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PROLONGED RELEASE OF THEOPHYLLINE FROM AQUEOUS SUSPENSIONS

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ABSTRACT

The dissolution of theophylline from aqueous suspensions was measured by the U.S.P. paddle method. Theophylline release was retarded in the presence of xanthan gum, 1%, sodium alginate, 0.5%, and equi-weight mixtures of gelatin type B and iota carrageenan, 1%. These suspensions formed gels _in situ_ in Simulated Gastric Fluid, U.S.P. Diffusion cell studies suggested that theophylline transport within the formed matrix was due to diffusion through immobilized liquid water. Evidence in support of a diffusion controlled dissolution mechanism in these systems were linearity of the initial section of plots of dissolution against the square route of time, the lack of effect of theophylline particle size on dissolution rate, and the tendency for release from a particular system to become independent of polymer concentration once a sufficiently high concentration was reached.

INTRODUCTION

Theophylline is widely used in the treatment of asthma and other respiratory diseases. Liquid dosage forms are needed for the treatment of the many children and adults who find it difficult to swallow a tablet or capsule. Commercially available liquids are usually hydroalcoholic solutions or aqueous suspensions, the latter having the therapeutic advantage of eliminating alcohol from the formulation.

Although theophylline is a valuable, widely-prescribed entity, it has a narrow therapeutic range, generally considered to be 10 to 20 µg/mL (1). In a study of serum level versus toxicity in 87 patients, it was found that 81 percent of those with serum levels from 20 to 29.9 µg/mL showed at least one toxic symptom. Four patients in the study had seizures associated with serum levels over 40 µg/mL (2).

Theophylline is rapidly absorbed and eliminated. Following administration of a nonalcoholic liquid preparation to normal adult human subjects, the absorption half life was 0.27 +/- 0.07 hr; serum elimination half life values of 6.19 +/- 0.31 hr were obtained in the same study (3).

Rapid absorption and elimination, combined with the small separation between minimally effective therapeutic blood levels and those that result in undesirable side effects make frequent administration of carefully controlled doses necessary. Sustained release dosage forms help to lower the potential for untoward effects and to permit less frequent dosing by maintaining blood levels in the therapeutic range for periods longer than is attainable following administration of a single dose.

Barzegar-Jalali and Richards (4) determined the effect of several polymers on bioavailability of aspirin from suspensions, in rabbits. They found that both peak blood concentration and area under the blood-time curve from 0 to 9 hours were proportional to the logarithm of apparent viscosity at a shear rate of 100 sec^{-1}. An increase in viscosity enhanced aspirin absorption, apparently because of prolongation of stomach residence time of the acidic drug.

For drugs better absorbed from the small intestine than the stomach, the same effect may result in a retardation of absorption. Polymer-drug complexation (5) and slowed dissolution resulting from high bulk viscosity (6) are other factors that could be responsible for a reduction in absorption rate.

Our goal was to design prototype liquid suspensions of theophylline that change into a gel matrix upon entering the acidic gastric fluid environment, which has been reported as being under mild agitation (7, 8). Theophylline dissolution would then be slowed because of the imposition of a diffusion step within the series of transfers leading to the appearance of dissolved drug in the stomach. In other words, the dissolution rate (hence the in vivo absorption rate) would be limited by diffusion through the gel matrix. In this study, several polymer systems were evaluated as potential agents for promoting in situ gel formation. Diffusion and dissolution studies were used to determine polymer effectiveness and verify the principal mechanism of polymer action.

EXPERIMENTAL

Materials

Theophylline anhydrous (Eastman Kodak, Rochester, New York), xanthan gum (Kelco SS-4749, Kelco Division of Merck and Company, San Diego, California), sodium alginate (Kelgin-F, Kelco Division of Merck and Company, San Diego, California) iota carrageenan (Gelcarin DG, Marine Colloids Division of FMC Corporation, Springfield, New Jersey), and gelatin type B (Pharmagel B, Ruger Chemical Company, Irvington, New Jersey) were used as received. Other materials were U.S.P. grade.

Suspension Preparation

Theophylline suspensions that did not contain gelatin and carrageenan were made by adding the proper weight of theophylline anhydrous powder to a tared glass jar containing the required weight of distilled water preserved with 0.25% w/w chlorobutanol. After forming an aqueous slurry of the theophylline, powdered polymeric excipients were slowly added with agitation by a counter-rotating mixer (Brookfield Engineering, Stoughton, Massachusetts) until a fine dispersion was formed. Then the cap was screwed on and the jar stored at 4°C overnight or until used.

For suspensions containing gelatin and carrageenan, anhydrous theophylline powder was slurried in preserved distilled water; carrageenan then was added and dispersed using a counter-rotating mixer. The required weight of gelatin was added to preserved water, heated to 75-85°C. The gelatin and carrageenan mixtures were then combined with alternate mechanical stirring and hand shaking. Hard, lumpy aggregates that formed were eliminated by passing the entire batch through a hand homogenizer.

Dissolution Testing

Standard U.S.P. Teflon-coated stainless steel paddles and glass round bottom beakers were utilized. Stirring speed was maintained constant by commercial feedback control circuitry at 50 rpm. This speed was slow enough to avoid breaking up the gelled suspension sample and was in keeping with the mild agitation conditions believed to exist *in vivo*. However, it was rapid enough to make the concentration of dissolved theophylline uniform throughout. The dissolution medium consisted of 1000 mL of Simulated Gastric Fluid U.S.P., without enzyme, kept at 37°C in a water bath equipped with a heater-circulator.

Prewarmed, de-aerated suspension was drawn up into a 0.27 cm inner radius glass tube using an attached 3 mL disposable syringe joined by a segment of plastic tubing. Two mL of suspension were drawn up, the tube was wiped clean and excess suspension removed from the tube end. Next the tube end was placed into the dissolution medium and the syringe plunger depressed slowly to extrude one mL; the suspension was cut off from the tube end with a razor blade.

At each time interval, a precisely measured sample of the dissolution medium was removed and diluted to bring the theophylline concentration into the linear range of the standard calibration curve. Absorbance of theophylline was measured at 272 nm using a single beam spectrophotometer. The precise amount of theophylline in the suspension sample was determined at the end of the dissolution experiment by stirring vigorously to dissolve all of the theophylline and measuring the absorbance. Interference from the excipients was negligible. Drug concentration in the beaker never exceeded one percent of solubility, maintaining a sink condition. These experiments were conducted in duplicate or triplicate.

Diffusion Studies

The lower receptor compartments from two Franz-type diffusion cells (Crown Glass, Somerville, New Jersey) were clamped together to form a two-chambered horizontal cell (Figure 1). The receptor chamber was stirred by a small magnetic stir bar mounted at the end, as shown in the figure. A 1.2 µm filter membrane separated the donor compartment, which contained the unstirred suspension, from the stirred receptor compartment. The temperature of circulating water was maintained at 37.0°C by a thermostat.

Prewarmed, de-aerated samples of suspension were loaded into the donor chamber of the diffusion cells using a syringe with thin plastic tubing attached. The receptor consisted of Simulated Gastric Fluid U.S.P. without enzyme. For receptor fluid sampling, a plastic catheter attached to an 18 gauge needle was used. The receptor fluid was removed frequently and replaced with the same volume to maintain sink conditions. The analytical procedure was the same as that for the dissolution studies. After two to three hours of release study progress, the donor cell was disassembled and its suspension contents were extruded by air at low pressure to allow measurement of the depletion zone

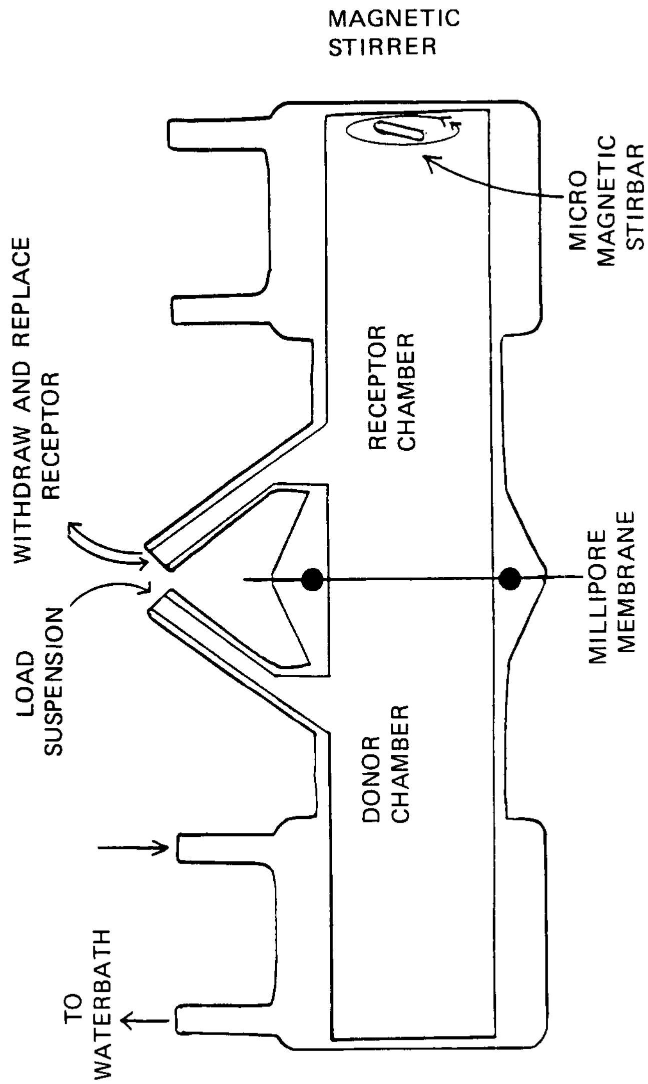

FIGURE 1. Diagram of diffusion cell setup. (From D. W. Woodford, Ph.D. Thesis, Rutgers University, 1983).

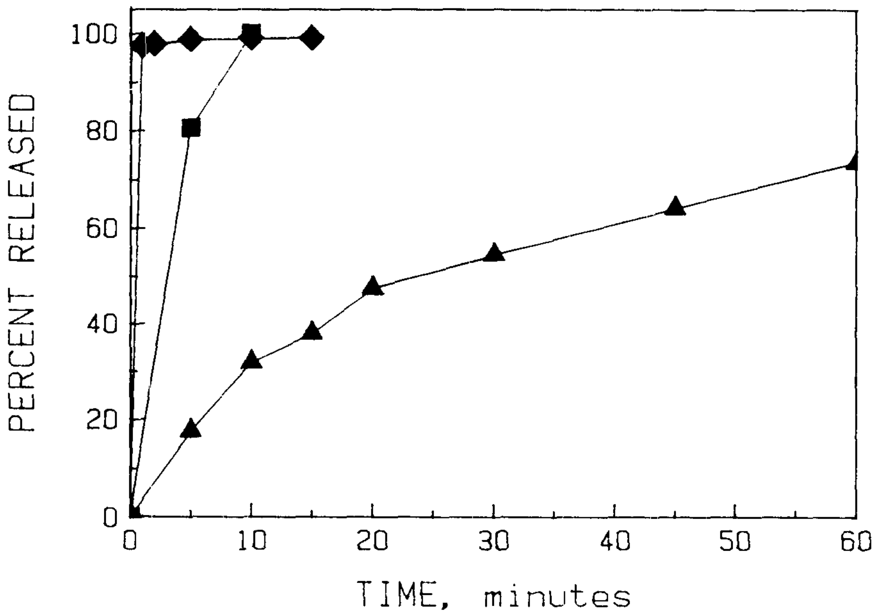

FIGURE 2. Effect of various concentrations of xanthan gum on release of theophylline from 4% suspensions, paddle method at 50 rpm. ● No xanthan gum; ■ 0.3% ▲ 1%.

thickness. These experiments were conducted in duplicate.

RESULTS AND DISCUSSION

Figure 2 contains dissolution profiles for theophylline from 4% suspensions containing various concentrations of xanthan gum. Dissolution of theophylline from suspensions containing no gum was extremely rapid; most of the drug went into solution in less than one minute. Dissolution was not significantly delayed in the presence of 0.3% of the gum (Figure 2, Table 1) despite the large elevation

TABLE 1

Time Required for Dissolution of 50% of the Theophylline Present in Suspensions Containing 4% Theophylline and Various Polymers.

Polymer	t50% (minutes)
None	<1
Xanthan gum, 0.3%	<5
Xanthan gum, 1%	25
Sodium alginate, 0.5%	31
Sodium alginate, 1%	39
Sodium alginate, 1.5%	40
Sodium alginate, 3%	45
Gelatin-carrageenan, 0.6%	15
Gelatin-carrageenan, 1%	25
Gelatin-carrageenan, 3%	23

in viscosity that took place at this concentration (9). A xanthan gum concentration of 1% was required to materially slow dissolution.

Aqueous xanthan gum dispersions exhibit a gel-like state whose resistance to breakdown by shear depends on gum concentration (9). This property, rather than any effect on bulk viscosity, is responsible for the delay in dissolution that takes place in xanthan gum formulations.

Dissolution experiments were conducted on 4% theophylline suspensions based on sodium alginate. This material becomes insoluble in water below pH 4 and it was observed that the formulation bolus formed a rubbery surfaced "capsule" when the suspension came into contact with the acidic dissolution medium. Inclusion of 0.5% alginate in the suspension resulted in a significant reduction in the dissolution rate of theophylline (Figure 3). Further increases in polymer concentration reduced the release rate of theophylline slightly (Figure 3, Table 1).

In several experiments, calcium salts were added to the suspensions to enhance the strength of the alginate matrix gel formed. There was no significant effect of calcium, either in the dissolution medium or in the suspension, on drug release in these experiments.

The gelatin/carrageenan combination was chosen for study because the carrageenan retains its negative charge over a large pH range due to the strongly ionized sulfate groups on the molecule whereas the gelatin, having an isoelectric point of 5.5, varies in net molecular charge depending on the pH. This permits preparation of a fluid suspension or solution at neutral pH, at which point both polymers have a net negative charge. Reduction of the pH to that of gastric fluid converts the gelatin to the cationic form, resulting in mutual precipitation of the polymers and production of a gel matrix. In our experiments, a one to one weight ratio was selected because of approximate stoichiometric equivalence of the polymers at that ratio. Maximal delay in dissolution occurred when the total gelatin/carrageenan polymer concentration was 1.0% or more (Figure 4, Table 1). Separate suspensions that varied in the average particle size

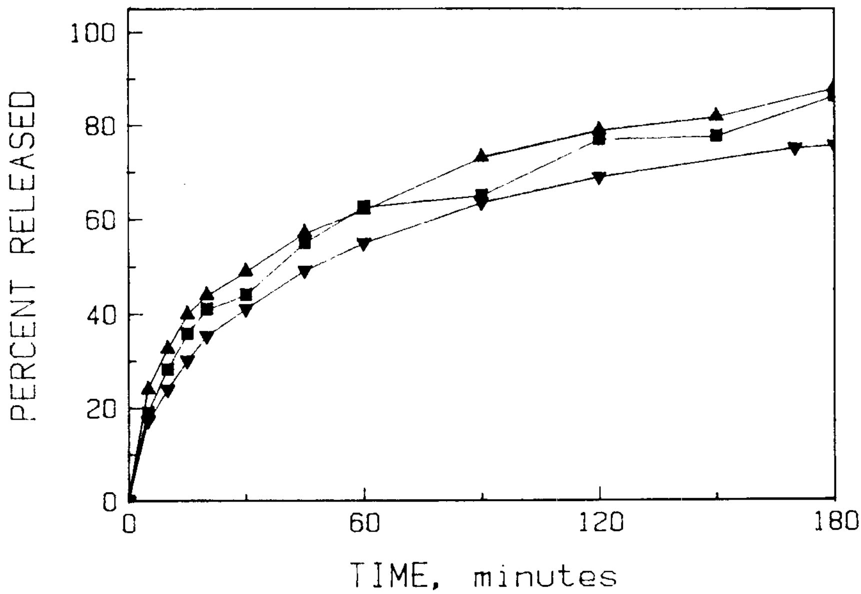

FIGURE 3. Effect of various concentrations of sodium alginate on release of theophylline from 4% suspensions, paddle method at 50 rpm. ▲ 0.5%; ■ 1%; ▼ 3%.

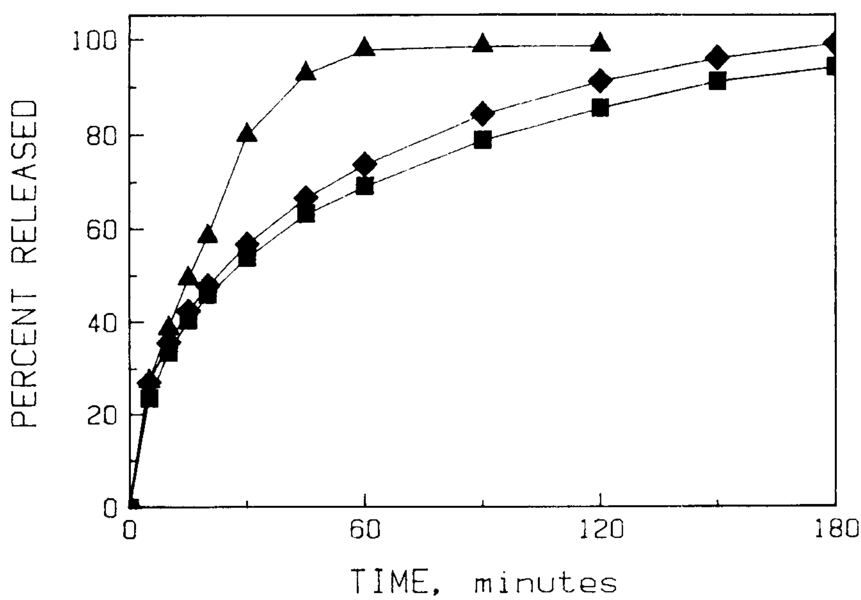

FIGURE 4. Effect of various concentrations of gelatin/carrageenan, 1:1, on release of theophylline from 4% suspensions, paddle method at 50 rpm. ▲ 0.6%; ■ 1%; ◆ 3%.

of theophylline were prepared. There was essentially no difference in the respective dissolution profiles.

Significant retardation of drug release from all of these suspensions depended on the formation of a cohesive, non-disintegrating mass. From visual observations made during conduct of dissolution experiments, the liquid to gel transformation appeared to be instantaneous at the liquid/formulation boundary, with the result that the fluid interior of the suspension was immediately trapped within an enclosing membrane. In the case of shear rate dependent gelation (xanthan gum formulations), the entire fluid appeared to solidify immediately upon termination of shear after delivery of the formulation bolus to the dissolution vessel. With the other systems, the gelled layer thickness increased with time until the entire liquid mass was converted into a gel, apparently as a result of hydronium ion diffusion from the medium. Drug concentration in the dissolution medium slowly increased with time as drug diffused from the formulation mass, which substantially retained its original shape and volume.

The lack of effect of theophylline particle size on release rate and the tendency of release rates to approach a limiting value with increasing polymer concentration for each effective polymer system are in agreement with a release mechanism based on diffusional transfer following *in situ* gel formation. In an effort to further verify the diffusional release mechanism, additional dissolution experiments were conducted, along with measurements of theophylline diffusion from corresponding formulations under

controlled conditions. Because our initial set of suspensions based solely on sodium alginate sedimented rapidly, the new alginate formulations contained xanthan gum 0.3% to eliminate this problem.
The same xanthan gum concentration was included in the systems made with combinations of carrageenan and gelatin to retard sedimentation and improve gel characteristics.

The cumulative amount released to the receptor chamber was plotted against the square root of time. Typical results, for suspensions containing theophylline, 4%, sodium alginate and xanthan gum, are shown in Figure 5. Following an initial curved region resulting from the combined resistance of the membrane and the gel matrix, the plots became linear as diffusion through the gel was essentially rate limiting.

We determined the solubility of theophylline in Simulated Gastric Fluid U.S.P. at 37°C to be 11.1 mg/mL. For systems containing theophylline, 10 mg/mL, the diffusion coefficient, D, was calculated from Eq. 1, a rearrangement of the equation for diffusion from a solution into a sink which applies until about 30% of the drug has been released (10).

$$D = \frac{M^2 \pi}{4 A^2 C^2} \qquad (1)$$

In this equation, M represents the slope of a plot of amount released vs. the square root of time, A is the surface area and C is the initial theophylline concentration. At higher concentrations, the theophylline was in suspension and the equation

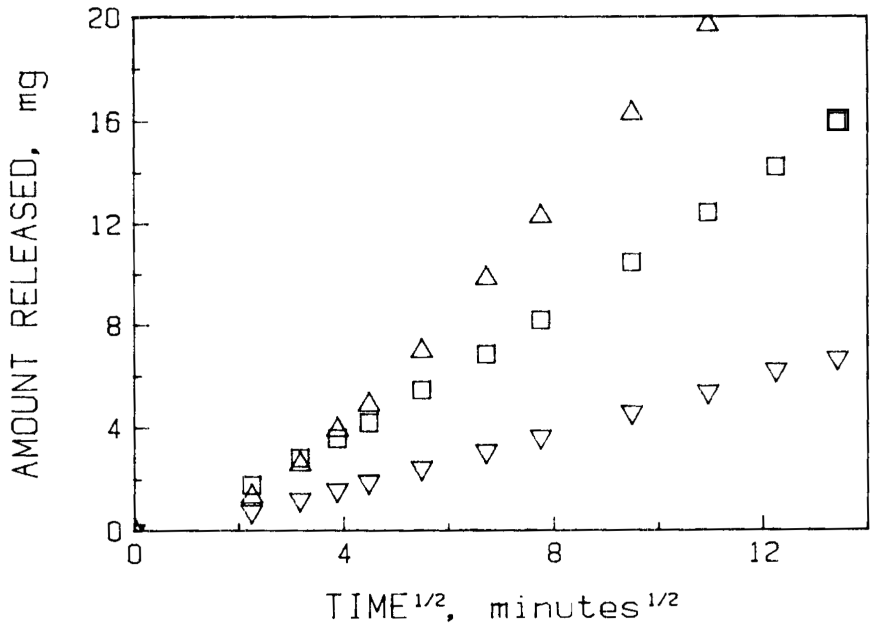

FIGURE 5. Release of theophylline in diffusion cell from gels containing sodium alginate, 1%, xanthan gum, 0.3% and various concentrations of theophylline. ▽ 1%; □ 4%; △ 8%.

describing release from a suspension into a sink (11) was rearranged to yield Eq. 2.

$$D = \frac{M^2}{A^2 (2C - S) S} \tag{2}$$

Here, S represents theophylline solubility while the other symbols have the same meaning as above.

Values for the calculated diffusion coefficients are listed in Table 2. The mean was 9.36×10^{-6} cm^2/sec, with a standard deviation of 2.09×10^{-6} cm^2/sec.

TABLE 2

Diffusion Coefficient for Theophylline Calculated From Diffusion Cell Experiments.

Polymer(s)	Diffusion Coefficient x 10^6 (cm^2/sec)		
	Theophylline Concentration		
	1%	4%	8%
Xanthan gum 1%	6.88	9.64	9.52
Sodium alginate 1% xanthan gum 0.3%	9.26	9.48	13.5
Gelatin 0.3% carrageenan 0.3% xanthan gum 0.3%	10.6	6.26	9.10

There was no trend with respect to either concentration or formulation.

Upon completion of the diffusion experiments the cells were disassembled. A clear depletion zone below the membrane surface was evident for every suspension. The alginate and gelatin-carrageenan suspensions had gelled to a much greater depth (about 13-15 times that of the depletion zone) indicating that hydronium ion diffused in much more rapidly than theophylline diffused out. At the low concentrations of polymer in these systems, interference of polymer strands with theophylline transport was calculated to reduce diffusivity by no more than 1%. The diffusion coefficient for the drug therefore represents that through acidified, immobilized water.

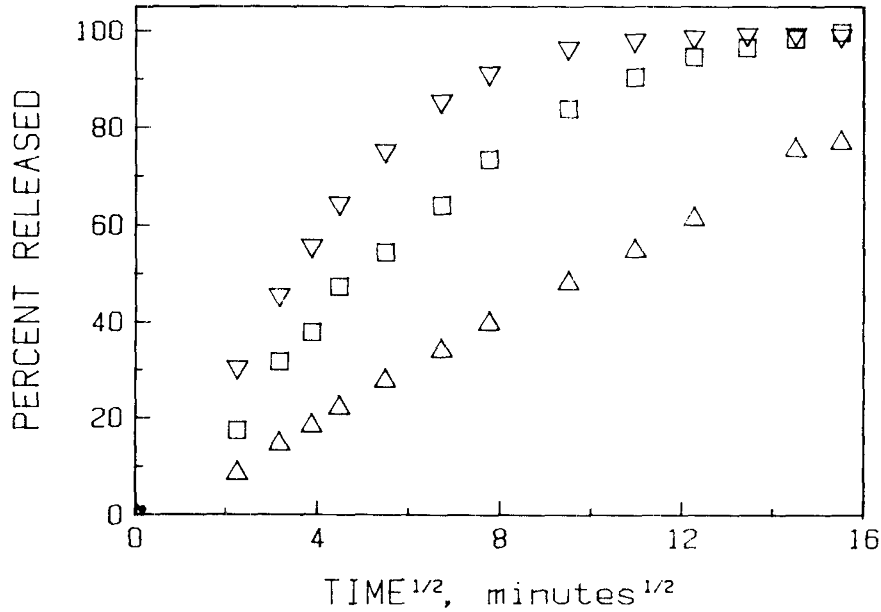

FIGURE 6. Release of theophylline from suspensions containing 1% xanthan gum and various concentrations of theophylline, paddle method, 50 rpm. ▽ 1%; □ 4%; △ 8%.

Dissolution of theophylline from suspensions with the same composition as those studied in the diffusion experiments were evaluated by the paddle method. Results are shown in Figures 6-8. Plots of amount released as a function of the square root of time were linear at first and then began to curve downward. This behavior is expected for release of drug from a cylindrical or spherical homogeneous matrix (12, 13). For up to approximately 25 to 30% released, the release data are well described by the simpler homogeneous slab matrix model, which predicts a linear relationship between amount released and the square root of time.

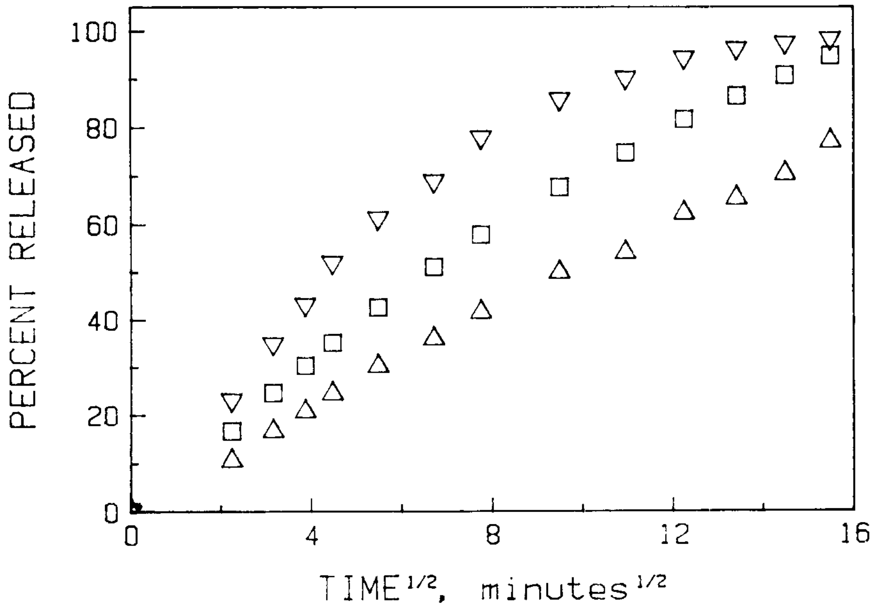

FIGURE 7. Release of theophylline from suspensions containing 1% sodium alginate, 0.3% xanthan gum and various concentrations of theophylline, paddle method, 50 rpm. ▽ 1%; □ 4%; △ 8%.

Several factors, in addition to theophylline concentration, affect the release rate. These include the shape of the matrix in the diffusion vessel, which determines the effective surface area. Alginate suspensions tended to form a spherical matrix, while the other systems produced more elongated shapes with a higher surface area. Syneresis, which has been observed in gelatin and alginate gels (14, 15) would result in contraction of the gel along with an increase in the theophylline concentration within. The increase

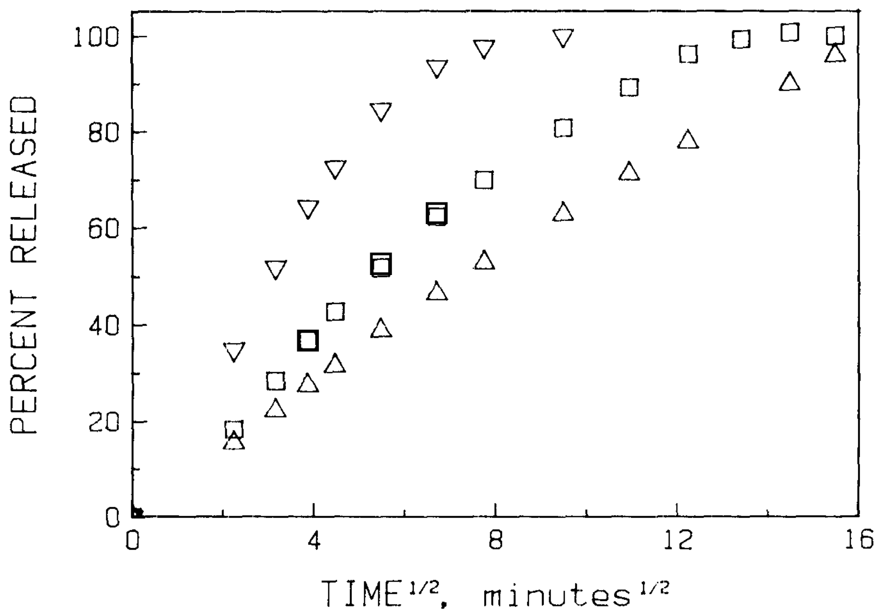

FIGURE 8. Release of theophylline from suspensions containing 0.3% each of gelatin type B, carrageenan and xanthan gum, paddle method, 50 rpm. ▽ 1%; □ 4%; △ 8%.

in concentration is proportional to the decrease in volume; however, the initial release rate is approximately proportional to the square root of concentration. At the same time, the surface area of the matrix, to which release rate is proportional, would decrease by about the 2/3 power of the change in volume. Both factors work in opposite directions, so that a small amount of syneresis would probably not affect the dissolution curve significantly.

CONCLUSIONS

Several theophylline suspensions exhibited *in situ* gelatin upon introduction into Simulated Gastric Fluid U.S.P., without pepsin. Gelation mechanisms include shear dependent "soft gel" formation (xanthan gum), polymer precipitation (sodium alginate) and mutual precipitation of oppositely charged polymers (gelatin-carrageenan). The rate of drug release, which is controlled by diffusion through immobilized water, is reduced in the presence of these polymers. These *in vitro* studies indicate that preparation of aqueous theophylline suspensions with prolonged release characteristics is feasible. The results of *in vivo* investigations will be reported subsequently.

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