity (ε), mass of drug present per unit tablet volume (A), tortuosity (τ), equilibrium solubility (C_s)

TABLE 1

Computed Tablet Parameters for Various Tablet Formulations Studied[a]

Matrix:Drug Ratio	pH 1.2		pH 3.0		pH 7.4	
	Porosity (ε)	Mass of Drug/ Unit Tablet Volume (A, g/mL)	Porosity (ε)	Mass of Drug/ Unit Tablet Volume (A, g/mL)	Porosity (ε)	Mass of Drug/ Unit Tablet Volume (A, g/mL)
3:2	0.413 ± 0.002	0.454 ± 0.001	0.407 ± 0.004	0.458 ± 0.001	0.405 ± 0.002	0.458 ± 0.001
4:1	0.226 ± 0.002	0.212 ± 0.000	0.261 ± 0.002	0.213 ± 0.000	0.256 ± 0.004	0.215 ± 0.001
9:1	0.190 ± 0.004	0.103 ± 0.000	0.193 ± 0.004	0.103 ± 0.000	0.194 ± 0.001	0.103 ± 0.000
19:1	0.167 ± 0.004	0.050 ± 0.000	0.166 ± 0.005	0.050 ± 0.000	0.165 ± 0.003	0.050 ± 0.000

[a]values of ε and A are mean ± SD of six determinations.

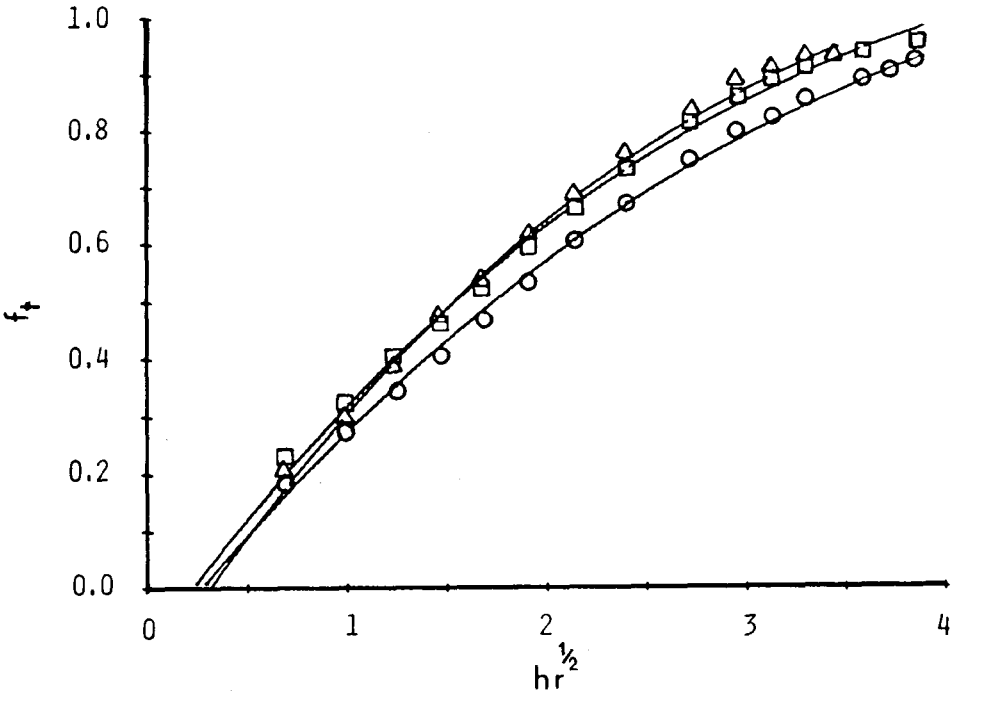

FIGURE 1: Fraction of Sodium Salicylate Released (f_t) from Tablets Having Matrix:Drug Ratio of 9:1. Flow Rate, 50 mL/min. Key: (△), Dissolution Fluid pH 1.2; (□), Dissolution Fluid pH 3.0; (○), Dissolution Fluid pH 7.4.

of the drug and the diffusion coefficient. It has been reported (3) that sodium salicylate release from a nondisintegrating plastic matrix is independent of the pH and the flow rate of the dissolution fluid. The diffusion coefficient of a drug being a constant, porosity (ε), tortuosity (τ) and the mass of drug present per unit tablet volume are the only parameters to control the release of drugs from such a plastic matrix tablet. The results obtained in this study are in agreement with other reports (6-9). Although

TABLE 2

Computed Release Rate Constant (K_r) and Root Lag Time ($t_o^{1/2}$) as a Function of Dissolution Fluid pH[a]

	pH 1.2		pH 3.0		pH 7.4	
Matrix:Drug Ratio	K_r, $hr^{-1/2}$	$t_o^{1/2}$, $hr^{1/2}$	K_r, $hr^{-1/2}$	$t_o^{1/2}$, $hr^{1/2}$	K_r, $hr^{-1/2}$	$t_o^{1/2}$, $hr^{1/2}$
3:2	0.157 ± 0.006	0.259 ± 0.015	0.164 ± 0.009	0.071 ± 0.032	0.170 ± 0.008	0.030 ± 0.012
4:1	0.116 ± 0.003	0.341 ± 0.014	0.105 ± 0.003	0.111 ± 0.055	0.102 ± 0.001	0.094 ± 0.017
9:1	0.101 ± 0.001	0.276 ± 0.086	0.094 ± 0.002	0.226 ± 0.031	0.084 ± 0.001	0.271 ± 0.016
19:1	0.082 ± 0.001	0.354 ± 0.019	0.081 ± 0.002	0.409 ± 0.029	0.076 ± 0.001	0.478 ± 0.045

[a]values of K_r and $t_o^{1/2}$ are mean ± SD of six determinations.

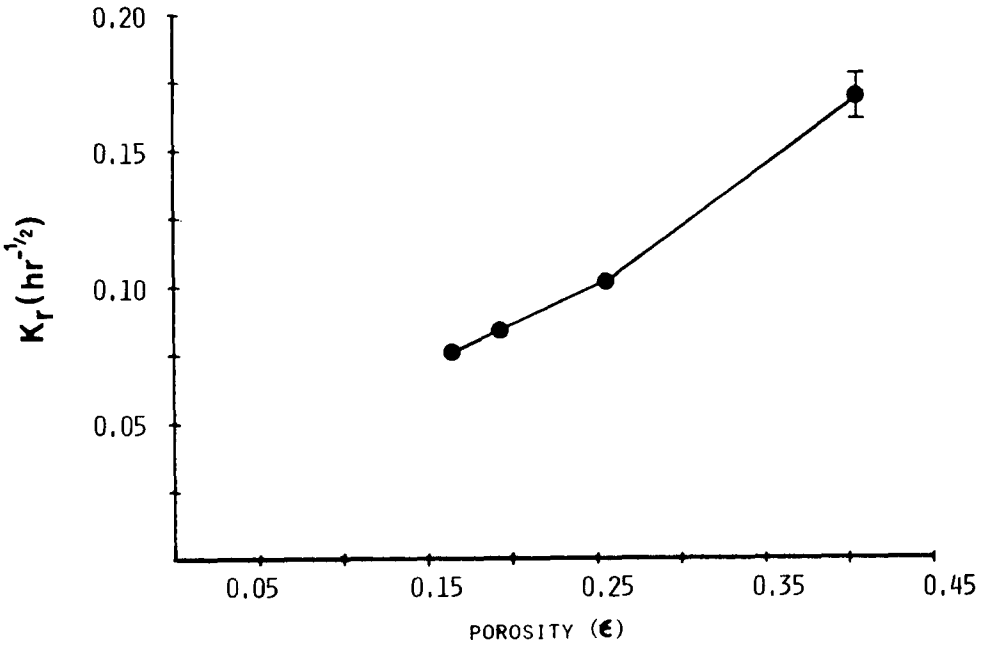

FIGURE 2: A Plot of the Release Rate Constant (K_r) Against the Porosity of the Matrix (ε) for Sodium Salicylate Tablets. Flow Rate 50 mL/min. pH of the Dissolution Fluid 7.4. Mean ± SD of 6 Determinations.

the release of drug was found to vary directly with the mass of drug (A) per unit tablet volume and with the porosity (ε) of the matrix, no linear relationship was observed between the rate constant and parameters investigated.

In vitro performance does not always assure in vivo performance; however, in most instances, factors influencing the release of drug are used for evaluating potential drug formulations. If the release of a drug is pH and flow rate independent as reported previously for sodium salicylate (3), then factors such as porosity and tortuosity of the matrix and

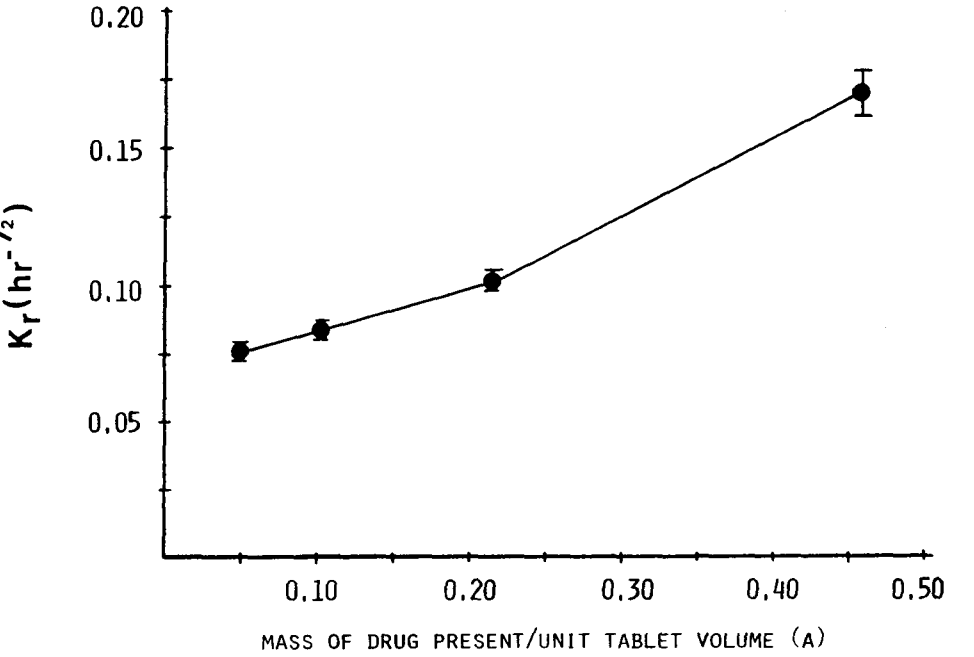

FIGURE 3: A Plot of the Release Rate Constant (K_r) Against the Mass of Drug Present Per Unit Tablet Volume (A) for Sodium Salicylate Tablets. Flow Rate 50 mL/min. pH of the Dissolution Fluid 7.4. Mean ± SD of 6 Determinations.

the mass of drug present per unit tablet volume may become more critical in controlling the release of drug from such matrix formulations.

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