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XANTHAN GUM AND ALGINATE BASED CONTROLLED RELEASE THEOPHYLLINE FORMULATIONS

M. Fu Lu, L. Woodward, S. Borodkin

Pharmaceutical Products Division
Abbott Laboratories
1401 Sheridan Road
North Chicago, IL 60064

ABSTRACT

The oral absorption of theophylline from two sustained release formulations, formulated using xanthan gum or sodium alginate, has been investigated in the beagle dog. A commercial product was used for comparison. Dissolution tests and an *in vivo* dog study both indicated that the xanthan gum tablet released drug at a constant rate and performed as a pH independent zero-order controlled release formulation. With the alginate tablet, faster dissolution rates were observed when acid medium was present. The pH dependent release behavior of the alginate formulation is explained. Drug release mechanisms which are influenced by the gel behaviors in these two polymers are discussed. The relative oral bioavailabilities of these two formulations in dog were 74-84% compared to immediately releasing capsules, and three-fold that of the commercial product with an equivalent dose.

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INTRODUCTION

Several sustained release oral theophylline preparations have been developed for twice-a-day or once-a-day administration (1-3). Extensive information is available for controlled release theophylline dosage forms compared to other drugs. Oral delivery of theophylline is complicated by its critical plasma concentration range, potential incomplete absorption, relative short elimination half life and occasional poor GI tolerance (4).

In the present study theophylline was used as a model drug to investigate two controlled release formulations based on hydrogels, xanthan gum and sodium alginate. The beagle dog was selected for the *in vivo* phase as a good animal model for bioequivalency of and pharmacokinetic studies of controlled release theophylline dosage forms (5-7).

Xanthan gum and sodium calcium alginate, selected in the current study, are high molecular weight biosynthetic polysaccharides produced in a pure culture fermentation process and are extraordinarily enzymatically resistant. They offer potential utility as drug carriers because of their inertness and biocompatability. Broad applications and usages of alginate have been studied. Entrapment for cells within calcium alginate spheres has become the most commonly used technique of immobilizing living cells (8,9). A number of controlled drug release alginate systems were studied, such as gentamicin implants (10), pilocarpine ophthalmic film (11), and sulfadiazine tablets (12). Xanthan gum has received less attention in drug delivery research, but has been frequently used in the aqueous suspension

formulations. Each of these polymers has the ability to potentially increase the stomach retention time through bioadhesion (13,14) or swelling to an enlarged size.

A number of studies have discussed gel swelling controlled release from hydrogel drug delivery (15-17), and how drug-polymer interactions, drug solubility and additives can complicate the release kinetics (18,19). The pH as well as other physical and chemical variables in solution have different effects on the gel properties of xanthan gum and sodium alginate, which are termed major factors in controlling the drug release mechanism. Xanthan gum is compatible with virtually all salts, and solution pH and temperature have very little effects on the viscosity of its gel. In contrast to xanthan gum, the gel rheological properties of alginate are highly dependent on pH and types of ion present in solution. The main interest of the present work was to investigate whether theophylline hydrogel matrix formulations could provide controlled or sustained release, and identify whether the *in vitro* release could be correlated to *in vivo* kinetics. In order to prepare a uniform drug-polymer matrix, a compressed tablet dosage form was chosen for convenience. The information may also be applicable to design other solid dosage forms for theophylline or other drugs depending on their pharmacokinetic patterns.

EXPERIMENTAL

Materials - Theophylline anhydrous USP, was purchased from Aldrich Chemical Co. Xanthan gum (Keltrol) and sodium calcium alginate

(Kelcosol), were gifts from Kelco Company. Theo-24 capsules (G.D. Searle and Co., Lot 983-603) were purchased.

Tablet Preparation - Uniformly blended polymer and drug mixtures were compressed to 5/8" diameter round tablets using a laboratory press (Carver Press Model C). A constant pressure of 4000 lb was applied during compression. Tablets contained 50% polymer and 50% theophylline base.

In Vitro Release Test - Release of theophylline was determined using USP apparatus 2 at a stirring rate of 50 rpm. The 900 ml of dissolution fluid was maintained at 37(± 0.5)°C. Samples were collected by pipet at half hour intervals over a ten hour period, and analyzed spectrophotometrically with an HP 8451A Spectrophotometer at 272 nm. Hydrochloric acid (0.1 N) and potassium phosphate buffer (0.05M, pH 6.8) were used as dissolution media.

Dog Study Design - Three male beagle dogs, weighing 7-8 kg, were involved in the entire study. Initially, each dog was orally administered a gelatin capsule containing 125 mg of unformulated theophylline base. Subsequently, three formulations; (1) tablet containing 250 mg theophylline and 250 mg of Keltrol, (2) tablet containing 250 mg theophylline and 250 mg Kelcosol, and (3) commercial controlled release capsule (Theo-24) containing 250 mg of theophylline were administered to these dogs. The test was a three way cross over design with one week dosing interval. All

dogs were fasted over night for about 18 hours prior to dosing. Blood samples were taken through jugular vein and collected into heparinized tubes at 1, 2, 3, 4, 5, 6, 8, 10, 15 and 24 hours post-dosing. Plasma samples were separated and analyzed for theophylline using a fluorescence polarization immunoassay procedure (TDx system from Abbott Laboratories, Diagnostics Division, North Chicago, IL.)

Data Analysis - Area under plasma concentration time curve, AUC, was calculated using the trapezoidal rule. C_{max} was defined as the maximum observed theophylline concentration and T_{max} the time corresponding to C_{max}. In the event the maximum theophylline level was relevant at more than one time point, the T_{max} was defined as the first occurrence of this measurement. Cumulative absorption plots for sustained release formulations were obtained using the Wagner-Nelson method (20). The first-order elimination rate constant used in these computations was the mean elimination rate observed in the same 3 dogs after the oral administration of a single 125 mg dose of immediately released theophylline capsule. The elimination rate was calculated using the one-compartment open model method.

RESULTS

In Vitro Release Study - Figure 1 plots cumulative percentage of theophylline released against time. The results clearly indicated different dissolution characteristics for the xanthan gum and alginate formulations. Zero-order release was observed with

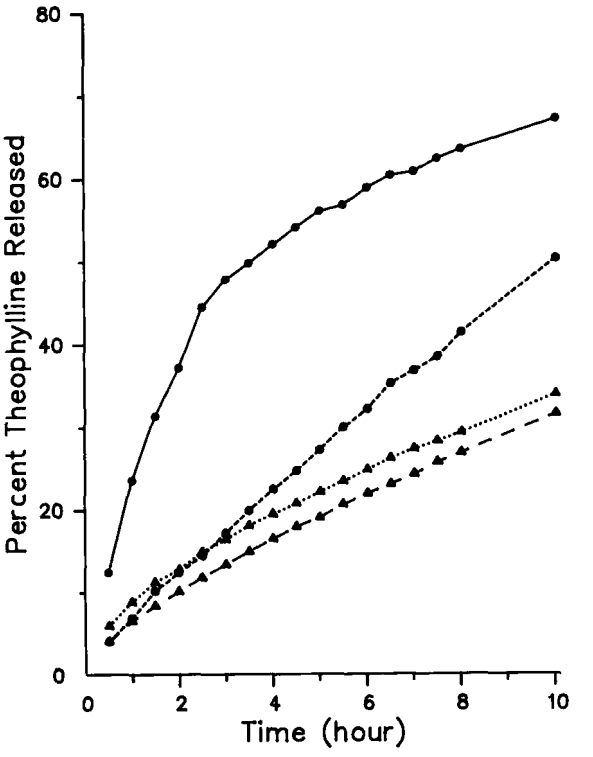

FIGURE 1

Mean dissolution profiles for two controlled release theophylline formulations at 37°. key: xanthan gum tablet (▵) in 0.1 N HCl; (▲) in pH 6.8 buffer; alginate tablet (○) in 0.1 N HCl; (●) in pH 6.8 buffer

xanthan gum tablets in both the 0.1N HCl and pH 6.8 media. The data were subjected to linear regression analysis and the dissolution rates and the correlation coefficients were calculated and shown in Table I. The pH had no effect on the xanthan gum formulation, in terms of dissolution rates or kinetic patterns.

In contrast, the solution pH had a great effect on the dissolution profiles of alginate tablets. A constant average release rate of 5.2 %/hr, was calculated in pH 6.8 phosphate

Table I

In Vitro Zero-Order Release Rates of Theophylline from Xanthan Gum and Alginate Tablets (N=3), in 0.1 N HCl and pH 6.8 Buffer, at 37°C

Formulation		0.1 N HCL Mean (range)	pH 6.8 Buffer Mean (range)
Xanthan Gum Tablet	Ko (%/hr)	2.8 (2.2-3.6)	2.6 (1.7-4.1)
	r	0.970 (0.951-0.986)	0.973 (0.945-0.988)
Alginate Tablet	Ko (%/hr)	- -	5.2 (4.2-6.5)
	r	- -	0.975 (0.956-0.990)

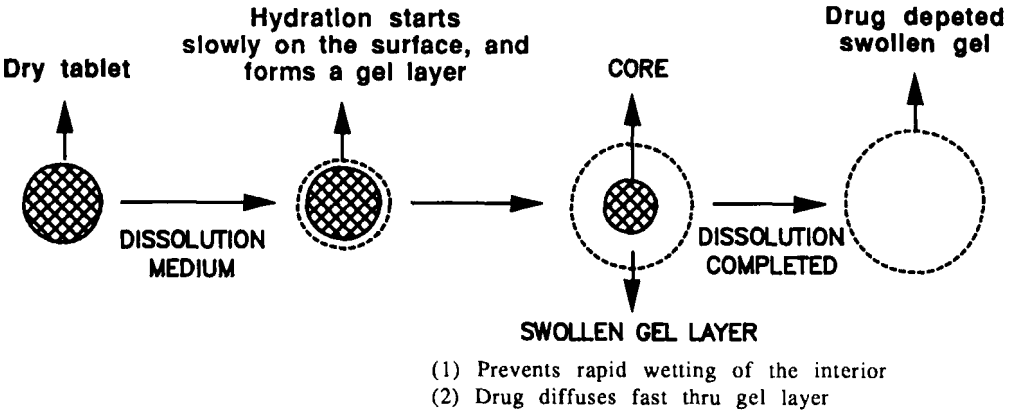

FIGURE 2

Hypothesis of hydration/gelation/swelling controlled release mechanism from xanthan gum tablets in 0.1 N HCl and pH 6.8 buffer, and alginate tablets in pH 6.8 buffer

buffer, while the alginate tablets gave a rapid initial burst followed by non-linear release in the presence of acid. Based on this observation, it might be anticipated that the drug from alginate tablets would be released more rapidly in the stomach.

Figure 2 illustrates a hypothetical gel swelling controlled release mechanism based on physical observations made during dissolution testing of xanthan gum (acid and pH 6.8) and alginate tablets (pH 6.8). As shown in Figure 2, once the tablet was surrounded by an aqueous environment, the surface of individual tablets tended to hydrate and form a gel layer to prevent rapid penetration of solution into the inner layer. After drug leached out of the gel layer, an obvious sharp boundary formed to separate the dry core (drug and polymer matrix) from the swollen and drug-depleted gel layer. The size of the tablet increased

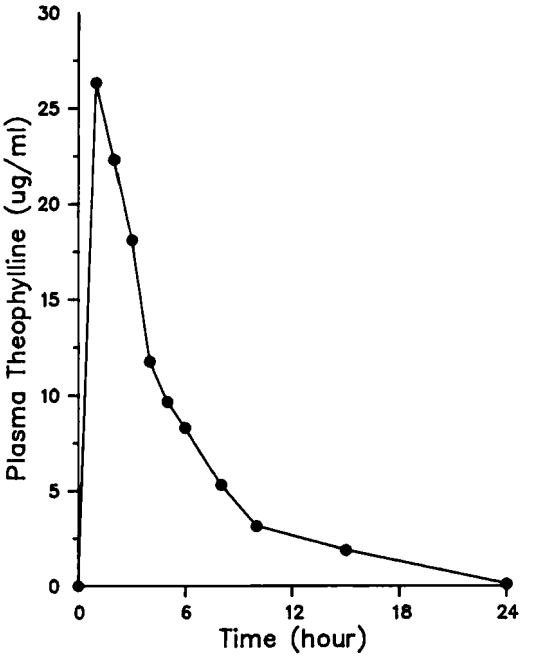

FIGURE 3

Mean plasma concentration (ug/ml) vs time (hour) after oral administration of 125 mg immediately released theophylline

significantly due to the polymer hydration and remained one complete gel unit after drug released out.

The gel swelling process was not observed with alginate tablets in acid media. Due to the chemical conversion of sodium alginate to insoluble and nonswellable alginic acid by acidity, tablets appeared unswollen and porous in acid environment.

In Vivo Dog Study - The mean plasma theophylline concentration-time curve obtained following oral administration of 125 mg theophylline base to three dogs is shown in Figure 3.

TABLE II

Pharmacokinetic Parameters of Theophylline Following Oral Administration of 125 mg Theophylline Base To Three Beagle Dogs

Pharmacokinetic Parameter		Mean (range)	C.V. (%)
C_{max}	ug/ml	26.3 (23.5-31.9)	15
T_{max}	hr	1.0 (1.0-1.0)	0
Ke	hr-1	0.14 (0.13-0.15)	8
T1/2	hr	4.9 (4.5-5.3)	8
AUC	hr x ug/ml	136 (122-157)	11

Pharmacokinetic parameters computed from this study are shown in Table II. In the dogs used in the present study, the terminal half-lives, 4.5-5.3 hour, after an oral dose were similar to those previously reported (7). The AUC value and terminal half life obtained from this experiment were used to calculate the relative bioavailability and dose absorption-time profile of three controlled release formulations.

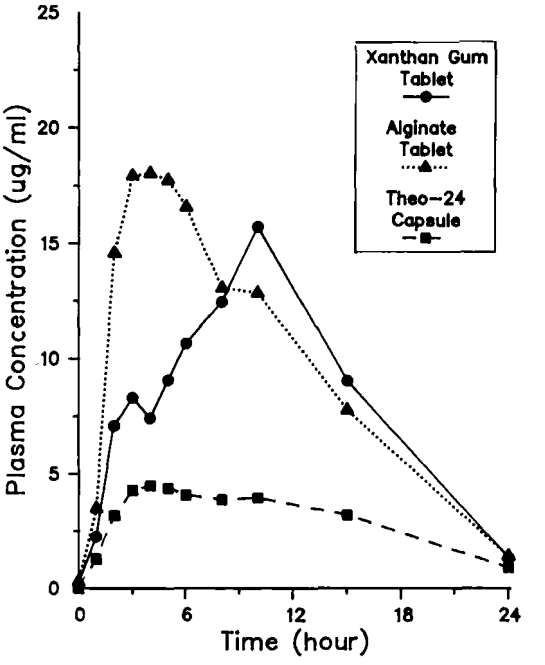

FIGURE 4

Mean plasma concentrations of theophylline in dogs following an oral administration of three controlled release formulations at dose 250 mg/dog. key: xanthan gum tablet (•); alginate tablet (▵); commercial product (■)

Figure 4 shows mean average plasma theophylline concentration-time profiles after administration of two experimental sustained release formulations, along with one commercial product. A summary of the results of the statistical analysis is presented in Table III.

Figure 5 plots the mean percentage of drug absorbed with respect to time after administration of xanthan gum and alginate tablets. The data from the xanthan gum formulation showed a good fit to zero-order release kinetics with a correlation coefficient

Table III

Pharmacokinetic Parameters For Three Sustained Release Theophylline Formulations: (A) Reference Capsule, (B) Xanthan Gum Tablet, and (C) Alginate Tablet

Formulation		AUC (hr*ug/ml)	C_{max} (ug/ml)	T_{max} (hr)	F (%)
A	Mean	71.9	4.	4.0	26.4
	S.D.	18.0	0.7	1.0	6.6
	C.V.	25.0	15.2	25.0	25.0
B	Mean	199.4	15.7	10.0	73.3
	S.D.	14.5	1.8	0.0	5.3
	C.V.	7.3	11.6	0.0	7.3
C	Mean	223.9	18.2	3.7	84.5
	S.D.	15.8	3.8	0.6	6.0
	C.V.	7.1	20.8	15.8	7.1
Significant Difference ($p<0.05$)		**A<B,C**	**A<B,C**	**B>A,C**	**A<B,C**

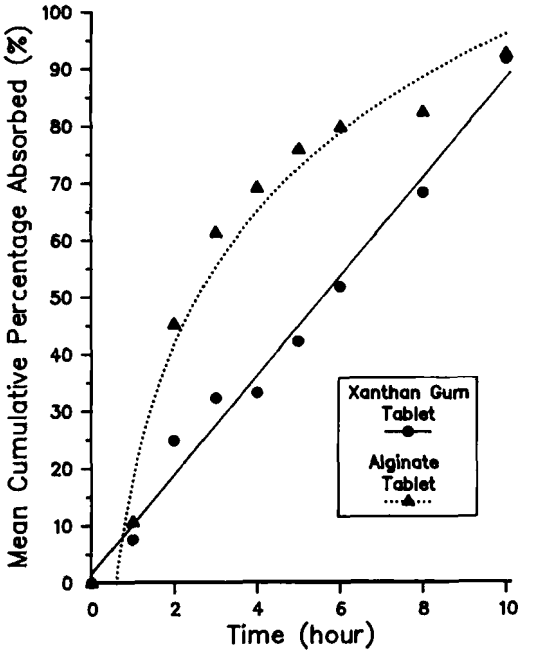

FIGURE 5

Mean cumulative percentage of available dose absorbed between 0 and 10 hours from xanthan gum and alginate controlled release theophylline formulations. key: xanthan gum tablet (□); alginate tablet (△)

of 0.98. In contrast the alginate tablet formulation appeared to fit first order absorption best.

DISCUSSION

The linear *in vivo* and *in vitro* kinetics (shown in Fig. 5 and Fig. 1) observed with the xanthan gum formulation were consistent. Zero-order kinetics indicate that the drug release from xanthan gum formulation was controlled by a constant slow gel hydration rate (or solvent front penetration rate), rather than a fast drug

diffusion rate in the swollen region (15-17). A similar polymer swelling process for hydrogel matrix systems has been discussed by a number of authors (22,23).

Dogs receiving xanthan gum formulation had a significantly longer mean T_{max} than either the alginate formulation or commercial product (10 hours vs 4 hours). This delayed T_{max} indicates a long residence time of the xanthan gum tablet in the GI tract, which is consistent with the gel swelling mechanism described and observed during the dissolution tests. The lower mean T_{max} from the alginate formulation compared to the xanthan gum tablet is also consistent with the observed dissolution performances. The dissolution testing indicated that alginate tablets would rapidly release theophylline in stomach acid in a non-linear release profile normally associated with a diffusion controlled monolithic system (23,24).

Both hydrogel tablets were absorbed almost completely based on comparison to the immediately releasing capsules when factored for dosage. However, dogs receiving the commercial capsule had significantly lower mean AUC and C_{max} values. The relative bioavailability of the commercial product was 26.4% compared to immediately releasing theophylline capsules in the present study. This was slightly lower than the 38% compared to an oral liquid formulation(21) and 31% compared to an IV dose of aminophylline (5) previously reported. The incomplete absorption of this commercial formulation compared to that from the hydrogel formulas is most likely attributable to differences in release mechanism.

This dosage form relies on gradual release from coated beads and the short gastrointestinal transit time in dogs would limit release.

In this study, the *in vitro* dissolution testing was used to provide a fundamental understanding of some of the physicochemical properties of the formulations. It was not an attempt to establish quantitative associations of *in vitro* release to *in vivo* absorption. Dissolution conditions, such as stirring rate, could have a significant influence on the *in vitro* release rates of theophylline tablets (25). However, qualitatively, the *in vivo* results correlated quite well with the *in vitro* testing in the present study. It confirmed that for drug delivery research, *in vitro* dissolution testing can give valuable biopharmaceutical information.

CONCLUSION

It has been shown that controlled release theophylline dosage forms can be prepared with a simple hydrogel matrix system, in which the *in vivo* kinetic processes may be controlled by the characteristics of polymer chosen in the formulation. Xanthan gum which has been primarily used as a suspending agent in liquid formulation may deserve more attention in solid controlled release dosage form development. It is also believed that the findings from this study may be applied to a broad range of water soluble drugs.

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