Evaluation of the Physicochemical Properties and Dissolution Characteristics of Mesalamine: Relevance to Controlled Intestinal Drug Delivery

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The physicochemical properties of mesalamine and the effect of pH and buffer concentration on the dissolution rate of pure mesalamine and mesalamine with Carbopol 974P were investigated. The aqueous solubilities at 25 and 37°C were 0.844 and 1.41 mg/mL, respectively. Consistent with the observed pK_{a_1} (2.30) and pK_{a_2} (5.69) of mesalamine, the solubility–pH profile is increased at pH <2.0 and pH >5.5 and is minimized from pH 2.0 to pH 5.5. The flux data were consistent with the solubility data from pH 1.0 to pH 5.5. The flux increased and plateaued at pH values 5.5 to 7.0 and was dependent on the bulk buffer concentration. At low bulk buffer concentrations, mesalamine reduces the pH in the diffusion layer, which results in a decrease in flux. The medium with the highest buffer capacity has a greater ability to increase the surface pH and dissolution rate. The addition of Carbopol reduces the flux and the sensitivity of the dissolution rate of mesalamine to increasing bulk buffer concentration. This reduction is postulated to be due to neutralization of the basic dissolution media, gel formation, and possible drug–polymer interactions.

KEY WORDS: mesalamine; 5-aminosalicylic acid; physicochemical properties; dissolution rate; flux; Carbopol; controlled release.

INTRODUCTION

Mesalamine, 5-aminosalicylic acid, is efficacious in the treatment of inflammatory bowel disease. However, systemic circulation of the drug may be associated with acute pancreatis (1,2) and nephrotoxicity (3,4). Minimizing the rate and extent of absorption of mesalamine would not only reduce the occurrence of adverse effects, but also maintain a high concentration of the drug directly at the diseased intestinal site for an extended period of time. Thus, the efficacy of mesalamine in the treatment of inflammatory bowel diseases may be optimized with a controlled release drug delivery system which maximizes topical exposure of the drug to the diseased tissue and minimizes systemic absorption of the drug.

Mesalamine is an amphoteric molecule, and the solubility and ionization characteristics are dependent upon pH and the pK_a values of the carboxyl and amino groups of the molecule. The structural formula and ionization scheme of mesalamine are depicted in Fig. 1. The cationic species (+Ao) predominates at pH values below the isoelectric point, the dipolar species predominates near the isoelectric point, and the anionic species (oA−) predominates at pH values above the isoelectric point. The pK_a values and pH influence the solubility and determine the predominant species in solution. In turn, the solubility and ionization properties affect the intrinsic release rate and membrane transport characteristics of the drug. The determination of the physicochemical properties and intrinsic dissolution rate of mesalamine will provide a basis for meaningful characterization of the controlled-release rate properties of the drug. The purpose of this study was to determine the physicochemical properties of mesalamine and to evaluate the effects of pH and buffer concentration on both the intrinsic dissolution rate and the release rate of the drug in the presence of the acidic, gel-forming polymer, Carbopol.

MATERIALS AND METHODS

Chemicals

Mesalamine and salicylic acid were obtained from Sigma Chemical Co., St. Louis, MO. Carbopol 974P was kindly provided by BF Goodrich Co., Cleveland, OH. Citric acid, monobasic potassium phosphate, dibasic sodium phosphate, hydrochloric acid, and sodium hydroxide were obtained from Fisher Scientific Company, Fair Lawn, NJ.

Solubility

The intrinsic aqueous solubility at 25 and 37°C was determined by adding an excess of mesalamine to unbuffered, purified water. The aqueous solubility as a function of pH at 37°C was determined at pH values ranging from 1.0 to 6.7 by adding an excess of mesalamine to unbuffered water and adjusting the pH with NaOH and HCL. All samples were placed in a constant temperature shaker bath and equilibrium was established in 24 hr. The pH was recorded at equilibrium, and the concentration of all saturated solutions was determined by dilution in citrate buffer (pH 3.5) and subsequent spectrophotometric analysis at a maximal wavelength of 298 nm using a Shimadzu 160U Spectrophotometer.

pK_a Determinations

The pK_{a_2} (amino) of the drug was obtained spectrophotometrically by utilizing the shift in the UV spectrum of mesalamine with pH. The absorbance of aqueous, unbuffered solutions of mesalamine (40 μg/mL) was measured at 298 nm as a function of pH values ranging from 3.9 to 8.0. The pH values of all solutions were obtained by adjustment with HCl or NaOH. The pK_{a_2} (amino) was calculated by analysis of spectrophotometric data using the method described by Connors (5). No shift in the UV spectra was observed when the pH of the solutions was less than 3.8, and the pK_{a_1} (carboxyl) could not be obtained via this method.

The pK_{a_1} (carboxyl) was obtained by the determination of the solubility of mesalamine ranging in pH from 1.0 to 2.5 at 25°C using the methods described above. The pK_{a_1} was calculated by analysis of the solubility data using the method described by Albert and Serjeant (6).

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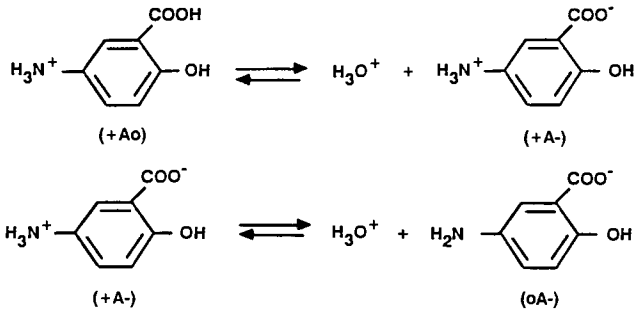

Fig. 1. Structural formula and ionization scheme of mesalamine. Cationic, amphoteric, and anionic species are represented as +Ao, +A−, and oA−.

Dissolution Rate Studies

Nondisintegrating, flat-faced tablets, 1.27 cm in diameter, of salicylic acid, mesalamine, or mesalamine with 1.0, 2.5, 5.0, and 10.0% Carbopol were prepared for dissolution. Tablets were prepared by compressing approximately 500 mg of drug powder at 4.5×10^3 kg for 1 min with a stainless-steel punch and die in a hydraulic press (Carver Laboratory Press, Model B). Tablets were compressed to form a smooth surface flush with that of the die.

The dissolution apparatus was similar to the rotating disk method employed by Nogami *et al.* (7). The apparatus consisted of a cylindrical glass cell with a rounded bottom immersed in a water bath maintained at 37°C. The dissolution medium (300 mL) was placed into the cell and allowed to reach and maintain 37°C. The die containing the flat-faced tablet was inserted into the dissolution medium. The shaft and holder were rotated overhead at 100 rpm by a controllable synchronous motor.

The dissolution apparatus was calibrated by comparing the experimental flux of salicylic acid with the flux calculated using the Levich equation (8). Salicylic acid was chosen as a model compound because of its structural similarity to mesalamine and well-established physicochemical properties (9,10). The region of rotational speed studied was assumed to be diffusion controlled. The experimental flux was determined at two stirring speeds, 50 and 100 rpm, and was predicted using the Levich equation (8). The studies with salicylic acid were performed at a pH (pH 1.0) below the pK_a of the molecule to ensure that dissolution was not influenced by ionization.

The dissolution rate and flux of salicylic acid, mesalamine, and mesalamine/Carbopol tablets were determined by measuring the cumulative amount of drug released in buffered dissolution media over a period of 30 or 60 min. Samples of dissolution medium were removed at 5- or 10-min intervals and immediately replaced with an equal volume of dissolution medium. The pH values of the buffered media after the dissolution studies were intermittently monitored and found to be constant. The approximate pH of the surface of the mesalamine/Carbopol tablets was determined by inserting pH paper into the gel-like surface after the dissolution study.

All samples were analyzed spectrophotometrically by measuring the absorbance of the samples of salicylic acid or mesalamine in 0.1 *N* HCl at wavelengths of 302 and 298 nm. Data corrections were made for previously removed samples in determining the amount of drug dissolved at each interval.

The pH of the surface of the dissolving tablet and relative flux of mesalamine as a function of bulk pH were calculated using a model developed by Aunins *et al.* (11) (see Appendix) for the dissolution of a weak acid in an aqueous solution containing a triprotic buffer. The properties of mesalamine and the buffers used in the dissolution experiments which were necessary for the use of the model are tabulated in Table I (12–14). A value of 2.8×10^{-5} was assumed for the diffusion coefficient of the hydroxide and hydroxyl ion (11,15,16). The diffusion coefficient of mesalamine was obtained by using the experimental flux at the isoelectric pH and calculating a value from the Levich equation (8).

RESULTS

The physicochemical properties of mesalamine, including the pK_a values, intrinsic solubility, and pH of saturated solutions, are tabulated in Table II. The U-shape of the experimental solubilities is shown in Fig. 2 and is consistent with previously determined data (17). The observed solubility increased at acidic pH values (pH <2.0) and more basic values (pH >5.5), corresponding to the ionization of the carboxyl and amino groups, respectively. At pH values between 2.0 and 5.5, solubility was minimized due to the existence of only the dipolar species.

In the calibration of the dissolution vessel, the experimental values for the flux of salicylic acid compared well with the calculated values. At 50 and 100 rpm, the calculated values were 4.22×10^{-6} and 5.97×10^{-6} g/cm² sec, and the experimental values ($n = 6$) were $3.76 \pm 0.06 \times 10^{-6}$ and $5.41 \pm 0.05 \times 10^{-6}$, respectively. Assuming the solubility and diffusion coefficient values used in the Levich equation (8) to vary between 5 and 10%, the calculated values may vary between 3.34×10^{-6} to 5.12×10^{-6} and 5.28×10^{-6} to 6.68×10^{-6} at 50 and 100 rpm. The experimentally determined values were within these ranges and considered acceptable.

Consistent with the pH-dependent observed solubilities above, the flux decreased rapidly with increasing pH to approximately pH 2.0, and between pH 2.8 and pH 4.0, the flux was minimal and apparently pH independent (Fig. 3). Above pH 4.0, the flux increases, but the magnitude of the increase at pH values greater than 5.5 is reduced despite the high

Table I. Physicochemical Properties of Mesalamine and Buffers Used in the Model for the Dissolution of a Weak Acid in an Aqueous Triprotic Buffer Solution (11)

Compound	Solubility ($\times 10^3$ *M*)	pK_{a_1}	pK_{a_2}	pK_{a_3}	*D* ($\times 10^6$ cm²/sec)
Mesalamine	9.21[a]	—	5.69[c]	—	7.46[c]
Citrate	—	3.13[b]	4.76[b]	6.40[b]	6.40[d]
Phosphate	—	2.15[b]	7.10[b]	12.3[b]	10.0[e]

[a] Intrinsic, aqueous solubility determined experimentally at 37°C.
[b] From Ref. 12.
[c] Determined experimentally.
[d] From Ref. 13.
[e] From Ref. 14.

Table II. Physicochemical Properties of Mesalamine[a]

Physicochemical property	25°C	37°C
pK_{a_1}	2.30 ± 0.09	—
pK_{a_2}	5.69 ± 0.04	—
Intrinsic solubility (mg/ml)	0.844 ± 0.021	1.41 ± 0.021
pH of saturated solution	4.05 ± 0.04	3.64 ± 0.04

[a] Each value is the mean from three or four experiments.

solubility of the drug at these pH values (Fig. 2). The calculated and experimental relative flux and calculated surface pH of mesalamine as a function of the bulk pH values above 5.6 are tabulated in Table III. The agreement between the observed and the predicted flux was good for each bulk pH and both buffer solutions. The flux at pH values greater than 5.6 increased with an increase in the buffer concentration of the dissolution medium. This is demonstrated by the increase in the relative flux in the phosphate (0.20 *M*) compared to the citrate (0.067 *M*) solution.

Figure 4 shows the effect of Carbopol on the release rate of mesalamine. The addition of increasing percentages of Carbopol results in corresponding reductions in the total amount dissolved over 60 min. The release rate of mesalamine is reduced in both 0.067 and 0.20 *M* phosphate solutions in the presence of Carbopol, and the sensitivity of the release rate to the increase in buffer concentration is diminished. The pH of the gel-like surface of the tablet determined via pH paper was estimated at 5.2 and 5.5 for the 0.067 and 0.20 *M* bulk buffer concentrations, respectively.

DISCUSSION

Similar to the models of Aunins *et al.* (11) and Mooney *et al.* (15,16), Fig. 5 is a representation of a steady state model of a solid amphoteric drug dissolving in buffered acid and basic medium. At low pH values, the zwitterionic form, +A−, diffuses into the diffusion layer and reacts with the incoming buffer species, BH, generating +Ao and B^- (Fig. 5, top). At higher pH values, mesalamine reacts with the incoming buffer species, B^-, generating oA− and BH (Fig. 5, bottom). At pH values above and below the isoelectric point, the dissolution rate is increased due to the production of the ionized forms of the drug, +Ao and oA−. Minimum solubility and dissolution rate are observed at pH values near the isoelectric point because the zwitterionic form of the drug is the predominant diffusing species.

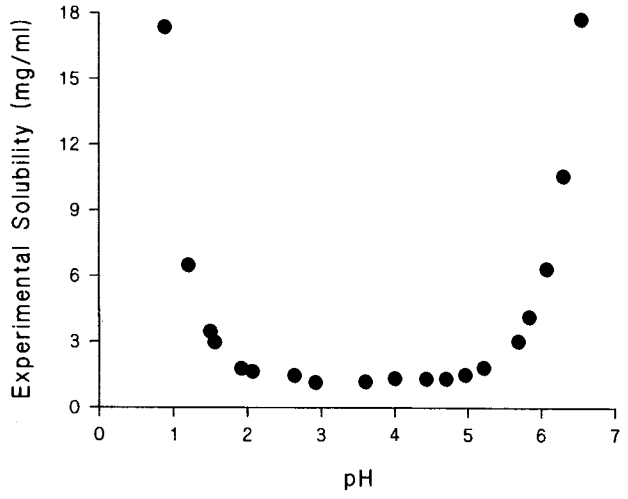

Fig. 2. Representative experimental pH–solubility profile of mesalamine. Equilibrium solubility of mesalamine at 37°C in unbuffered, saturated solutions of mesalamine ranging in pH from 1.0 to 6.7.

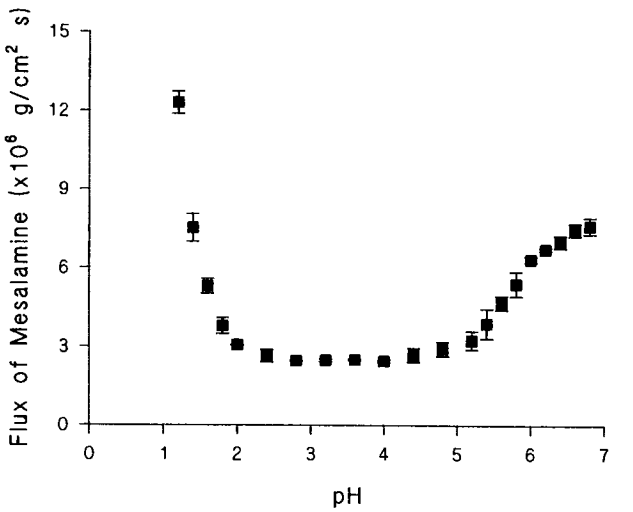

Fig. 3. Flux of mesalamine as a function of pH. pH 1.0 to 2.2 in HCl/KCl buffer (0.1 *M*) and pH 2.2 to 6.6 in citrate buffer (0.06 *M*). Data are plotted as the mean from at least two experiments.

The formation of +Ao and oA− is a function of the pK_a and intrinsic solubility of the drug, pH at the surface of the dissolving tablet, pH of the bulk solution, and pK_a and buffer concentration of the bulk solution (11,15,16). Mooney and co-workers demonstrated that the rate of dissolution of a solid is dependent on the pH at the dissolving surface, as well as the pH in the bulk solution. The ability of the drug to influence the microenvironmental pH is dependent upon its buffer capacity and intrinsic solubility (11,15,16). When the bulk solution has a low buffer concentration or buffer capac-

Table III. Relative Experimental (R_{exp}) and Calculated (R_{cal}) Flux and Calculated Tablet Surface pH (pH_o) of Mesalamine in Citrate and Phosphate Buffer Solutions[a]

	Citrate, 0.06 *M*			Phosphate, 0.2 *M*		
Bulk pH	R_{exp}	R_{cal}	pH_o	R_{exp}	R_{cal}	pH_o
5.6	1.86	1.56	5.44	—	1.49	5.26
5.8	2.12	1.75	5.56	1.75	1.69	5.50
6.0	2.43	1.99	5.68	2.07	2.04	5.70
6.2	2.67	2.27	5.79	2.81	2.58	5.89
6.4	2.87	2.59	5.89	3.49	3.38	6.07
6.6	2.97	2.91	5.97	4.74	4.51	6.23
6.8	3.05	3.20	6.03	6.28	6.00	6.39

[a] *R* is the flux at a given pH divided by the flux at the isoelectric point. R_{cal} and pH_o were calculated using a model for the dissolution of a weak acid dissolving in a triprotic buffer (11). The experimental rates were measured at 37°C using a rotating-disk apparatus at 100 rpm. Each R_{exp} is the mean from two or three runs.

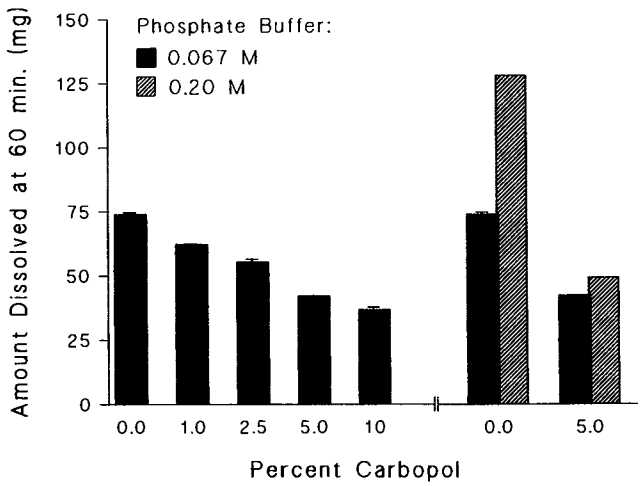

Fig. 4. The effect of increasing concentrations of Carbopol and buffer concentration on the dissolution rate of mesalamine at pH 8.0. Data are plotted as the mean from at least two experiments.

ity, the dissolving drug influences the microenvironmental pH and, hence, the dissolution rate. A dissolution medium with a high buffer concentration has a greater ability to influence the surface pH and control the dissolution rate (11,16).

The ability of mesalamine to influence the microenvironmental pH and reduce its own dissolution rate, or flux, is demonstrated in Fig. 3. At low pH values, the flux was consistent with the solubility due to the inability of the drug to maintain the pH of the diffusion layer with the high concentration of incoming hydrogen ions from the bulk medium. The increased flux is due to the high solubility and diffusion

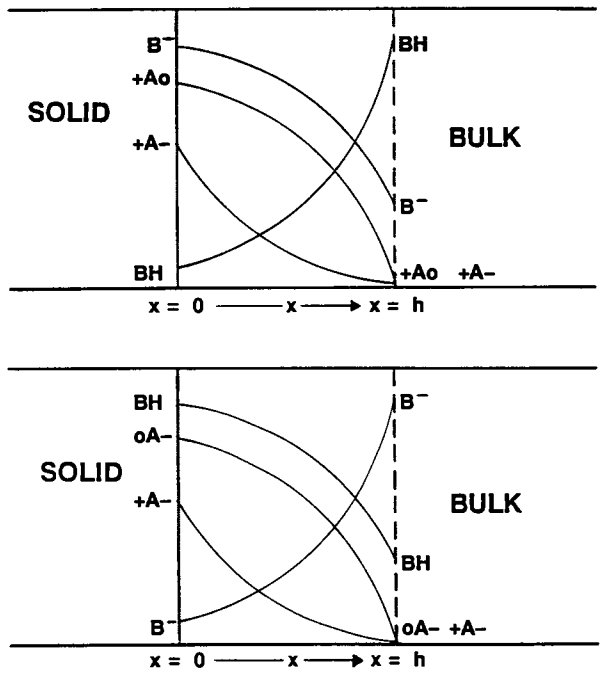

Fig. 5. Models of the dissolution of a solid amphoteric drug, +A−, in acidic (top) or basic (bottom) buffered media (bulk). h is the diffusion layer thickness. +Ao and oA− are the products of the reaction between +A− and the incoming buffer species, BH or B^-.

of +Ao, the most predominant species at these pH values. At pH values near the isoelectric point, the minimal flux is due to the minimal solubility and diffusion of +A−. Although the solubility of the drug is increased above the isoelectric point, the flux did not increase proportionally because of the self-buffering capacity of mesalamine. At pH >5.5, mesalamine dissolves and dissociates, generating hydrogen ions which lower the pH in the diffusion layer. This lower microenvironmental pH results in a lower total solubility and flux of the drug. The concentration of the incoming buffer, B^-, from the bulk solution was insufficient to increase the pH in the diffusion layer and cause an increase in flux by promoting the generation of the more soluble anionic species, oA−. The effect of mesalamine and the concentration of the buffer in the bulk media on the microenvironmental pH is shown in Table III. The agreement between the calculated and the experimental values demonstrates the ability of mesalamine to affect the microenvironmental pH and thereby influence the rate of dissolution. In both buffer solutions, the surface pH is consistently lower than that of the bulk pH. However, mesalamine was less able to influence the dissolution rate in the medium with the higher buffer concentration. The pH at the surface of the tablet and relative flux are higher in the medium with the higher buffer concentration (phosphate). The concentration of phosphate buffer (B^-) was sufficient to influence the pH in the diffusion layer and cause a corresponding increase in the solubility and flux of the drug by generating the anionic species.

The addition of Carbopol results in a reduction of the dissolution rate (Fig. 4) and decreased sensitivity of the dissolution rate to increasing bulk buffer concentration. These effects are likely to be due to the ability of the acidic polymer to neutralize incoming base (18) and therefore maintain a lower microenvironmental pH and solubility of the drug. The approximate surface pH values of 5.2 and 5.5 for the 0.067 and 0.20 *M* buffer solutions support the premise that the Carbopol is neutralizing the incoming base from the bulk. In addition, before reaching the bulk medium, the drug diffuses through a gel which is formed at the surface of the tablet. This gel formation will decrease the diffusivity of the drug (19). Furthermore, interactions between the drug and the polymer may contribute to a reduction in the transport of the drug through the surface gel. The diffusion of ionizable drugs through ionizable gels is affected by charge (20,21). All of these mechanisms are likely to contribute to the decrease in the dissolution rate.

CONCLUSIONS

The effects of the inclusion of Carbopol in the dosage form, in combination with the ability of mesalamine to control the microenvironmental pH, may offer a mechanism to control the rate of release and membrane transport of the drug. These results demonstrate the feasibility of controlling mesalamine release in the alkaline colonic environment. The relative contribution of each mechanism to the reduction of the dissolution rate of mesalamine in the presence of Carbopol may be unraveled by studying the transport of uncharged, cationic, and anionic molecules through the gel as a function of pH. The development of a drug delivery system which minimizes systemic absorption, maximizes topical ex-

posure, and controls release can be obtained by exploiting the relationship between pH and solubility and by selection of a polymer which will control drug transport via neutralization, gel formation, and drug–polymer interactions.

APPENDIX

Model for the Dissolution of a Weak Acid in Aqueous Solution Containing a Triprotic Buffer (11)

The five independent reactions occurring in the diffusional boundary layer are

$$H_2O \rightleftharpoons H^+ + OH^-$$
$$-A+ \rightleftharpoons -Ao + H^+$$
$$BH_3 \rightleftharpoons BH_2^- + H^+$$
$$BH_2^- \rightleftharpoons BH^{2-} + H^+$$
$$BH^{2-} \rightleftharpoons B^{3-} + H^+$$

The corresponding equilibrium constants for these reactions are

$$K_w = [H^+][OH^-]$$
$$K_a^A = \frac{[H^+][-Ao]}{[-A+]}$$
$$K_a^1 = \frac{[BH_2^-][H^+]}{[BH_2^-]}$$
$$K_a^2 = \frac{[BH^{2-}][H^+]}{[BH_2^-]}$$
$$K_a^3 = \frac{[B^{3-}][H^+]}{[BH^{2-}]}$$

When all diffusivities, equilibrium constants, and bulk solution properties (subscripted h) of all the components are known, the hydrogen ion concentration is determined by the following fifth-order polynomial, which can be solved iteratively by the Newton–Raphson method (22):

$$E[H^+]_o^5 + F[H^+]_o^4 + G[H^+]_o^3 + L[H^+]_o^2 + M[H^+]_o + N = 0$$

where

$$E = -\Theta D_H$$
$$F = \Theta\{D_H[H^+]_h - D_{OH}[OH^-]_h - D_B[B^{3-}]_h + D_{BH2}[BH_2^-]_h + 2D_{BH3}[BH_3]_h\} - \eta D_H - 2D_{BH3}\epsilon/(K_a^1K_a^2K_a^3)$$
$$G = \Theta\mu + \eta\{D_H[H^+]_h - D_B[B^{3-}]_h + D_{BH2}[BH_2^-]_h + 2D_{BH3}[BH_3]_h - D_{OH}[OH^-]_h\} - D_H\tau - D_{BH}\epsilon/(K_a^2K_a^3)$$
$$L = \eta\mu + \tau\{D_H[H^+]_h - D_{OH}[OH^-]_h - D_B[B^{3-}]_h + D_{BH2}[BH_2^-]_h + 2D_{BH3}[BH_3]_h\} - D_HD_B$$
$$M = \tau\eta + D_B\{D_H[H^+]_h - D_{OH}[OH^-]_h + \epsilon - D_B[B^{3-}]_h + D^{BH2}[BH_2^-]_h + 2D_{BH3}[BH_3]_h\}$$
$$N = D_B\eta$$
$$\mu = D_AK_a^A[+A-]_o + D_{OH}K_w$$
$$\epsilon = D_{BH3}[BH_3]_h + D_{BH2}[BH_2^-]_h + D_{BH}[BH^{2-}]_h + D_B[B^{3-}]_h$$
$$\tau = D_{BH}/K_a^3$$
$$\eta = D_{BH2}/(K_a^2K_a^3)$$
$$\Theta = D_{BH3}/(K_a^1K_a^2K_a^3)$$

The relative flux, R_{cal}, is

$$R_{cal} = \{D_{-A+}[-A+]_o + D_H([H^+]_o - [H^+]_h) + D_{OH}([OH^-]_h - [OH^-]_o) + D_B([B^{3-}]_h - [B^{3-}]_o) + D_{BH2}([BH_2^-]_o - [BH_2^-]_h) + 2D_{BH3}([BH_3]_o - [BH_3]_h)\}/(D_{-A+}[-A+]_o)$$

where

$$[B^{3-}]_o = \frac{\epsilon}{D_B + \tau[H^+]_o + \eta[H^+]_o^2 + \Theta[H^+]_o^3}$$
$$[BH_2^-]_o = [H^+]_o^2[B^{3-}]_o/(K_a^2K_a^3)$$
$$[BH_3]_o = [H^+]_o^3[B^{3-}]_o/(K_a^1K_a^2K_a^3)$$

Nomenclature

$-A+$	Zwitterionic species of amphoteric molecule
B^{3-}	Unprotonated buffer
BH_2^-	Diprotonated buffer
BH_3	Triprotic buffer
D	Diffusion coefficient (cm^2/sec)
H^+	Hydrogen ion
K_a^A	Acid dissociation constant
K_a^1	First buffer dissociation constant
K_a^2	Second buffer dissociation constant
K_a^3	Third buffer dissociation constant
K_w	Water dissociation constant
OH^-	Hydroxyl ion

Subscripts

+A−	Zwitterionic component
B	Component B^{3-}
BH2	Component BH_2^-
BH3	Component BH_3
h	At the outer edge of the diffusional boundary layer
H	Component H^+
o	At the solid/liquid interface in the diffusion layer
OH	Component OH^-

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