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Research Article

A Novel, Self-Correcting Membrane Coating Technique

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A novel coating process, leading to formation of uniform, defect-free coating on solid dosage forms, is proposed. The coating process, termed "diffusion-controlled interfacial complexation," involves a chemical reaction between a reactant incorporated in the solid unit to be coated and a polymer solution, forming the coating medium. The reaction results in the formation of an insoluble reactant–polymer film around the solid. The rate of film/membrane formation is controlled by the rate of diffusion of reactant through the reactant–polymer film. In the model system, calcium acetate was selected as the reactant and algin as the polymer. The coating process was mathematically characterized in terms of rate of increase in film thickness, film weight, and depletion of reactant. Compressed tablets coated using the above process provided zero-order release in distilled water.

KEY WORDS: self-correcting coating; membrane coating; tablet coating; calcium alginate; sustained release; controlled release; guaifenesin; pH effect; interfacial reaction.

INTRODUCTION

Contemporary pharmaceutical coating processes such as fluidized beds and rotating pans apply coating through physical deposition of material on the core. These processes can be nondiscriminating, repetitive, and potentially damaging to the core and coating already applied.

The processes are nondiscriminating, as they provide indiscriminate deposition of the coating material through a spray zone on a batch of agitated solid units, e.g., a batch of tablets. This process is repeated over a prolonged period of time (several deposition of coating on each tablet) so that all tablets may eventually receive sufficient coating. Depending on the number of passages through the coating zone, however, some tablets may receive too little coating and others too much coating, which may result in uneven coating (1). Also, because of the attrition involved, the coating processes may be damaging to the coating and/or the core.

While pharmaceutical coating processes are adequate for many purposes (2), including taste-masking and protecting drug from oxygen and light, they are less than ideal for achieving predictable, even coating on individual units. For membrane-controlled drug delivery systems, variations in coat thickness may lead to corresponding variations in the drug release profile (3). Also, a crack or a hole developed in the coat because of attrition could lead to dose dumping.

The majority of commercial membrane-controlled oral drug delivery systems is the coated bead/granule type. These contain a large number of coated units placed inside a capsule dosage form, providing a statistical average in release profile even when significant deviation in release may exist between individual coated beads and/or dose dumping by a few units. Membrane-coated tablets, on the other hand, have all of their drug encapsulated inside a single coating. Variations in coat thickness could directly cause variations in drug release profile. This reflects one of the major disadvantages of current coating technology.

To obtain predictable and reproducible release profiles, it is therefore essential to have a defect-free, uniform coating on the tablets. One way to achieve this is through development of a coating system which monitors the coating needs of individual tablets, i.e., the coating system automatically corrects the amount of coat being applied to the individual tablets, depending on the extent of coat already present. Also, during the coating process, if a defect develops in a coat, it would be automatically corrected. Such a coating technique may be described as *self-correcting*.

SELF-CORRECTING COATING CONCEPT

A novel, self-correcting coating technique is reported. The technique, diffusion-controlled interfacial complexation, ensures equal coating of all units. The concept differs from conventional coating processes in that while the latter involves physical deposition of coating material, the new technique uses chemical reaction at the interface. A reactant is incorporated in a tablet matrix, which is then placed in a polymer solution. The reactant dissolves in the polymer solution and immediately complexes with the polymer to form a reactant–polymer complex film (Fig. 1). The rate at which further film is formed is controlled by the diffusion of reactant through the film already formed.

If, for any reason, a particular tablet receives less coat-

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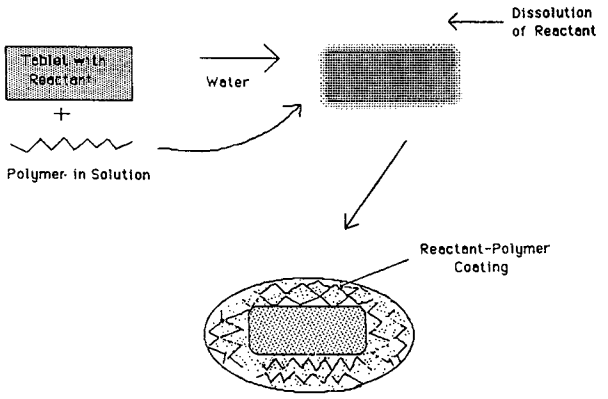

Fig. 1. Coating process—diffusion-controlled interfacial complexation.

ing, more reactant diffuses through it since the coating is thinner. Thus, the rate of coating for that tablet becomes faster than for an average coated tablet. On the other hand, if a tablet is coated excessively, because the coating is thicker, reactant diffuses through it more slowly and the rate of coating for that tablet automatically decreases.

The above reaction is interfacial in nature. While interfacial reactions involving a liquid core have been used for various polymerization processes and their kinetics and mechanism have been reported (4–6), there is very little information available on the application of an interfacial reaction to a solid core (7). Also, kinetics and mechanism of such coating have not been investigated. We evaluated the mechanism and kinetics of interfacial complexation using a solid core and propose the above reaction as a self-correcting membrane coating technique.

Assumptions involved in the coating process are that the rate of coating is controlled by the rate of availability of reactant, i.e., reactant and polymer react instantly to form an insoluble film. It is assumed that the reactant is available only from the tablet and under equilibrium conditions, after diffusing through the film. Further, the rate of reactant diffusion is assumed to be inversely proportional to the thickness of the reactant–polymer film.

For successful application of the concept, desirable attributes were developed for the reactant, polymer, and reactant–polymer combination. The reactant should have a high solubility and diffusivity in solvent for the polymer, compatibility with the drug and other excipients, lack of toxicity, and therapeutic activity, chemically stability, and ease of incorporation in the formulation. Desirable attributes for the polymer are solubility in a nontoxic solvent and low viscosity in solution. For an ideal reactant–polymer system, the rate of reaction between the reactant and the polymer should be faster than diffusion of reactant through the reactant–polymer film. Further, the reactant–polymer complex should form a suitable coating material for controlled drug delivery.

Based on the above assumptions and desirable attributes, ionic reactions were preferred for their spontaneity. Therefore, we chose reaction of calcium ions with sodium alginate in solution to form cross-linked, water-insoluble calcium alginate hydrogel. Calcium alginate is water insoluble but water permeable (8,9) and calcium alginate films control the release of drugs (10,11). Reaction for formation of calcium alginate is instantaneous and proceeds as follows (8,9):

$$2\ \text{NaAlginate} + Ca^{2+} \text{ —— } \text{CaAlginate} + 2\ Na^{+}$$

MATERIALS AND METHODS

Preparation of Granules for Compression

Calcium acetate, anhydrous, USP (Syntex, Nutritional and Chemical Division, Springfield, MO), was incorporated into granules using a wet-granulation procedure to obtain a uniform matrix containing guaifenesin, NF (drug, 70%) (Penick Corp., Lyndhurst, NJ), sorbitol, USP (binder, 10%) (ICI America, Inc., Wilmington, DE), and calcium acetate, anhydrous, USP (reactant, 20%) (Syntex, Nutritional and Chemical Division, Springfield, MO). The wet mass was passed through a 16-mesh sieve and dried in a tray dryer at 40°C for 2.5 hr, followed by room temperature equilibration for 3 or more additional hr. The granules obtained were dry-sieved to get 20/60 mesh size and lubricated with magnesium stearate, NF (Mallinckrodt Inc., St. Louis, MO), 60 mesh to achive a final concentration of 0.5%.

Preparation of Compressed Tablets

The lubricated granules were compressed on a single-station tablet press (Model E, 518-1, Stocks Equipment Division, Pennwalt Corp., Warminster, PA) using deep concave 0.25-inch round tooling with the machine speed of about 30 rpm. The tablets were evaluated for weight variation, thickness, hardness, dissolution, and total drug content.

Coating of Tablets

The tablets obtained were carefully added to 1.0% (w/w) aqueous sodium alginate (polymer) (Manugel DMB obtained from Kelco, Division of Merck & Co., San Diego, CA) solution under mild agitation using a magnetic bar. Addition of tablets to the polymer solution required careful handling—an indiscreet, rapid addition lead to "twinning," where two or more tablets were connected or enclosed by a common coat. Also, initially, the magnetic stirrer speed was set high to achieve good dispersion of tablets. As the coating progressed, however, the stirrer speed was reduced.

As the tablets came in contact with aqueous alginate solution and tablet surface dissolved, calcium acetate (reactant) cross-linked with the alginate to form a water-insoluble calcium alginate film around the tablet. Further film formation was controlled by the rate of diffusion of calcium ions through the calcium alginate film already formed. Coated tablets thus formed were removed at 10, 20, 40, and 70 min and quickly rinsed with distilled water to remove any sodium alginate not cross-linked and loosely adhering to the surface of the coat. The coated tablets were treated with 50% (w/w) calcium chloride solution for 3 min to complete cross-linking and dehydrate the coat. Excess calcium chloride on the coated tablets was removed by rinsing them with absolute ethanol for 3 min. This also facilitated subsequent air drying (48 hr) of the tablets. The tablets were then stored with silica gel desiccant capsules in an enclosed container for at least a week.

Evaluation of Tablets and Microscopy

Dried, coated tablets were evaluated for appearance, size (diameter and thickness), weight, morphology, and drug release profile. Scanning electron microscopy was performed on selected formulations. The dried coated tablets were cut and coated with a thin layer of gold metal using an SEM coating unit (Model E1500, Polaron Instruments, Inc., Doylestown, PA). The specimens thus prepared were observed under a scanning electron microscope (dual-stage scanning electron microscope, ISI-DS 130) and photographed.

Drug release studies were performed on the coated tablets using USP dissolution apparatus 2 (paddle method). Four tablets were placed in separate dissolution flasks with 900 ml of distilled water and a paddle speed of 50 rpm. Dissolution samples were taken using an automated dissolution apparatus and analyzed at 272 nm for guiafenesin released (12).

Verification of Mathematical Models for Coating

Verification of the mathematical model for increase in coat thickness and coat weight was performed by coating tablets for 5, 10, 20, 40, and 70 min. Coated tablets were cut and the calcium alginate coat was separated. The coat was rinsed with water, then wiped dry, and the thickness and weight of the coat were determined. Tablet cores, combined with coat rinsing, were assayed for drug and calcium acetate remaining.

RESULTS

Evaluation of Core Tablets

Results of the tests performed on core tablets are summarized in Table I. Under dissolution conditions, the core tablets dissolved completely in less than 15 min.

Evaluation of Coated Tablets

Figure 2 shows cross sections of coat obtained (see Verification of Mathematical Models for Coating), under identical magnifications. The translucent coat appeared to be uniform in thickness. Also, the coat thickness appeared to increase with coating time.

Contrary to this, a pale yellow coating was observed on the dried, coated tablets. Twinning was observed among a few tablets. Tablets coated for more than 20 min had wrinkled coat. The wrinkles may have formed by shrinking of calcium alginate hydrogel during drying. Results of weight and size determination of tablets are summarized in Table II. A consistent increase in weight and size of the coated tablets was observed, with a very narrow weight distribution. However, a wide thickness distribution was observed, probably as a result of surface wrinkles.

Table I. Physical Characteristics and Total Assay of Core Tablets

Test	Results
Appearance	Deep convex, white tablets
Weight (mg)	159.5 ± 3.9[a]
Thickness (mm)	4.98 ± 0.07[a]
Hardness (kP)	17.5 ± 2.4[a]
Total assay (mg)	111.1 ± 2.7[b]

[a] Average ± SD of ten determinations.
[b] Average ± SD of three determinations.

Scanning electron micrographs (SEM) of cross sections of dried coated tablets showed clear zones of core and the coat (Fig. 3). The coat thickness increased with an increase in the coating time. Also, minute amounts of dried solid was observed on the outer surface of the coating and the amount appeared to increase with an increase in the coating time. The solid is probably dissolved calcium acetate and guaifenesin, migrating along with water to the surface of the coating.

Effect of Coating Time on Tablet Core and Coat

Increase in coating time led to an increase in the membrane thickness (Table III) and coat weight (Table IV) and a decrease in both guaifenesin and calcium acetate content, as shown in Fig. 4.

Kinetics of Drug Release

Triphasic drug release profiles were obtained from the membrane-coated tablets (Fig. 5). During the initial 5–10% release, the rate of release nonlinearly increased as the calcium alginate membrane hydrated, swelled, and increased in permeability. This was followed by a predominant, 75–85% zero-order release, also described as equilibrium release phase. Finally, 5–10% nonlinearly decreasing release was observed, occurring presumably because of exhaustion of solid drug in the core. Also, the duration of drug release increased with an increase in the coating time.

DISCUSSION

Wet granulation was preferred to obtain a more uniform calcium acetate distribution in the granules. Sorbitol was preferred over contemporary polymeric binders so that drug and calcium acetate diffusion from tablet core would be devoid of any gelatinous polymeric layer.

The coating polymer, alginic acid, is a copolymer composed of guluronic and manuronic acid units. It is the guluronic acid in alginate that preferentially binds with calcium ions (8,9). Therefore, alginate with a higher guluronic acid content (Manugel DMB) was chosen and evaluated as a coating polymer. Immediately after the tablet coating, the coat was flexible, with a yellowish, translucent appearance. To make the coat more rigid and improve its handling characteristics, the coated tablets were treated with calcium chloride and alcohol. At the completion of both treatments, the coat thickness decreased and the coat was firm with better handling characteristics.

Drug release profiles through calcium alginate membrane have been shown to be affected by the level of moisture present in the membrane (13). Therefore, to achieve consistent moisture levels in the membrane, coated tablets were stored with the silica gel desiccant.

MATHEMATICAL MODEL FOR THE COATING PROCESS

Mathematical models were developed to predict the rate

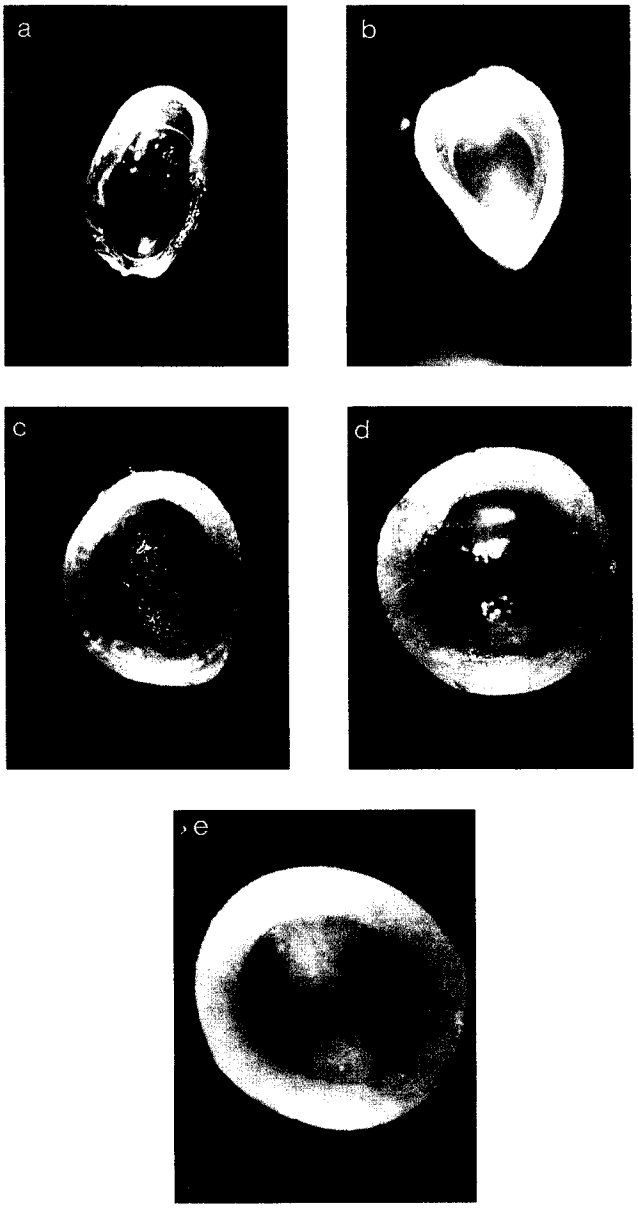

Fig. 2. Photographs of cross section of tablet coat: (a) 5 min of coating; (b) 10 min of coating; (c) 20 min of coating; (d) 40 min of coating; (e) 70 min of coating.

of increase in film thickness and weight. Assumptions involved in derivation of these mathematical model are as follows.

1. The core and coat are spherical in shape.
2. Reactant is available for reaction as soon as the core is placed in the coating solution, i.e., there is no lag time.
3. The inner radius of the coating (a) does not change with coating time, i.e., the coating does not grow inward.
4. There is an excess of reactant in the core. The rate of coating is never hindered by unavailability of reactant to diffuse through the film. This may not be true for the following conditions.
   a. The proportion of reactant in the tablet is low, and therefore, a significant amount of drug has to dissolve from the core for the reactant to become available.
   b. The tablet is very hard and the reactant availability is dissolution rate limited.
   c. The drug and/or the core excipients have a very low solubility and retard dissolution of the reactant.

Table II. Physical Characteristics of Coated Guaifenesin Tablets

Coating time (min)	Weight (mg)[a]	Size (mm)[a]	
		Thickness	Diameter
0	159.5 ± 3.9	6.40 ± 0.01	4.98 ± 0.07
10	181.4 ± 2.3	6.95 ± 0.09	5.57 ± 0.11
20	192.8 ± 4.3	7.13 ± 0.09	5.63 ± 0.07
40	216.8 ± 3.3	7.47 ± 0.14	6.05 ± 0.03
70	239.6 ± 2.8	7.61 ± 0.05	6.31 ± 0.03

[a] Average ± SD of four or more determinations.

Mathematical Model for Film Thickness

Assumptions for Film Thickness

Increase in Film Thickness Is Proportional to Rate of Availability of the Reactant. Therefore, the rate of increase

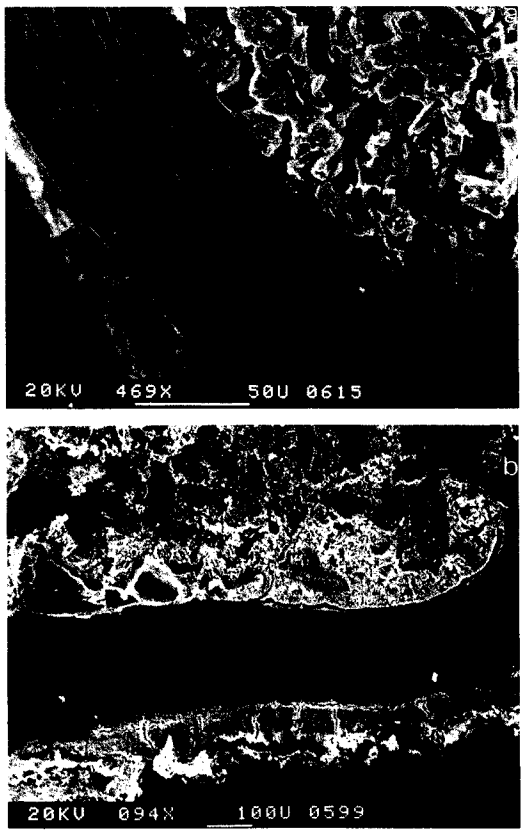

Fig. 3. Scanning electron micrographs of cross sections of dried coated tablets: (a) 10 min of coating; (b) 70 min of coating. Drug, guaifenesin; coating polymer, Manugel DMB.

Table III. Effect of Coating Time on Coat Thickness[a]

Coating time (min)	Thickness (mm)[b]	$b^2(2b - 3a)$
5	0.68 ± 0.07	−27.73
10	0.95 ± 0.06	−22.73
20	1.30 ± 0.07	−12.26
40	1.79 ± 0.12	9.68
70	2.22 ± 0.12	36.57

[a] Regression constants for linearized Eq. (19): slope, 1.000 ± 0.020; intercept, −32.29 ± 1.18; correlation coefficient (r^2), >0.998.
[b] Average ± SD on six coat halves; total, 25 or more determinations.

in film thickness is proportional to the rate of release of reactant. Mathematically, the following relationship is obtained.

$$\frac{d(b-a)}{dt} \alpha \frac{dM_t}{dt} \tag{1}$$

Immediately after placing the tablet in a coating solution, the reactant at the surface of the tablet dissolves and reacts with the polymer to form a reactant–polymer coating. Further release of reactant is then governed by the equation for release from diffusion-controlled reservoir systems, given by (4)

$$\frac{dM_t}{dt} = \frac{4\Pi DK(C_1 - C_2)ab}{(b-a)} \tag{2}$$

Assuming that D, K, and C_1 are constant and C_2 is zero during steady state, the following equation is obtained:

$$\frac{dM_t}{dt} \alpha \frac{b}{(b-a)} \tag{3}$$

From Eqs. (1) and (2),

$$\frac{d(b-a)}{dt} \alpha \frac{b}{(b-a)} \tag{4}$$

Increase in Film Thickness Is Inversely Proportional to Surface Area Being Coated. Since the area of a sphere is given by $4\Pi b^2$,

$$\frac{d(b-a)}{dt} \alpha \frac{1}{4\Pi b^2} \tag{5}$$

Table IV. Effect of Coating Time on Coat Weight[a]

Coating time (min)	Weight (mg)[b]	$W - 3a/2z\ (zW + a^3)^{2/3}$
5	57 ± 11	−212.93
10	106 ± 15	−206.15
20	196 ± 13	−187.12
40	332 ± 3	−147.42
70	469 ± 6	−98.46

[a] Regression constants for linearized Eq. (20): slope, 1.749 ± 0.055; intercept, −220.31 ± 3.24; correlation coefficient (r^2), >0.996.
[b] Average ± SD of three determinations.

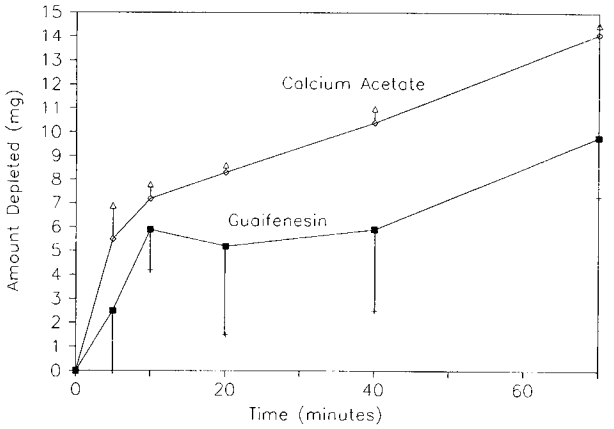

Fig. 4. Depletion of drug and reactant as a function of coating time. (■) Average guifenesin depleted; (+) average − SD for guaifenesin; (◇) average calcium acetate depleted; (△) average + SD for four determinations.

From Eqs. (4) and (5),

$$\frac{d(b-a)}{dt} \alpha \frac{b}{(b-a)} \times \frac{1}{4\Pi b^2} \tag{6}$$

Therefore,

$$\frac{d(b-a)}{dt} \alpha \frac{1}{4\Pi(b-a)b} \tag{7}$$

Since a is a constant,

$$\frac{d(b-a)}{dt} = \frac{db}{dt}$$

Therefore,

$$\frac{db}{dt} \alpha \frac{1}{4\Pi(b-a)b}$$

or

$$\frac{db}{dt} = \frac{H}{(b-a)b}$$

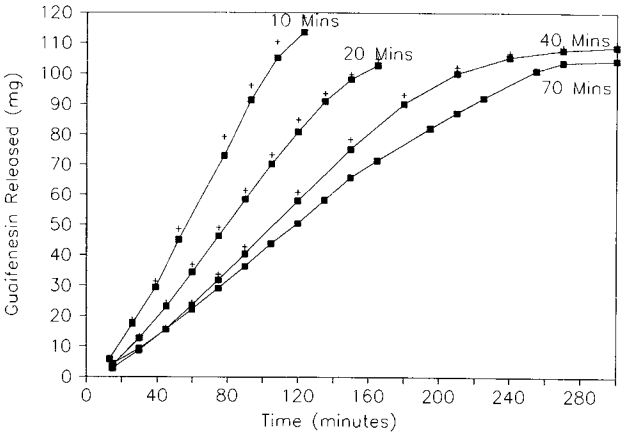

Fig. 5. Effect of coating time on guaifenesin release. (■) Average; (+) average + SD of four determinations.

Upon rearranging, we get $db[(b - a)b] = H\,dt$, i.e.,

$$db(b^2 - ab) = H\,dt \tag{8}$$

Upon integration from 0 to t,

$$\left[\frac{b^3}{3} - \frac{ab^2}{2}\right] = Ht + E \tag{9}$$

At $t = 0$, $b = a$, and Eq. (9) becomes

$$\left[\frac{a^3}{3} - \frac{a^3}{2}\right] = 0 + E$$

Therefore, the value of E is $-a^3/6$. Upon substituting the value of E in Eq. (9) and rearranging, the following relationship is obtained:

$$b^2(2b - 3a) + a^3 = Ht \tag{10}$$

Mathematically predicted coat thickness ($b - a$) as a function of time (t) [Eq. (10)] is shown in the upper curve in Fig. 6 (assuming that $a = 3.2$ mm and $H = 1.00$ mg/min). It is evident that the coat thickness is predicted to increase with an increase in coating time. Also, the increase in coat thickness with coating time is nonlinear, i.e., the coat thickness appears to increase rapidly at first and then the rate of increase appears to decline. This is due to two reasons. First, per unit time, less reactant is expected to diffuse through the increased coat thickness. Second, surface area increases with coat thickness, and therefore, more coating is required to achieve the same increase in thickness.

The lower curve in Fig. 6 shows the predicted rate of increase in coat thickness (db/dt) with coating time. Immediately after the coating process begins, the rate of increase in coat thickness is very high. However, the rate of increase is predicted to decline rapidly and soon approach zero.

Coat thickness obtained from the experimental data was plotted against coating time (Fig. 7). The data points were superimposed with the curve obtained from the mathematical model [Eq. (10)]. An excellent correlation was observed between the theoretically predicted rate of increase in coat thickness and the experimental data (Table III). The mathematical equation predicting coat thickness with respect to coating time is given by

$$b^2(2b - 3a) = Ht - a^3 \tag{10}$$

The equation was linearized by taking the first term on the left side as a function of b, $[f'(b)]$, where $f'(b) = b^2(2b - 3a)$. Thus, Eq. (10) becomes

$$F'(b) + a^3 = Ht \tag{19}$$

This is a linear equation with one independent variable, time (t), and one dependent variable, function of b $[f'(b)]$. The linear regression data for the equation are shown in Table III. The theoretical intercept, $-a^3$, is predicted to be -32.77 and correlates very well with the intercept obtained by linear regression of the experimental data (-32.29 ± 1.18). Also, the correlation coefficient obtained (0.998) is indicative of a near-perfect fit with the mathematically predicted coat thickness.

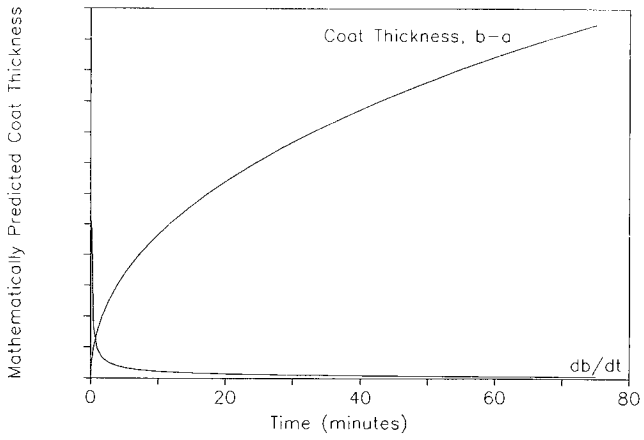

Fig. 6. Mathematically predicted film thickness as a function of time.

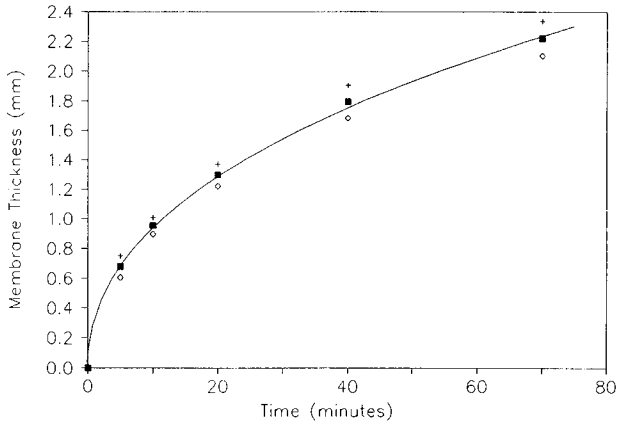

Fig. 7. Increase in film thickness as a function of coating time. (■) Average; (+) average + SD; (△) average − SD of 25 or more determinations.

Mathematical Model for Film Weight

Assumption for Film Weight

Film Formation Process Is Dependent on Availability of a Reactant. Therefore, the rate of increase in film weight is proportional to the rate of release of reactant. Mathematically, the following relationship is obtained:

$$\frac{dW}{dt} \alpha \frac{dM_t}{dt} \tag{11}$$

From Eqs. (3) and (11),

$$\frac{dW}{dt} \alpha \frac{b}{(b - a)}$$

Upon rearranging, we get $dW \times [(b - a)/b] \alpha\, dt$, i.e.,

$$dW(1 - a/b) \alpha\, dt \tag{12}$$

Weight of film is given by $W = (4\Pi/3)(b^3 - a^3)\rho$. Upon rearranging, the following relationship is obtained.

$$W \times \frac{3}{4\Pi\rho} = b^3 - a^3 \tag{13}$$

let

$$\frac{3}{4\Pi\rho} = z, \qquad \text{a constant}$$

Upon rearrangement and substitution of z, Eq. (13) becomes

$$b^3 = Wz + a^3$$

or

$$b = (Wz + a^3)^{1/3} \tag{14}$$

From Eqs. (12) and (14), we get

$$dW - dW \frac{a}{(Wz + a^3)^{1/3}} \propto dt$$

or

$$dW - dW \frac{a}{(Wz + a^3)^{1/3}} = H'dt \tag{15}$$

Integration from 0 to t provides

$$W - \frac{3a}{2z}(zW + a^3)^{2/3} = H't + E' \tag{16}$$

at $t = 0$, $W = 0$. Incorporation of these values in Eq. (16) provides

$$E' = \frac{-3a^3}{2z} \tag{17}$$

From Eqs. (16) and (17), we get

$$W - \frac{3a}{2z}(zW + a^3)^{2/3} = H't - \frac{3a^3}{2z} \tag{18}$$

Upon plotting mathematically predicted coat weight (W) as a function of time (t), a curve similar to that in Fig. 6 was obtained. Experimental data obtained fitted the mathematical model for coat weight, as indicated by the solid line in Fig. 8. Equation (18) was linearized by assigning $f(W)$ as a function of coat weight such that

$$f(W) = W - \frac{3a}{2z}(zW + a^3)^{2/3}$$

Thus, Eq. (18) becomes

$$f(W) = H't + \frac{3a^3}{2z} \tag{20}$$

From the experimental value of W obtained, $f(W)$ was calculated and regressed against coating time (Table IV). The correlation ($r^2 = 0.998$) indicated that the increase in coat weight was accurately predicted by the mathematical model. Also, the intercept obtained by regression (-220.31 ± 3.24 closely matched the theoretical intercept of -216.18).

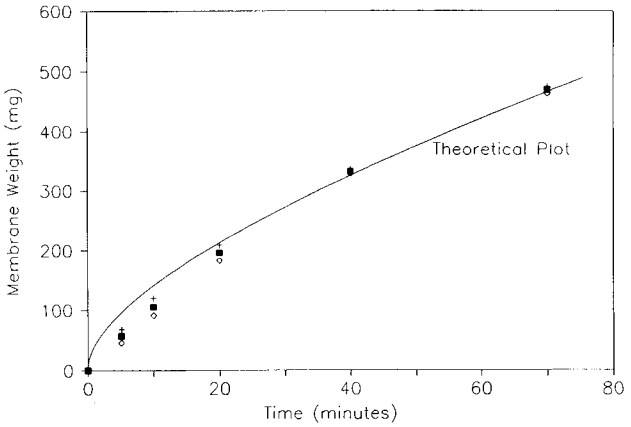

Fig. 8. Increase in film weight as a function of coating time. (■) Average; (+) average + SD; (△) average − SD of four determinations.

Depletion of Reactant

The amount of calcium acetate depleted corresponded with the increase in weight of calcium alginate coat (Fig. 9; $r^2 = 0.990$). Experimental validation of the mathematical models support the assumptions made for the coating process. Thus, the coating process is validated to be driven by diffusion of reactant through the reactant–polymer film, i.e., the formation of coat is diffusion controlled.

Along with the reactant, a small amount of drug was also lost during coating. The amount of drug lost appeared to increase with coating time and this loss may provide one of the limitations of this coating process for an expensive, water-soluble drug.

Drug Release Kinetics

Consistent with the model for membrane-controlled drug release systems, the calcium alginate-coated tablets gave a predominantly linear release. Also, with an increase in coating time (resulting in an increase in coat thickness), the rate of drug release decreased, further confirming the theory that drug release is controlled by the membrane thickness.

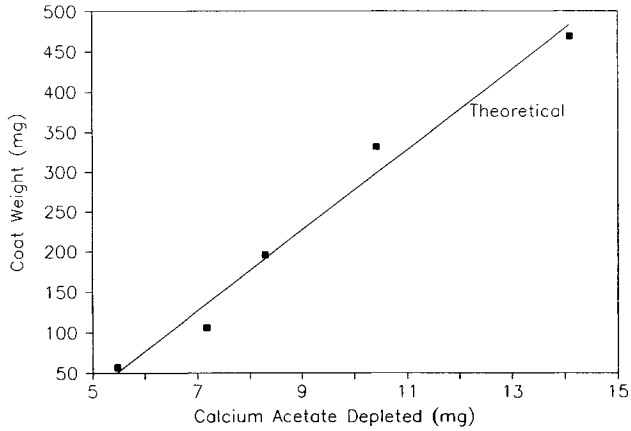

Fig. 9. Plot of amount of calcium acetate depleted against coat weight. (■) Average of four determinations.

CONCLUSIONS

1. Uniform membrane coating of tablets is achieved by diffusion-controlled interfacial complexation.
2. The coating process is accurately predicted by mathematical models.
3. Linear release profiles are attained by the coated guaifenesin tablets.

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NOMENCLATURE

A	Surface area of the device/membrane $(mm)^3$
a	Inner radius of coat (mm)
b	Outer radius of coat (mm)
C_1	Concentration of dissolved drug inside the core (mg/ml)
C_2	Concentration of dissolved drug in dissolution medium (mg/ml)
D	Drug diffusion coefficient per unit surface area of membrane
dC/dx	Concentration gradient (mg/ml/mm)
DK	Permeability (P) of drug through membrane
dM_t	Mass of diffusing substance released at time t (mg)
E,E'	Constants of proportionality
H,H'	Constants of proportionality
K	Partition coefficient of drug across membrane
l	Thickness of membrane (mm)
ρ	Density of calcium alginate film (g/ml)
S	Solubility of drug at 37°C (mg/ml)
t	Time from beginning of coating process (minutes)
W	Weight of film (mg)
Z	Constant, equal to $3/(4\Pi\rho)$

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