DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(3), 387-394 (1994)

KINETICS AND MECHANISM OF DRUG RELEASE FROM CALCIUM ALGINATE MEMBRANE COATED TABLETS

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ABSTRACT

Compressed tablets containing guaifenesin (model drug), calcium acetate (reactant) and pharmaceutical excipients were prepared. The tablets were coated with calcium alginate hydrogel using a novel, self-correcting membrane coating technique. Effects of coating time, the type of alginate polymer and pH of the dissolution medium on the rate of drug release were evaluated. In distilled water, zero order drug release profiles were obtained from the coated tablets. The release rate decreased with an increase in the coating time (increased coat thickness) and molecular weight of alginate polymer. The release rate constants correlated with model for spherical reservoir system and, were used to calculate permeability of guaifenesin in the calcium alginate coatings. Alginate polymer with higher guluronic acid content provided acid stable coating and higher molecular weight polymer produced membrane with lower permeability for guaifenesin.

INTRODUCTION

Several natural as well as synthetic polymers have been evaluated for controlled drug delivery. Alginic acid, a naturally occurring polymer has been evaluated for sustained drug delivery in the form of sodium alginate, a water soluble polymer (1) and, calcium alginate, an ionically cross-linked, water-insoluble polymer (2). However, the mechanism of release from calcium alginate coated systems is at best sketchy. Also, the effect of molecular weight or copolymer composition of alginic acid polymer on drug release from calcium alginate hydrogel has not been reported.

Chemically, alginic acid is a copolymer made almost exclusively of alpha-L-(1-4) linked guluronic acid units and beta-D-(1-4) linked mannuronic acid units

(3,4). Since it is the guluronic acid that preferentially binds with calcium ions, with increase in the guluronic acid content (and therefore, decrease in mannuronic acid content), calcium alginate polymer may have higher cross-linking and also, improved acid stability. Therefore, alginates with different guluronic acid content and molecular weight were evaluated. Guaifenesin, a non-ionic, water soluble drug was chosen as a model drug.

MATERIALS

Calcium acetate, anhydrous, USP was obtained from Syntex, Nutritional and Chemical Division, Springfield, Missouri, calcium chloride, anhydrous, hydrochloric acid, monobasic potassium phosphate, sodium chloride and sodium hydroxide were obtained from Fisher Scientific Co., guaifenesin, NF was obtained from Penick Corp., Lyndhurst, N.J., Kelco Gel HV, LV and Manugel DMB were obtained from Kelco, Div. of Merck & Co., San Diego, CA, magnesium stearate, U.S.P. was obtained from Mallinckrodt Inc., St. Louis, Mo, mannitol U.S.P. and triethanolamine were obtained from Rugar Chemical Co., Inc., Irvington, N.J., sorbitol, U.S.P. was obtained from ICI Americans, Inc., Wilmington, DE.

METHODS

Compressed tablets containing 70% guaifenesin, 20% calcium acetate, 10% sorbitol and 0.5% magnesium stearate were prepared using wet granulation technique. Wet granulation was preferred to obtain a uniform calcium acetate distribution in the granules. Sorbitol was preferred over contemporary polymeric binders so that drug and calcium acetate diffusion from tablet core will be devoid of any viscous polymeric layer.

Three different alginate polymers namely, Kelco Gel LV (low molecular weight, 29% guluronic acid), Kelco Gel HV (high molecular weight, 29% guluronic acid and Manugel DMB (medium molecular weight, 69% guluronic acid) were evaluated. Tablets were placed in sodium alginate solution to obtain coating using a novel coating technique, diffusion controlled interfacial complexation (5). Briefly, tablets were carefully immersed in 1.0% w/w aqueous sodium alginate solution kept under mild agitation using a magnetic bar. As the tablets came in contact with aqueous alginate solution, calcium acetate (reactant) dissolved from the tablets and cross-linked with the alginate polymer to form a water-insoluble calcium alginate film around the tablet. Further film formation occurred by diffusion of calcium ions through the calcium alginate film already formed. Coated tablets thus formed were removed at different time intervals and rinsed with distilled water. The coating was further hardened by treatment with calcium chloride solution and ethanol NF. The tablets were then allowed to air dry for 48 hours.

During the aqueous coating, guaifenesin could be dissolving along with calcium acetate and therefore, the amount of guaifenesin depleted during coating was determined. Scanning electron microscopy (SEM) was performed on the coated tablets. Dried coated tablets were evaluated for appearance, morphology and drug release. The release studies were performed using USP

TABLE I
EFFECT OF COATING TIME ON EQUILIBRIUM COAT THICKNESS

Coating Time	Coat Thickness (microns)[1]		
(minutes)	Kelco Gel HV	Kelco Gel LV	Manugel DMB
10	48.4 ± 14.4	104.8 ± 15.7	64.6 ± 13.7
20	116.9 ± 25.7	127.8 ± 22.3	69.3 ± 15.6
30	NA	158.1 ± 31.6	NA
40	NA	NA	117.4 ± 34.5
70	287.0 ± 64.3	183.6 ± 33.3	317.7 ± 74.0

1: Average ± standard deviation of 25 or more determinations
NA: Not available

dissolution apparatus II, paddle method with 900 ml of dissolution medium (distilled water, pH 1.2 simulated gastric juice without enzyme (6), simulated intestinal juice without enzyme (6) or, triethanolamine- hydrochloric acid buffer, pH 7.4), agitated at a speed of 50 rpm aand analyzed using automated dissolution sampling followed by spectrophotometric analysis at 272 nm (5). At the end of dissolution, tablet coat were cut and average coat thickness was determined using optical microscopy.

RESULTS AND DISCUSSION

Evaluation of Coated Tablets

A pale yellow coating was observed on the dried, coated tablets, with twinning observed among a few tablets. Tablets coated for more than 20 minutes had wrinkled coats, probably due to the shrinking of calcium alginate hydrogel during drying. Scanning electron micrographs (SEM) of cross-section showed clear zones of core and the coat. Also, minute amounts of dried solid (calcium acetate and guiafenesin) were observed on the outer surface of the coating.

Assay of tablet core revealed loss of guaifenesin during coating. The loss was found to be dependent on coating time, with 10 mg of guaifenesin lost at 70 minutes coating time for Manugel DMB coated tablets (5). While this contrasts with the rapid dissolution of the uncoated tables in dissolution medium (complete dissolution in 15 minutes), it can be explained based on two factors. First, during coating, the tablets instantaneously developed a coating of calcium alginate that restricted diffusion of guaifenesin. Such diffusive barrier did not exist for uncoated tablet dissolution. Secondly, guaifenesin dissolution is temperature dependent and at the temperature of coating (room temperature), guaifenesin is expected to take longer time to dissolve.

Effect of Coating Time on Equilibrium Coat Thickness

Equilibrium coat thickness increased non-linearly with an increase in the coating time (Table I). The low molecular weight alginate polymer (Kelco Gel

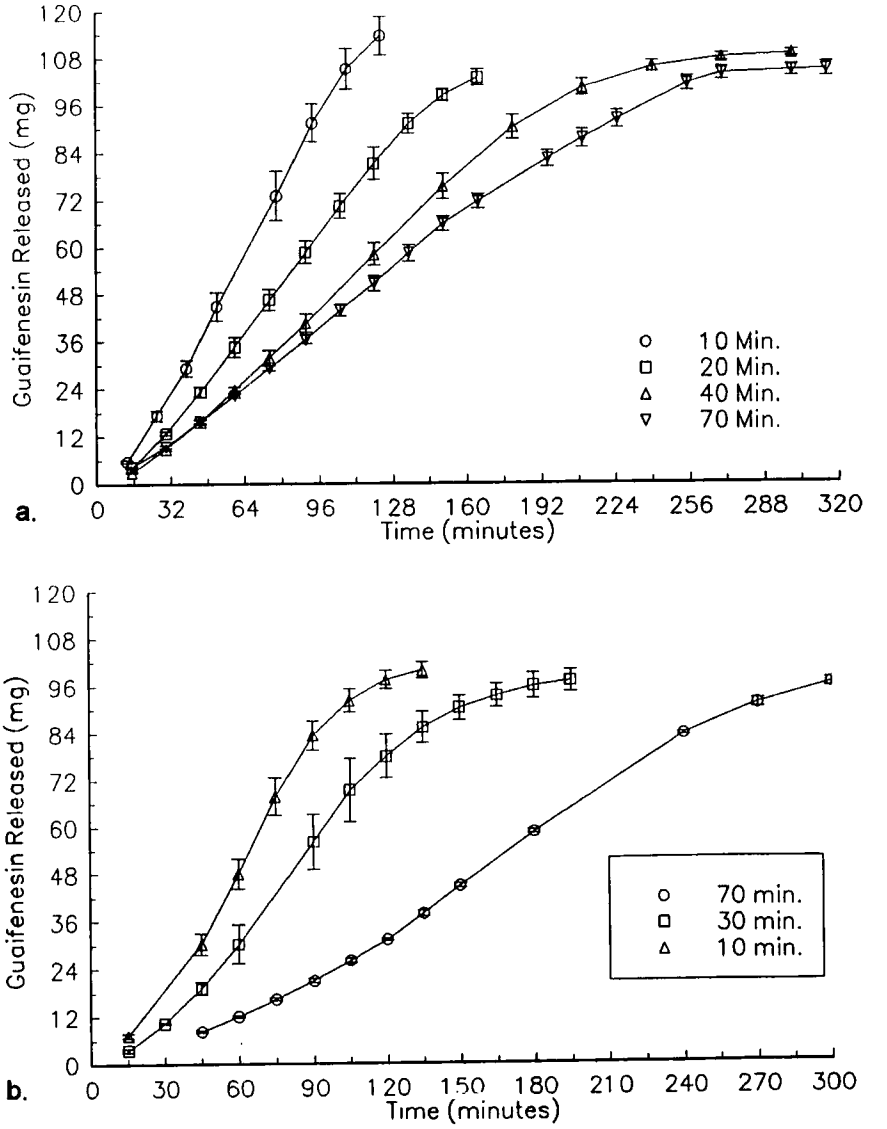
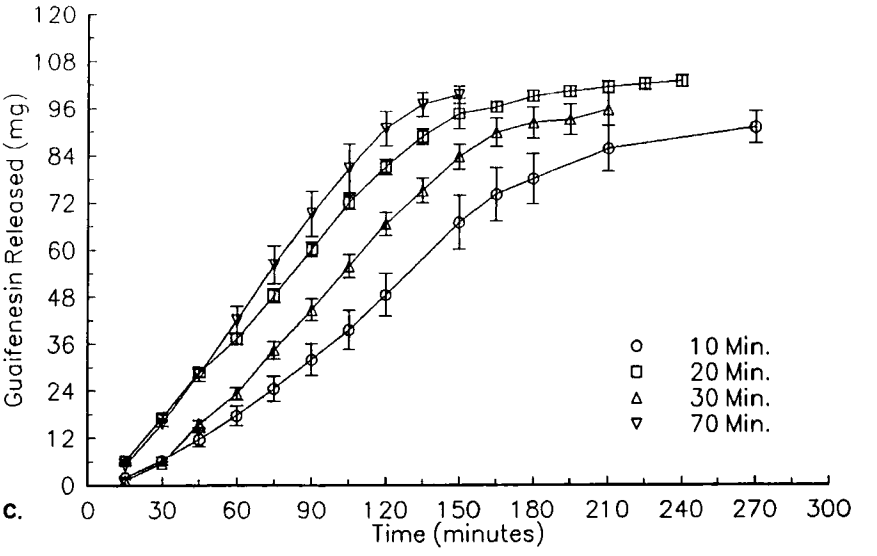


Fig. 1 Drug Release Profiles in Distilled Water
Average ± S.D. of 4 tablets
a. Manugel DMB Polymer
b. Kelco Gel HV Polymer
c. Kelco Gel LV Polymer



c.

Fig. 1. Continued

LV) developed the thickest coating at the lowest coating time studied and, the thinnest coating at the highest coating time studied.

Kinetics and Mechanism of Drug Release

Using distilled water as dissolution medium, triphasic drug release profiles were obtained from the calcium alginate membrane coated tablets (Fig. 1 a-c). During the initial 5-15% release, the rate of release increased non-linearly as the calcium alginate membrane hydrated, swell and increased in permeability. This was followed by a predominant, 75-85% zero order release, also described as the equilibrium release phase. During this phase, presumably, the membrane retained constant permeability and drug reservoir inside the membrane maintained constant drug concentration (due to excess solid drug in the core). After exhaustion of solid drug from the core, the final 5-10% drug release was observed to be non-linearly decreasing. The guaifenesin release rate constant for the different coating and polymer conditions correlated with the trend observed with equilibrium coat thickness.

The rate of drug release from spherical membrane reservoir systems is given by (8):

$$\frac{dM_t}{dt} = \frac{4\ D\ K\ (C_1-C_2)\ a\ b}{(b-a)} \quad \text{...(Eq. 1)}$$

Other terms remaining constant, $\frac{dM_t}{dt} \alpha \frac{b}{(b-a)}$ ...(Eq. 2)

TABLE II
EFFECT OF EQUILIBRIUM COAT THICKNESS ON DRUG RELEASE RATE

Coating	Kelco Gel HV		Kelco Gel LV		Manugel DMB	
Time	f(b)	dM_t/dt	f(b)	dM_t/dt	f(b)	dM_t/dt
(Minutes)		$mg/(min)^2$		$mg/(min)^2$		$mg/(min)^2$
10	67.07	1.190 ± 0.036	31.55	0.842 ± 0.016	50.54	1.073 ± 0.019
20	28.37	0.782 ± 0.023	26.03	0.704 ± 0.011	34.16	0.760 ± 0.008
30	NA	NA	20.51	0.646 ± 0.013	NA	NA
40	NA	NA	NA	NA	13.68	0.555 ± 0.006
70	12.02	0.405 ± 0.009	18.17	0.532 ± 0.014	11.07	0.459 ± 0.012
Regression Constants						
Slope	0.0136 ± 0.0029		0.0210 ± 0.0345		0.0144 ± 0.0016	
Intercept	0.3056 ± 0.1143		0.1754 ± 0.0357		0.3165 ± 0.0508	
Correlation	0.979		0.975		0.988	

1: Average ± standard deviation of 25 or more determinations
2: Equilibrium release rate ± standard error of mean for average of 4 tablets
NA: Not available

Therefore, for diffusion controlled spherical reservoir systems, a plot of dM_t/dt against b/(b-a) should be linear. Values of b, external coat radius were obtained from two sources for the coating polymer Manugel DMB. Coat thickness were obtained from the tablet coat left at the end of dissolution. The spherical reservoir system model was also applied to the equilibrium coat thickness obtained for the three polymers (Table II). Good correlation (r^2 ranging from 0.999 to 0.975) were obtained between release rate constant and function of coat thickness, thus verifying the release to occur through a membrane-controlled spherical reservoir system.

Slope obtained from the above regressions represents a function of permeability of guaifenesin across the calcium alginate membrane (slope represents the "4 Π D K (C_1-C_2) a" part of Eq. 1). Therefore, division of slope with "4 Π (C_1-C_2) a" would give us DK = P, permeability of drug through the polymer. Using the values of C_1 as 335 mg/ml at 37 ^oC (9) and C_2 as zero in sink conditions and "a" as 3.2 mm (inner radius of tablets), permeability values of 1.098 ± 0.2341 , 1.696 ± 0.2826 and 1.163 ± 0.1292 [ml/(mm-min) x 10^{-6}] were obtained for calcium alginate polymers of Kelco Gel HV, Kelco Gel LV, and Manugel DMB, respectively. From the permeability constants, it is apparent that the permeability of guaifenesin is the highest in a low molecular weight alginate (Kelco Gel LV) and the lowest in a high molecular weight polymer (Kelco Gel HV).

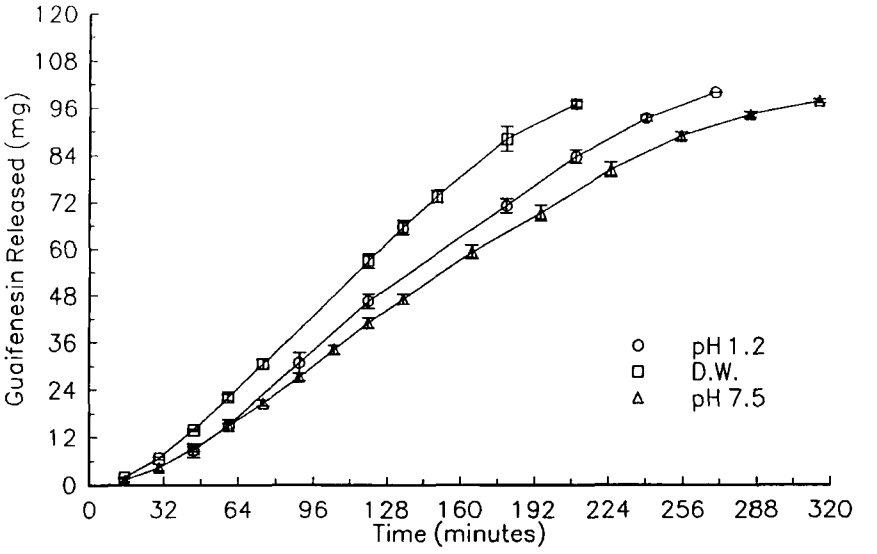


Fig. 2 Effect of pH on Drug Release Profiles - Manugel DMB Polymer
Average ± S.D. of 4 tablets

Effect of pH of Dissolution Medium

Two coated tablet formulations namely, Kelco Gel LV polymer, 40 minutes coating time and Manugel DMB polymer, 70 minutes coating time were evaluated to determine the effect of pH of dissolution medium on the drug release profiles. For tablets coated with Kelco Gel LV polymer and 40 minutes coating time, the release rate constant in pH 1.2 dissolution medium was about twice that in distilled water. The tablet coat appeared to dissolve in the acidic medium and a very thin membrane was retrieved at the end of dissolution. Guaifenesin release in pH 7.5 phosphate buffer was erratic. White, insoluble deposits were observed to be covering the coating, disrupting and clogging the membrane and dramatically decreasing the release rate. These deposits were presumed to be from the binding of phosphate ions from the buffer to the calcium ions, both from the tablet core and, the membrane.

A two-pronged approach was used to solve the problem of membrane instability in the buffers. Firstly, for improved acid stability, Manugel DMB (alginate with higher guluronic acid content) was evaluated as a coating polymer. Secondly, disruption of the coat in pH 7.5 buffer was due to the interaction of phosphate ions with the calcium in the calcium alginate complex. Since phosphate ions are virtually nonexistent in human intestinal fluids (7), the phosphate buffer (pH 7.5) was replaced with a non-calcium binding triethanolamine-hydrochloric acid buffer of equivalent pH and buffer capacity (pH 7.4; buffering capacity, beta of 0.0256). Guaifenesin release profiles in distilled water, pH 1.2 and pH 7.5 medium for Manugel DMB coating polymer and 70 minutes coating time are shown in Fig. 2. The rate of guaifenesin release in pH 7.5 medium was not significantly different from that in distilled

water. Although the rate of drug release in pH 1.2 dissolution medium was about 15% faster than in distilled water, this exhibited a significant improvement in acid stability compared to release profiles from tablets coated with Kelco Gel LV, 40 minutes coating time.

CONCLUSIONS

1. Equilibrium guaifenesin release profiles correlated with the model for diffusion controlled interfacial complexation
2. Zero order release profiles were attained by the coated guaifenesin tablets
3. Guaifenesin permeability was affected by molecular weight of the alginate polymer. Higher molecular weight alginate polymer produced calcium alginate film with lower permeability for guaifenesin.

NOMENCLATURE

a	inner radius of coat
b	outer radius of coat
C_1	concentration of dissolved drug inside the core
C_2	concentration of dissolved drug in dissolution medium
D	drug diffusion coefficient per unit surface area of membrane
DK	permeability (P) of drug through membrane
dM_t	mass of diffusing substance released at time t
K	partition coefficient of drug across membrane
t	time from beginning of release study

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