Controlled Release of Substituted Benzoic and Naphthoic Acids Using Carbopol® Gels: Measurement of Drug Concentration Profiles and Correlation to Release Rate Kinetics

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Purpose. The objective of this study is to correlate drug release mechanism with measured drug concentration profiles in gel layers of Carbopol® matrices containing mesalamine or benzoic acid.

Methods. Release rate experiments with Carbopol® matrices were performed using a rotating disk apparatus. Matrices were frozen and the gel layer in the matrices was sliced using a microtome in a cryostat. Drug concentration profiles were determined by direct measurement of the concentration of the drug in the gel slices. The pH of the slices was measured using microelectrodes, and water content was measured by Karl Fisher titration.

Results. The concentration gradient in mesalamine matrices decreased over time and correlated with square root of time release rate kinetics. The concentration profiles of benzoic acid were unchanged over time and correlated with zero order release rate kinetics. Carbopol gel layers were highly hydrated (93–95% water). Gel layers in matrices with mesalamine had a more alkaline microenvironmental pH. This higher pH resulted in increased growth of the thickness of the gel layer and a reduction drug diffusivity in comparison to benzoic acid matrices.

Conclusions. The release rate kinetics of mesalamine and benzoic acid correlated to the measured concentration profiles. The shape of the concentration profiles is determined by the rate of growth of the Carbopol® gel layer and drug diffusivity.

KEY WORDS: Carbopol®; mesalamine; benzoic acid; concentration profiles; release rate mechanism; diffusion.

INTRODUCTION

The physicochemical properties of ionizable compounds influence the pH and ionic strength in the microenvironment of dissolving tablets (1–3) and polymeric matrices (4). The influence of the drug in the microenvironment is an important consideration when incorporating an ionizable compound into a polymeric matrix where the formation of a gel layer which controls drug release is pH-dependent. Gel layer formation influences drug release by decreasing drug diffusivity and increasing the diffusional pathlength of the drug in the matrix. The objective of this research is to link the physicochemical properties of drugs with gel layer formation and the release rate kinetics from pH-dependent polymeric matrices.

Carbopol® is a highly hydrophilic polyacrylic acid polymer which has gel-forming properties. When hydrated, the polymer uncoils and generates an increase in viscosity. Upon neutralization, the carboxyl groups ionize and the polymer expands to form a gel due to electrostatic repulsion of the negative charges. Gel formation is dependent on pH, ionic strength, and polymer concentration. Previous studies have demonstrated that gel layer formation in Carbopol® matrices controls the release of a series of substituted benzoic and naphthoic acids (4). The intrinsic solubility and ionization characteristics of these compounds established the microenvironmental conditions in the matrix and influenced pH-dependent Carbopol® gel formation. These studies demonstrated the interdependence of the physicochemical properties of the drug and polymer on gel formation which is necessary to obtain controlled release.

The release of drugs from initially dehydrated matrices involves the absorption of water, polymer chain relaxation processes and swelling, and dissolution and diffusion of the drug through a swollen polymer layer into the external medium (5–11). Drug release characteristics are commonly linked to water sorption with associated polymer chain relaxation processes (6–10,12) and polymer erosion (13–16). The mechanism of drug release is generally deduced from models and data obtained from the external dissolution medium. In these studies, the mechanism of drug release is elucidated from direct measurement of drug concentration profiles, pH profiles, and water content in the gel matrix. The microenvironmental profiles of two model compounds, mesalamine, or 5-amino salicylic acid, ($pKa_{carboxyl}$ 2.3 and pKa_{amino} 5.3) (3–4) and benzoic acid ($pKa_{carboxyl}$ 4.0) (1), were examined because of release rate differences. The influence of the rate of gel layer formation and drug diffusivity on the concentration profiles of these model compounds is linked with drug release rate kinetics.

MATERIALS AND METHODS

Materials

Mesalamine, gentisic acid, salicylic acid, 3-hydroxy-2-naphthoic acid, and 2-naphthoic acid were obtained from Sigma Chemical Co., St. Louis, Missouri. Benzoic acid, monobasic and dibasic potassium phosphate, hydrochloric acid, sodium hydroxide, and the coulometric titration reagents, Hydranal® Coulomat A, Hydranal® Coulomat CG, and Hydranal® Composite 5, were obtained from Fisher Scientific Co., Fair Lawn, New Jersey. Carbopol® 974P were kindly provided by BF Goodrich Co., Cleveland, Ohio. Tissue-Tek O.C.T. Compound 4583 was obtained from Miles Scientific, Naperville, Illinois.

Release Rate Experiments

Release rate studies were performed with compressed tablets of pure drug or drug physically mixed with Carbopol® 974P (10%). All experiments were performed at 37°C in pH 8.00 phosphate buffer (0.067 M) using a rotating disk appa-

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ratus as previously described (3). The flux of the pure drug was determined by measuring the cumulative amount of drug released into the dissolution medium over a period of 30 minutes. The flux of the drug mixed with Carbopol® was determined by measuring the cumulative amount of drug released over a period of 4 hours. All dissolution medium samples were analyzed spectrophotometrically (Shimadzu 160U Spectrophotometer) in 0.1 N HCl or pH 8.00 phosphate buffer at the wavelength where the drug exhibited maximal absorbance. All release rate studies were performed in triplicate.

To describe the curvature of the release profiles, the software program PCNONLIN was used to fit the release rate data to the relationship (13)

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t is the amount of drug released at time, t, normalized to the total amount of drug released in 4 hours, M_∞, k is the release rate constant of *n*th order, and *n* is the release exponent. The exponent *n* is used to characterize the mode of release, with $n = 0.5$ for square root of time kinetics and $n = 1.0$ for zero-order kinetics.

Determination of Concentration, pH, and Water Content Profiles

Release rate experiments were performed with mesalamine and benzoic acid as described above. At specific time points, tablets were removed from the dissolution medium and immediately frozen in liquid nitrogen. The base (unhydrated end) of the frozen tablets was affixed to a flat peg with embedding medium without disturbing the frozen gel layer. The frozen gel layer at the surface of the tablets was sliced using a microtome in a cryostat maintained at −22°C. The gel layer was sliced tangent to the tablet surface in 20–80 μm increments. If the frozen gel became cracked or broken during slicing, the tablet was discarded, and the experiment was repeated with a new tablet. Frozen slices were retrieved from the blade of the microtome using warmed glass slides (≈1 cm^2). The warm slide was positioned over the slice, and the frozen slices immediately adhered to the slide by melting onto the warm surface. Slices were weighed on a balance (sensitive to 0.01 mg) which was previously tared with the glass slide. Gel layer thickness was calculated as the sum of the thicknesses of the gel slices obtained before reaching the undissolved drug in the matrix.

Concentration profiles for mesalamine and benzoic acid were obtained by measurement of the drug concentration in each slice. Each weighed gel slice was placed in 0.1 N HCl. The mesalamine concentration in each gel slice was determined by spectrophotofluorometric analysis of these samples at excitation and emission wavelengths of $\lambda_{ex} = 300$ nm and $\lambda_{em} = 430$ nm, respectively. The concentration of benzoic acid was determined using spectrophotometric analysis at a wavelength of 225 nm. The concentration gradient was analyzed by linear regression of drug concentration in each gel layer as a function of distance.

The pH profiles were obtained by measuring the pH of melted gel slices with microelectrodes (MI-404 Flat Membrane pH Electrode/MI-401 Micro-Reference Electrode, Microelectrodes, Inc.). The solubility of mesalamine and benzoic acid at the dissolving drug surface was estimated using the pH of slices containing undissolved drug and the relationship

$$pH = pKa + \log\left(\frac{S - S_o}{S_o}\right) \quad (2)$$

where S is the total solubility at a given pH and S_o is the intrinsic solubility of the neutral species. Intrinsic solubilities of 1.4 (17) and 4.1 mg/ml (3) and pKa values of 5.3 (amino) (4) and 4.0 (1) were used for mesalamine and benzoic acid, respectively.

The water content of the gel layers of mesalamine and benzoic acid tablets was determined by measuring the weight of water per weight of gel slice by Karl-Fischer titration using a Fisher Scientific Coulomatic™ K-F Titrator® (Model 447).

The concentration, pH, and water content profiles are plotted as a function of fractional distance. The fractional distance at each timepoint, f^t, was calculated by

$$f^t = 1 - \frac{h^t}{T^t} \quad (3)$$

where h is the distance sliced into the gel layer at time, t, and T is the total thickness of the gel layer at t. A f^t value of 0 indicates the front of the dissolving drug in the gel layer. An f^t value of 1 indicates the position of the edge of the gel layer at each timepoint. The data is presented as the fractional distance normalized to the thickness of the gel layer at three hours, f, calculated by

$$f = f^t\left(\frac{T^t_{avg}}{T^3_{avg}}\right) \quad (4)$$

where T is the average total thickness of the gel layers at t and 3 hours. A f value of 0 indicates the front of the dissolving drug in the gel layer. An f value of 1 indicates the position of the edge of the gel layer at 3 hours.

Diffusion Experiments

The diffusivity of benzoic acid in Carbopol® gels was determined using a free diffusion method similar to that of Upadrashta and coworkers (18) and Schantz and Lauffer (19,20). Diffusion experiments were not performed with mesalamine due to drug instability in the experimental conditions.

Carbopol® gels (3.0 and 6.0% Carbopol®) were made by adding small portions of water to Carbopol® and vigorously triturating after each addition with a glass mortar and pestle. Once all the water had been added, the gel pH was adjusted to 4.5 or 7.0 with the addition of known volumes of 10 M sodium hydroxide. Gels with partially wetted polymer lumps were not used. Bubbles were removed from the gels by centrifugation for 12 minutes at 5000 rpm. The final pH was measured after the gels were stored overnight at 37°C and was within 0.2 units of the original pH.

Saturated benzoic acid solutions were made by adding an excess of drug to purified water and adjusting the pH to

4.5 with NaOH. Solutions were stirred for 12 hours at ambient room temperature. The final pH of the solution was 4.5. Solutions were filtered using a 0.45 μm membrane filter. For neutral benzoic acid solutions, the pH of the filtered solutions was increased to pH 7.00 using 10 M NaOH. NaCl was added to adjust the ionic strength to equal that of the Carbopol® gel which was estimated based on the ionization characteristics of the polymer (4) and amount of NaOH added for pH adjustment. The final concentration of benzoic acid was determined by spectrophotometric analysis as described above.

The Carbopol® gels were placed in 7 ml plastic syringes with the ends removed, such that the gels were flush with the open end. Each syringe was placed open-end (gel-side) down in a container with a bottom consisting of a filter paper fitted over a screen. The container was immersed into a large beaker containing benzoic acid solution at 37°C. The system was sealed to prevent evaporation and was placed on a stirring plate in an oven maintained at 37°C. After 24 hours, the syringes were removed from the container, and the gel was pushed out with a calibrating device operating on the plunger. Gel slices of uniform thickness were cut and weighed. Each slice was then placed into 20 ml of 0.1 N HCl and placed in a shaker for 24 hours. These samples were analyzed for benzoic acid content by spectrophotometric analysis. The final concentration of benzoic acid in the bulk solution was measured by spectrophotometric analysis at the completion of the experiment.

The diffusion coefficient, D, was calculated independently for each slice, i, by the relationship (18,20,21):

$$\frac{C_i}{C_o} = 1 - \text{erf}\left(\frac{x}{2(D_i t)^{1/2}}\right) \quad (5)$$

where C_i is the relative concentration of benzoic acid. C_i is defined as the benzoic acid concentration in each gel slice divided by the final benzoic acid concentration in the bulk solution after 24 hours. C_o is the concentration at the solution/gel interface, x is the distance from the gel surface to the center of the slice, and t is experimental time. The diffusion coefficient of benzoic acid in Carbopol® was calculated as the average of the values determined for each slice.

A widely used criterion for Fickian diffusion is that transport is proportional to the square root of time. The diffusion characteristics of benzoic acid in Carbopol® at 24 hours were evaluated using the equation

$$\ln\left(\frac{d\pi^{1/2}\Sigma C_i}{2C_o D^{1/2}}\right) = n_D \ln t \quad (6)$$

where n_D is the coefficient which must equal 0.5 if the diffusion mechanism is Fickian (18).

RESULTS

Release Rate Experiments

When initially dry Carbopol® matrices are exposed to an aqueous medium, polymer hydration and swelling results in the formation of a rubbery gel layer at the surface of the matrix and a hydrated layer with polymer and undissolved drug (4). The drug dissolves at the hydrated polymer/undissolved drug surface, diffuses through the gel layer, and is released into the bulk medium. The release rate profiles of the substituted benzoic and naphthoic acids from these matrices varied in degree of curvature. Curved release rate profiles indicate that the release rate is decreasing over time, whereas linear profiles indicate a constant release rate. The release exponent, *n*, is representative of the degree of curvature and varies between approximately 0.5 and 1.0 for all the compounds tested (Table I). Mesalamine exhibits the greatest degree of curvature and benzoic acid is most linear. The fraction of mesalamine released is linearly related to the square root of time ($n = 0.557$), which generally indicates that release is controlled by non-steady state diffusion (22). The linear relationship between the fraction of benzoic acid released and time ($n = 0.985$) is indicative of zero order release and steady state diffusion. Based on the value of *n*, mesalamine and benzoic acid were chosen as model representatives of the boundaries of release mechanism.

Drug Concentration Gradients

The drug concentration profiles in the gel layers of matrices containing the model compounds were analyzed in elucidate differences in the release mechanism. The measured concentration profiles in gel layers formed in mesalamine matrices are characterized by a high concentration of drug at the undissolved drug/gel interface which declines with distance to the gel/bulk medium interface (Figure 1). Inspection of the mesalamine profiles over time shows that the concentration gradient decreases. No changes in the concentration gradient are apparent in benzoic acid matrices (Figure 2). In both mesalamine and benzoic acid matrices, the first slices of the gel layer contained unusually high concentrations of drug. This result is attributed to visible sublimation of water from the gel layer surface while handling the frozen matrices at ambient room temperature. Evaporation of water from the gel surface would increase the drug concentration per weighed gel slice, yielding high drug concentrations in these slices.

The analysis of the concentration profiles is shown in Table II, including the concentration gradient determined by linear regression and 95% confidence intervals with corresponding p values ($\alpha = 0.05$) to denote the statistical difference of the value of the gradient from zero. The concentration gradient in the gel layer of mesalamine matrices at 30 minutes is not statistically different from zero, indicating that the concentration gradient is flat and independent of gel thickness. At 60 minutes, the concentration gradient is greatest and then gradually decreases over time. If the measured

Table I. Analysis of Release Rate Data for Substituted Benzoic and Naphthoic Acids

Compound	*n*
Mesalamine	0.557
Gentisic acid	0.675
2-Naphthoic acid	0.728
Salicylic acid	0.788
3-Hydroxy-2-Naphthoic acid	0.871
Benzoic acid	0.985

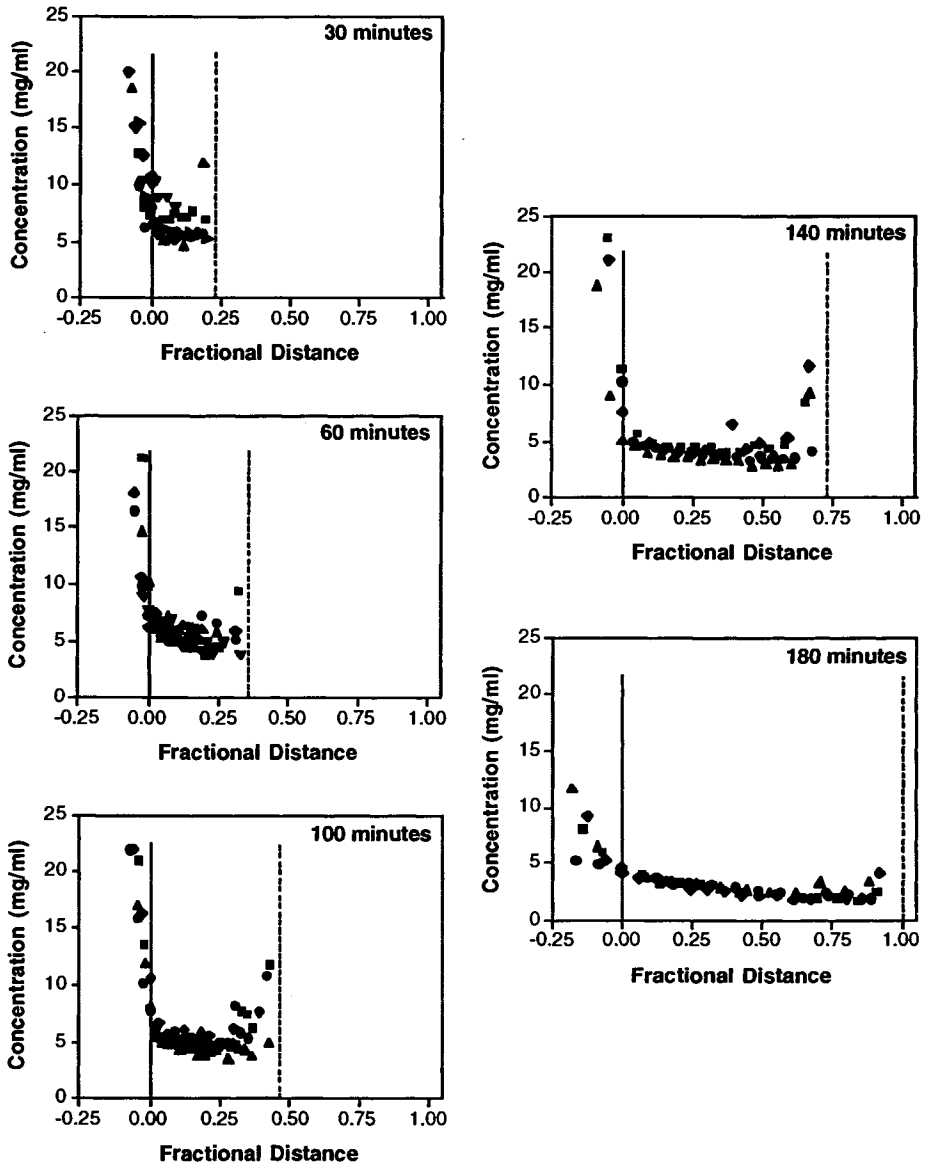

Fig. 1. Concentration profiles of mesalamine in gel layers of Carbopol® matrices at 30, 60, 100, 140, and 180 minutes.

concentration profiles represent the actual concentration gradients, then the intercepts of the concentration gradients at each time point should approach the solubility of mesalamine at the dissolving drug surface. However, these intercepts are considerably lower than the total solubility estimated from the surface pH and intrinsic solubility estimated at 20 mg/ml. The concentration gradient in the gel layer of benzoic acid matrices is not significantly different from zero over the time period studied. Hence, the concentration of benzoic acid across the gel layer is essentially constant. In this case, the average concentration of the drug at any point in the gel layer is indicated by the intercept. The intercept is constant at both the 60 and 180 minute time points, indicating no change in the level of drug concentration in the gel layer over time. Similar to matrices containing mesalamine, these intercepts are considerably lower than the solubility at the surface which is estimated at 22 mg/ml.

The release of a drug from a gel is directly dependent on the concentration gradient. The decrease in the concentration gradient in mesalamine matrices over time is consistent with the reduction in release rate over time in the release rate profile (n = 0.557). For benzoic acid, the lack of change of the concentration gradient is consistent with the constant release rate (n = 0.985).

pH Gradients

The pH of the microenvironment has a direct impact on the degree of polymer ionization and gel formation which influences the rate of growth of the thickness of the gel layer and drug diffusivity (4). Evaluation of these factors which will ultimately affect the shape of the concentration profile is necessary to understand the mechanism of drug release. Because of ionization and chemical reactions occurring between the drug, polymer, and bulk medium in the gel layer, a pH gradient exists in the gel layer between the undissolved

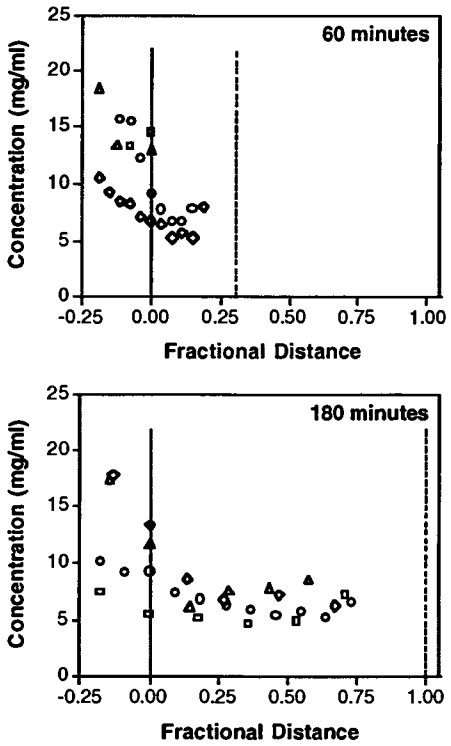

Fig. 2. Concentration profiles of benzoic acid in gel layers of Carbopol® matrices at 60 and 180 minutes.

drug/gel and gel/bulk medium interface as shown for mesalamine and benzoic acid in figures 3a and b. As the drug dissolves and diffuses through the gel layer and out to the bulk medium, it reacts with the bulk solution species diffusing into the gel layer. The resultant pH gradient is characterized by a relatively low pH at the dissolving weak acid front which increases with distance to a more alkaline pH at the gel/bulk solution interface. Mesalamine matrices are characterized by a more alkaline pH gradient (pH $\approx$ 6.6 to 7.3) compared to benzoic acid (pH $\approx$ 5.2 to 6.0). The degree of polymer ionization and gel viscosity will increase across the gel layer in a manner consistent with these pH gradients.

Water Content

The drug concentration profiles can potentially be influenced by polymer and water concentration gradients. These gradients can impact on gel layer thickness and drug diffusivity. However, the water content in the Carbopol® matrices is constant throughout the gel layer (Figures 4a and b). In most cases, the first gel slices were low in water content which is consistent with the observation of sublimation of water occurring at the gel surface and associated high drug concentrations discussed above. The average percent water contents for gel layers of mesalamine and benzoic acid matrices are 95.1 $\pm$ 0.9% and 93.3 $\pm$ 1.0%, respectively, indicating that the polymer is highly hydrated. The constant water content suggests that polymer concentration is also constant across the gel layer. Release is controlled by dissolution at the solid drug dissolution front and subsequent diffusion of the drug through an equilibrated gel rather than by water sorption mechanisms as observed by other investigators (6–10,12).

Rate of Growth of Gel Layer

Evaluation of these pH gradients and water content provides the basis to understand the factors which influence the rate of growth of the thickness of the gel layer. The shape of the concentration profiles is affected by rate of growth of the gel layer because the diffusional pathlength for the diffusing drug is increasing over time. Figure 5 demonstrates that the rate of growth of the thickness of the gel layer of mesalamine tablets greatly exceeds that of benzoic acid. Matrices with mesalamine have a higher microenvironmental pH which results in greater gel swelling and decreased polymer dissolution at the gel/bulk medium interface (4). Both of these factors increase the thickness of the gel layer in mesalamine matrices over time and therefore, affect the concentration profile and drug release rate. Benzoic acid matrices have a relatively lower microenvironmental pH. This results in a slower rate of growth of the gel layer due to less swelling and increased polymer dissolution (4).

Drug Diffusivity

Drug diffusion characteristics influence the shape of concentration profiles (18) and drug release. Drug diffusivity in gels is influenced by polymer hydration, polymer concentration, pH and ionic strength due to effects on polymer structure (23–28). Decreased drug diffusivity is attributed to drug-polymer interactions, obstruction effects, and increased microviscosity (20,25). With increasing Carbopol® concentration and pH, benzoic acid diffusivity decreased. This is indicated by the calculated diffusion coefficients listed in Table III. Diffusivity is reduced by increased obstruction at higher polymer concentrations. At neutral pH values, diffusivity is reduced because of increased polymer chain stiffness due to electrostatic repulsion and an increased number of negative charges (18,28). Negatively charged benzoic acid will be repelled by the negative charges on the polymer (18). The n values where close to 0.5, indicating that diffusion in Carbopol® gels is Fickian and not influenced by drug-polymer interactions (18). Although diffusion experiments with mesalamine were not possible due to instability, the diffusion characteristics of mesalamine and benzoic acid in Carbopol® are presumably alike. This assumption is based on their structural similarity, comparable aqueous diffusion coefficients (1,3), and lack of evidence of drug-polymer interactions as assessed by dialysis and solubility experiments in our laboratory.

DISCUSSION

Correlation of Drug Concentration Profiles with Drug Release Rate

In matrices containing mesalamine, the calculated intercept of the concentration gradient is lower than the estimated solubility of the drug. Assuming that the concentration of the drug at the drug/gel interface is approximately equal to its solubility, a steep gradient must exist immediately along the dissolving drug surface, but is not measurable

Table II. Analysis of Mesalamine and Benzoic Acid Concentration Profiles

Time (min)	dC/dx[a]	C.I. ±95%	p value[b]	i[c]	n
			Mesalamine		
30	−2.96 ± 4.33	8.91	$p > 0.20$ n.s.	6.62 ± 0.43	18
60	−10.4 ± 1.56	3.12	$p < 0.002$	6.64 ± 0.20	42
100	−4.36 ± 0.81	1.63	$p < 0.002$	5.62 ± 0.15	51
140	−2.51 ± 0.42	0.84	$p < 0.002$	4.72 ± 0.14	46
180	−2.18 ± 0.18	0.37	$p < 0.002$	3.67 ± 0.10	46
			Benzoic Acid		
60	−14.1 ± 7.49	19.3	$p > 0.1$ n.s.	7.50 ± 0.71	7
180	−2.48 ± 1.42	3.04	$p > 0.05$ n.s.	7.22 ± 0.56	17

[a] Change in concentration (mg/ml) per fractional distance obtained by linear regression.
[b] $\alpha = 0.05$.
[c] intercept (mg/ml).

by the technique used in this study. The concentration of the drug then gradually decreases with distance to the edge of the gel layer. The concentration gradient in the gel decreases over time and increasing thickness of the gel layer. This decrease in the concentration gradient in the gel is rate-limiting and directly correlates to the decreasing rate of drug release over time. For matrices containing benzoic acid, the low value of the intercept compared to the estimated solubility also suggest the existence of a sharp concentration gradient immediately along the dissolving drug surface. However, in contrast to mesalamine, the gel layer is thin, the concentration gradient is flat, and the amount of drug in the gel layer is constant over time. In this case, the rate limiting step exists in either the gradient at the dissolving drug surface or in the aqueous boundary layer at the gel/bulk medium interface. Because the level of the drug in the gel layer is constant, neither of these rate-limiting gradients are time-dependent. This result directly correlates with the constant rate of release of benzoic acid over time.

Role of Rate of Gel Layer Formation and Drug Diffusivity

The rate of gel layer formation and drug diffusivity were examined to identify the factors which determine the shape of the concentration shape. The gel layer of mesalamine tablets is greater than benzoic acid due to differences in the microenvironmental conditions. Carbopol® gel formation and swelling increases with an increase in pH from approx-

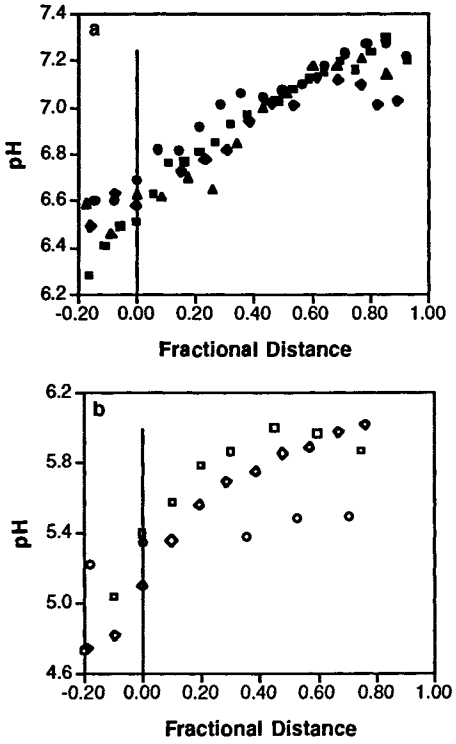

Fig. 3. pH profiles in gel layers of mesalamine (a) and benzoic acid (b) Carbopol® matrices at 180 minutes.

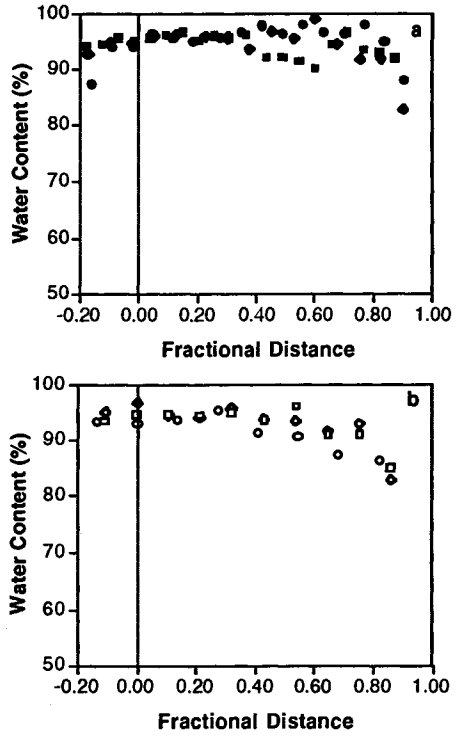

Fig. 4. Water content of gel layers in mesalamine (a) and benzoic acid (b) Carbopol® matrices at 180 minutes.

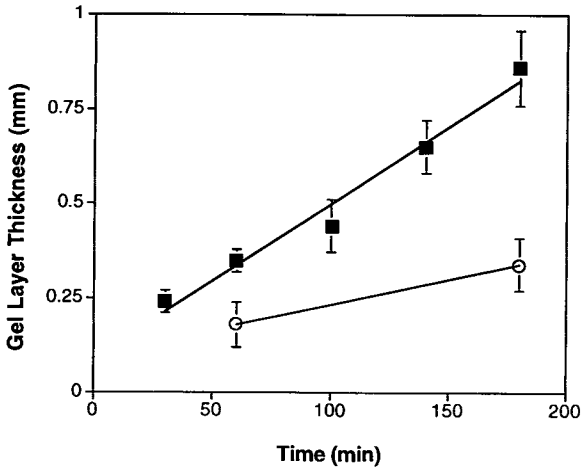

Fig. 5. Growth of gel layer thickness as a function of time in Carbopol® matrices containing mesalamine (■) and benzoic acid (○).

imately 4 to 8 (29). The more alkaline pH profile in mesalamine matrices (Figures 3a and b) results in greater swelling and decreased polymer dissolution which increases the thickness of the gel layer over time. In contrast, the more acidic pH profile in benzoic acid matrices will reduce the degree of swelling and increase polymer dissolution (4).

The rate of growth of the thickness of gel layer in mesalamine matrices is rapid compared to drug diffusivity. As the thickness of the gel layer increases over time, the drug has to diffuse a greater distance to reach the bulk medium. The inability of drug to diffuse at a rate comparable to gel growth results in a decreasing concentration gradient and release rate over time. In contrast, the rate of growth of the thickness of the gel layer for benzoic acid is remarkably slower. In these matrices, the rate of diffusion of the drug is sufficient to load and maintain a constant drug level in the gel. Furthermore, considering the effect of pH on benzoic acid diffusion, the diffusivity of mesalamine is likely to be reduced due to the higher microenvironmental pH in the matrix. A smaller diffusivity will contribute to the inability of mesalamine to diffuse at a rate comparable to the rate of gel growth. Alternatively, in benzoic acid matrices, the higher drug diffusivity may aid the establishment of a constant level of drug in the gel layer. The water content of the gel layers for both compounds are similar, and therefore, differences in drug diffusivity due to polymer concentration are not likely.

Differences in release mechanism were elucidated by direct measurement of the drug concentration gradients, pH profiles, and water content in gel layers. The physicochemical properties of a drug play an important role in establishing the microenvironmental conditions which directly impacts on gel structure and the kinetics of gel layer formation. The resultant rate of gel layer formation and drug diffusivity influences the shape of the concentration gradient and the mechanism of drug release.

Table III. Diffusion Coefficients and n_D values for Benzoic Acid in Carbopol Gels

Carbopol Concentration (%)	pH	D $(cm^2/s) \times 10^6$	n_D
0.0	—	12.0[a]	—
3.0	7.0	8.64 ± 0.22	0.498 ± 0.002
6.0	7.0	5.47 ± 0.18	0.498 ± 0.001
6.0	4.5	10.6 ± 1.4	0.498 ± 0.002

[a] Ref. (17).

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