# Drug Permeation Through Human Skin II: Permeability of Ionizable Compounds

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**Abstract** □ The aim of this study was to establish whether ionized as well as un-ionized forms of certain 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (chromone-2-carboxylic acids) with p$K_a$ values <2 permeated through excised human skin and, if so, to determine the permeability coefficients of the permeating species. The permeation properties of four carboxylic acids were studied as a function of concentration over the pH range 5–7 at 37°C with plexiglass diffusion cells. Plots of $J/C^{A^-}$ (the total flux due to un-ionized and ionized species obtained under steady-state conditions per unit concentration of ionized drug in the donor compartment) against $C^{H_3O^+}$ resulted in straight-line relationships. The intercepts of these plots were shown to equal $P^{A^-}$, whereas the slopes multiplied by the $K_a$ values of the compounds equalled $P^{HA}$, the permeability coefficients of the ionized and un-ionized species, respectively. With all four compounds, both species were found to permeate skin, although the permeability coefficients of the un-ionized species were ~$10^4$ greater than those for the ionized species. It was demonstrated that the relative contributions of the ionized and un-ionized species to the total flux, as well as the total flux, vary significantly, depending on the pH of the drug solution in the donor cell. This may provide a means of controlling the flux of these and similar compounds through human skin.

**Keyphrases** □ Permeation—permeability of ionizable compounds through human skin, 4-oxo-4*H*-1-benzopyran-2-carboxylic acids □ 4-Oxo-4*H*-1-benzopyran-2-carboxylic acids—ionizable compounds, permeability through human skin □ Absorption—percutaneous, permeability of ionizable compounds through human skin

Many compounds evaluated for their ability to undergo percutaneous absorption following application to the skin are weak to moderately strong electrolytes. Depending on the p$K_a$ of the compound and the pH of the vehicle, such compounds exist as an equilibrium mixture of ionized and un-ionized species in the immediate vicinity of the skin. To control properly the rate at which such electrolytes permeate human skin, it is necessary to determine the permeability coefficients of both forms of the drug. However, much of the theoretical background to percutaneous absorption has been developed through studies of nonelectrolytic permeating species (1, 2), and there is little information available regarding the effect of pH and p$K_a$ on the permeation of ionizable drugs through skin (3, 4).

According to the simple pH-partition hypothesis, only the un-ionized forms of drugs are able to pass through lipoidal membranes in significant amounts (5). If correct, then membrane permeability should be related to the amount of un-ionized drug present, as well as being strongly pH dependent. However, in studies on isolated intestinal membranes (6), it has been indicated that ionized as well as un-ionized sulfonamides can pass through such a barrier. By using rat gastrointestinal segments *in vivo*, the rate constants for absorption of the ionized forms of sulfaethidole and barbital were found to be only three to five times less than those for the un-ionized material (7). With excised human skin, the permeabilities of the ionized forms of ephedrine and scopolamine were calculated to be ~1/20th of those for their un-ionized forms (3). The permeation of ionized drug molecules through skin thus is possible and cannot be assumed to be negligible, especially at pH values at which large numbers of ionized molecules are present. Such conditions would exist with compounds with low p$K_a$ values present on the surface of normal skin.

Human skin is composed of three distinct layers—the stratum corneum, the epidermis, and the underlying dermis. The passage of molecules across the skin and into the capillaries present in the dermis occurs by passive diffusion. The resistance to diffusion is high in the stratum corneum; in contrast, the epidermis and dermis are relatively permeable (8). The steady-state flux ($J$) (in mol·cm$^{-2}$·h$^{-1}$) is given by (2):

$$J = P \cdot C = \frac{C \cdot K^{SC/V} D^{SC}}{\delta} \qquad \text{(Eq. 1)}$$

where $P$ is the permeability coefficient, and $C$ is the concentration of the permeating species in the vehicle. The terms $K^{SC/V}$ and $D^{SC}$ refer, respectively, to the stratum corneum–vehicle partition coefficient and diffusion coefficient of the permeating species within the stratum corneum, which has a thickness of $\delta$.

Assuming that both ionized ($A^-$) and unionized (HA) species contribute to the total steady-state flux of a permeating electrolyte (here considered to be a monoprotic acid), then:

$$J = J^{HA} + J^{A^-} = (P^{HA} \cdot C^{HA}) + (P^{A^-} \cdot C^{A^-}) \qquad \text{(Eq. 2)}$$

Since the relative concentrations of ionized and un-ionized species for such an acid are expressed as:

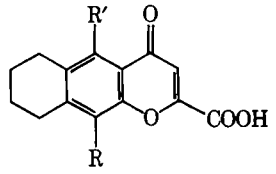
$$K_a = \frac{C^{H_3O^+} \cdot C^{A^-}}{C^{HA}} \qquad \text{(Eq. 3)}$$

then Eqs. 2 and 3 can be combined to give:

$$\frac{J}{C^{A^-}} = \left(\frac{P^{HA}}{K_a}\right) C^{H_3O^+} + P^{A^-} \qquad \text{(Eq. 4)}$$

Having determined the total steady-state flux as a function of chromone acid concentration and pH, a plot of $J/C^{A^-}$ *versus* $C^{H_3O^+}$ should be a straight line with a slope of $P^{HA}/K_a$ and an intercept of $P^{A^-}$. Equation 4 therefore allows estimation of the permeability coefficients of both un-ionized and ionized species. If the latter is zero, then the intercept will also be zero. Such an approach does not appear to have been used before in the determination of percutaneous absorption.

In the present study, the permeation properties of four related 4-oxo-4*H*-1-benzopyran-2-carboxylic acids (chromone-2-carboxylic acids) were investigated over a range of pH




I, R = $-CH_2CH_2CH_3$, R' = OH
II, R = $-CH_2CH_2CH_3$, R' = H
III, R = R' = H

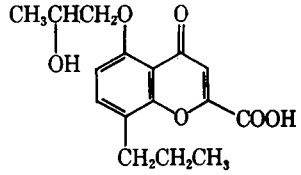



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**Table I—Data Derived from Steady-State Flux Determinations of Chromone-2-Carboxylic Acids as a Function of pH and Concentration**

| Compound | $C^{H_3O^+}$, mol·L$^{-1}$ × $10^7$ | $J/C^{A^-}$ Mean ± SD, cm/h$^{-1}$ × $10^5$ | $J/C^{A^-}$ Range | $n$ | $J/C^{A^-} = (P^{HA}/K_a)C^{H_3O^+} + P^{A^-}$ [a] | $n$ |
|---|---|---|---|---|---|---|
| I | 100.0 | 158.0 ± 28.6 | 100.7–202.7 | 9 | $= (139.0 \pm 21.1)C^{H_3O^+} + (20.2 \pm 12.5)10^{-5}$ | 26 |
| | 10.0 | 48.0 ± 20.2 | 15.0–86.4 | 9 | | |
| | 1.0 | 7.3 ± 6.3 | 0.7–17.9 | 8 | | |
| II | 100.0 | 53.7 ± 9.3 | 45.7–70.6 | 10 | $= (48.8 \pm 5.8)C^{H_3O^+} + (4.85 \pm 3.7)10^{-5}$ | 23 |
| | 10.0 | 11.4 ± 2.4 | 8.0–14.8 | 8 | | |
| | 1.0 | 2.9 ± 0.9 | 1.4–3.4 | 5 | | |
| III | 100.0 | 7.11 ± 2.87 | 2.85–12.34 | 13 | $= (4.99 \pm 1.52)C^{H_3O^+} + (2.51 \pm 0.93)10^{-5}$ | 35 |
| | 10.0 | 3.64 ± 1.80 | 1.10–6.36 | 12 | | |
| | 1.0 | 1.86 ± 1.10 | 0.45–4.18 | 10 | | |
| IV | 100.0 | 4.54 ● 3.93 | 0.86–10.06 | 11 | $= (4.04 \pm 2.40)C^{H_3O^+} + (0.51 \pm 1.63)10^{-5}$ | 24 |
| | 10.0 | 1.03 ± 0.40 | 0.61–1.66 | 7 | | |
| | 1.0 | 0.42 ± 0.25 | 0.13–0.77 | 6 | | |

[a] Equation derived from plot of individual values of $J/C^{A^-}$ *versus* $C^{H_3O^+}$.

values and concentrations. Equation 4 was then used to determine the permeability coefficients of the un-ionized and ionized species and to evaluate the effect of pH on the total steady-state flux observed and the relative contribution to this flux by the two species.

## EXPERIMENTAL SECTION

**Skin Samples**—As previously reported (9), samples of whole skin were removed from the inner thighs of cadavers within 48 h postmortem. The stratum corneum plus attached epidermis (SCE) was removed from the dermis as an intact sheet of tissue. These SCE samples were dried overnight in a desiccator at 25% relative humidity and then stored at 1 ± 0.5°C. Samples were rehydrated before use in the permeation studies. Because of the large number of studies conducted (>100), it was necessary to use skin samples from at least 10 different cadavers during the total series of experiments.

**Materials**—Buffer capsules[1] were used to prepare buffers at pH 5, 6, and 7. The pH 7.4 buffer and the solvents used in the HPLC assay of the chromone-2-carboxylic acids have been reported previously (9). A triglyceride of fractionated coconut oil fatty acids[2] (principally caprylic and capric), was used as received.

**Permeation Determinations**—Plexiglass diffusion cells were used to measure the permeation of the chromone-2-carboxylic acids across samples of SCE at 37 ± 0.5°C. Their design has been described previously (9). Solutions of each chromone acid were prepared in aqueous buffer at pH 5, 6, and 7. At least three different concentrations of chromone acid were used to cover the range of solubilities at a particular pH up to saturation. These solutions were placed in the donor compartments of the cells, whereas pH 7.4 buffer was placed in the stirred receptor compartments. Samples of known volume ranging from 25 to 100 μL were removed from the receptor compartments at known time intervals of ~2 h and immediately replaced with an equal volume of pH 7.4 buffer. The diluting effect of this replacement was taken into account when the total amount of chromone acid that had permeated the SCE at any one time was calculated. The removed samples were analyzed by HPLC (see below), and the permeation study was continued until it became clear that steady-state conditions were achieved (generally, 48–60 h). Values of the steady-state total flux of carboxylic acid were calculated and expressed as moles per square centimeter of skin per hour.

**Analysis**—Samples were analyzed by HPLC[3] immediately after they were removed from the receptor compartment. The following retention times were observed: compound I, 4.3 min (7:3 MeOH–$H_2O$, 0.5% $NH_4OAc$); compound II, 2.9 min (7:3 MeOH–$H_2O$, 0.5% $NH_4OAc$); compound III, 5.2 min (1:1 MeOH–$H_2O$, 0.5% $NH_4OAc$); compound IV, 4.5 min (1:1 MeOH–$H_2O$, 0.5% $NH_4OAc$). The solvent flow rate was 2.0 mL/min, and detection was by UV absorbance at 254 nm. Under these conditions, baseline separation was achieved between the single chromone acid peak and that due to unknown components leached from the skin. All four chromone acids were shown to be stable under the experimental conditions used and for at least the duration of a permeation run. Standard solutions were injected at each time interval when samples were withdrawn and assayed. The coefficients of variation ranged from 3.2 to 5.6% for the four compounds studied. In all cases, the limit of detection was 1–2 ng of chromone acid following the injections of a 100-μL sample.

[1] pHydrion; Micro Essential Labs, Brooklyn, N.Y.
[2] Miglyol 812; Kay-Fries Inc., Montvale, N.J.
[3] Model 440 absorbance detector with model 6000-A pumps, U6K injector, and model 660 solvent programmer; Waters Associates, Milford, Mass.

**Solubility Determination**—The aqueous solubilities of the chromone-2-carboxylic acids at 37°C were measured by adding excess compound to pH 5.0 buffer. The pH was readjusted to 5.0 with 0.1 M sodium hydroxide solution when necessary. After equilibration overnight, the mixtures were filtered and assayed by HPLC.

**Partition Coefficients**—Known weights of the four chromone-2-carboxylic acids were equilibrated between equal volumes of mutually saturated triglyceride[2] and the appropriate buffer solution at 37°C. The systems were gently shaken at frequent intervals over a period of 48 h, at which time samples of each phase were assayed by UV spectrophotometry. The apparent partition (distribution) coefficient D was calculated as the ratio of the total amount of drug in each of the two phases and subsequently converted into the true (*i.e.*, un-ionized) partition coefficient $K$ by:

$$D = K(1 - \alpha) \qquad \text{(Eq. 5)}$$

where $(1 - \alpha)$ is the fraction of un-ionized drug and $\alpha = 1/[1 + \text{antilog}(pK_a - pH)]$.

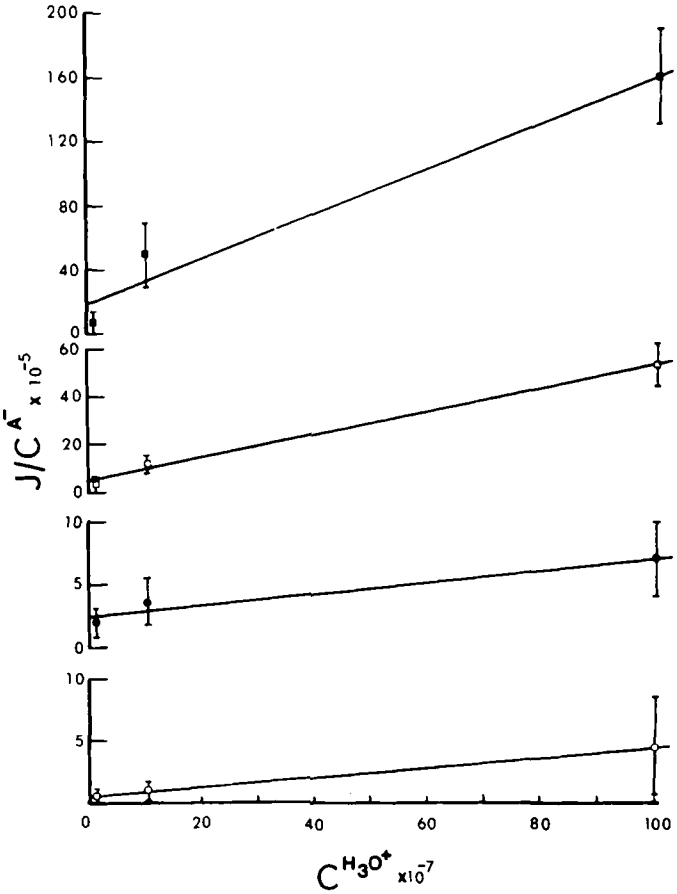


**Figure 1**—*Plot of* $J/C^{A^-}$ versus $C^{H_3O^+}$ *for the four chromone-2-carboxylic acids studied. Key: (■) I; (□) II; (●) III; (○) IV. Points and vertical bars represent the means and* SD, *respectively, of the individual values of* $J/C^{A^-}$ *at each pH (Table I).*

**Table II—Summary of Experimental Results**

| Compound | $S_5$, mol·L$^{-1}$ × $10^3$ | log $K^{M/W}$ | $K^{M/W}$·$S_5$, mol L$^{-1}$ | $P^{HA}$, cm·h$^{-1}$ | $P^{A^-}$, cm·h$^{-1}$ × $10^5$ | $D$, cm$^2$·s$^{-1}$ × $10^{10}$ |
|---|---|---|---|---|---|---|
| I | 2.09 | 4.39 | 51.3 | 1.63 ± 0.25[a] | 20.2 ± 12.5[a] | 0.18 |
| II | 12.6 | 3.35 | 28.2 | 0.66 ± 0.08 | 4.85 ± 3.73 | 0.82 |
| III | 89.2 | 2.22 | 14.8 | 0.09 ± 0.03 | 2.51 ± 0.93 | 1.51 |
| IV | 187 | 1.78 | 11.3 | 0.15 ± 0.09 | 0.51 ± 1.63 | 6.91 |

[a] 95% Confidence limits.

**Ionization Constants**—Two methods were used to determine the ionization constants. In the first, a conductometric method (10), all measurements were made at 25°C with a conductivity meter[4]. In the second, a partition–distribution method (11), a biphasic solvent system of dichloroethane–hexane–water was chosen to minimize ion-pair extraction. Large partition coefficients ($K$) were determined by the interchange technique (12). Distribution coefficients (D) were obtained at various pH values, and the ionization constant was calculated by using a rearranged form of Eq. 5, namely:

$$\log\left(\frac{K}{D} - 1\right) = \text{pH} - \text{p}K_a \qquad \text{(Eq. 6)}$$

## RESULTS AND DISCUSSION

The p$K_a$ values of the four chromone-2-carboxylic acids determined in aqueous solution are: 1.93 ± 0.06 (not as previously reported in Ref. 9), 1.87 ± 0.06, 1.75 ± 0.05, and 1.44 ± 0.05 for I, II, III, and IV, respectively. The values for III and IV were obtained by the partition as well as the conductance methods and were consistent with each other. Only the partition method was used with I and II, as the solubility of the undissociated forms were too low to allow use of the conductance method.

Plots of the number of moles of chromone-2-carboxylic acid permeated per square centimeter of SCE *versus* time showed an initial lag phase, followed by a linear steady-state phase 24 to 48 h after initiation of the permeation run. The steady-state total flux of the permeating species ($J$; in mol/cm$^2$/h) was calculated from the slope of the linear portion of each plot, and a value of $J/C^{A^-}$ was calculated for each individual determination. The mean, $SD$, range, and numbers of individual determinations are shown in Table I for the four compounds studied at each of the three pH values. Considering that over the course of the series of experiments it was necessary to use skin from at least 10 different cadavers, the $SD$ values observed are acceptable. Regression analysis of the individual values of $J/C^{A^-}$ *versus* $C^{H_3O^+}$ for each compound was used to compute the relationship expressed in Eq. 4. These results, together with the respective 95% confidence intervals, are also shown in Table I. In Fig. 1, the mean values of $J/C^{A^-}$ listed in Table I plotted against $C^{H_3O^+}$ for the four compounds are shown. The vertical bars represent the $SD$ values.

Utilization of the appropriate p$K_a$ value yields the values of $P^{HA}$ and $P^{A^-}$ listed in Table II. The data show positive, but small, intercepts, indicating that the chromone-2-carboxylate ions have finite permeabilities, although those for IV are not significantly different from zero. In all instances, the permeability of the un-ionized form is ~$10^4$ times greater than the permeability of the ionized form. In Table II are also presented the solubilities of the compounds in pH 5.0 buffer ($S_5$) and the triglyceride[2]–water partition coefficients ($K^{M/W}$), calculated as described above.

The triglyceride[2] was chosen as the oil phase in the partition system because preliminary studies (13) over a range of pH values have shown this system to conform closely to the expected theoretical relationship between log D and pH, thereby allowing calculation of log $K$ correctly from observed values of D. In contrast, partition data for I between SCE and water and stratum corneum and water as a function of pH showed a significant deviation from ideality (13). Accordingly, $K^{M/W}$ was used in the present study rather than $K^{SCE/W}$ or $K^{SC/W}$, as this parameter provides a more accurate index of the relative partitioning abilities of the four compounds studied.

By assuming a constant diffusion coefficient and stratum corneum thick-

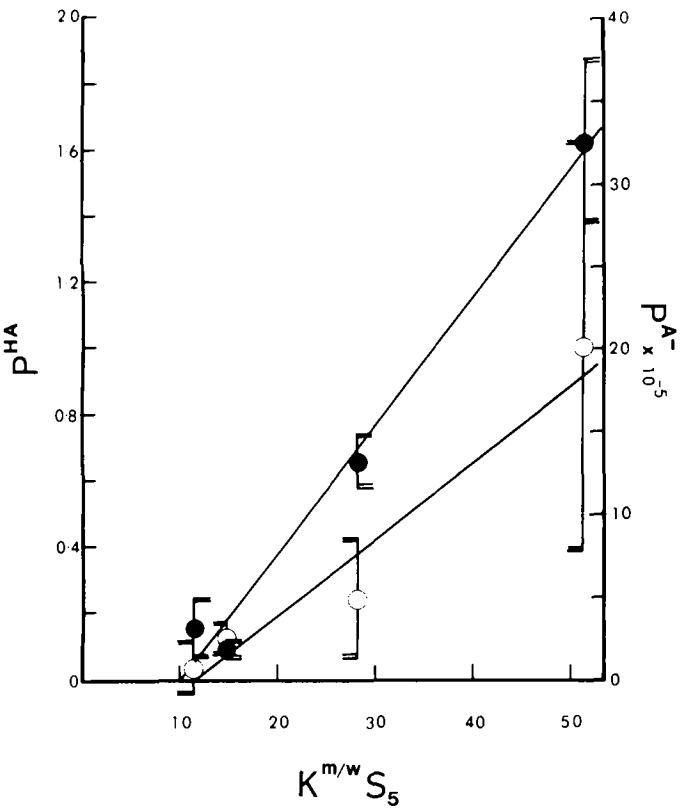


**Figure 2**—*Relationship between* $K^{M/W}$·$S_5$ *and* $P^{HA}$ *and* $P^{A^-}$. *Data are from Table II; vertical bars indicate 95% confidence intervals for each compound.*

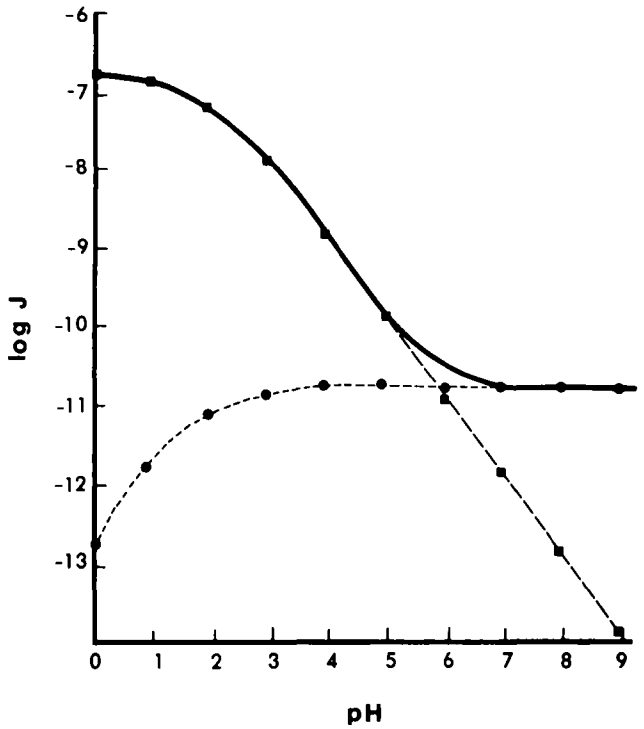


**Figure 3**—*Theoretical plot of the effect of pH on the total flux* J *and its components* $J^{HA}$ *and* $J^{A^-}$ *for I. Concentration of I is equal to* $10^{-7}$ *mol·cm*$^{-3}$; $pK_a$ *is equal to 1.93;* $P^{HA}$ *is equal to 1.63 cm·h*$^{-1}$; $P^{A^-}$ *is equal to 2.02* × $10^{-4}$ *cm·h*$^{-1}$. *Note that the flux (in mol·cm*$^{-2}$·*h*$^{-1}$) *is drawn on a log scale. Key: (■)* $J^{HA}$; *(●),* $J^{A^-}$; *(—)* J.

[4] Model B642; Wayne Kerr, Chicago, Il.

ness, it is predicted by Eqs. 1 and 2 that the steady-state total flux is proportional to the product of the partition coefficient of the drug between the stratum corneum and the vehicle and its solubility in the vehicle. Although realizing that $K^{M/W}$ was used in the present study rather than $K^{SC/W}$, such a trend nevertheless appears evident since as $K^{M/W} \cdot S_5$ decreases, so does $P^{HA}$ and $P^{A^-}$ (Fig. 2). This suggests the use of this parameter as a relative indicator of permeability when examining a series of analogues for their ability to penetrate human skin, without recourse to actual permeation studies. The data imply that $K^{M/W} \cdot S_5$ must exceed 10–11 mol $\cdot$ L$^{-1}$ before permeation of the chromone-2-carboxylic acids can be detected.

The values of $P^{HA}$ and $P^{A^-}$ obtained from these experiments can be used to determine how the relative permeation rates of the un-ionized and ionized species change with pH and how this affects the total steady-state flux, *i.e.*, $J^{HA} + J^{A^-}$. This is illustrated for I in Fig. 3, where it should be noted that the flux axis is given in log units. As the pH is increased above the p$K_a$ of 1.93, the concentration of the un-ionized species falls. This leads to a continuous reduction in flux due to the un-ionized species, $J^{HA}$, since the product $P^{HA} \cdot C^{HA}$ is also falling. At the same time, the concentration of the ionized species rises with increasing pH and then remains constant at a pH value 2 or more units above the p$K_a$. The net effect is a continuous decline in the total flux as the pH of the solution is increased; in the case of I, this increase is to pH 7. Above this pH, the permeation of chromone ions constitutes the major portion of the total flux, although it is important to remember that the magnitude of the total flux falls dramatically as the pH is raised above the p$K_a$. Thus, for monoprotic acids in which un-ionized and ionized species have widely separated permeability coefficients (*e.g.*, the chromone-2-carboxylic acids in which the difference between $P^{HA}$ and $P^{A^-}$ is $\sim 10^4$), the pH should be held to as low a value as possible when seeking to maximize the total flux through the skin. The optimal value is at least 1 pH unit below the p$K_a$, assuming satisfactory tolerance by the skin to such a pH. Minimal flux in the example described here occurs at a pH that is ~5 units or more above the p$K_a$.

Diffusion coefficients ($D$) for the four compounds are calculated from Eq. 1 by using the values for $K^{M/W}$ given in Table II and a measured stratum corneum thickness of 10 $\mu$m. Since $P^{HA}$ is much greater than $P^{A^-}$, $P$ was taken to be equal to $P^{HA}$. The values presented in Table II lie within the range normally found for compounds of this size when they are diffused through the stratum corneum (2).

In summary, the results of this study indicate that chromone-2-carboxylic acids permeate human skin both as un-ionized and ionized species, although the former are $\sim 10^4$ times more permeable. Because of the effect of pH on the relative concentrations of un-ionized and ionized species, it would appear to be possible to control the total flux of these compounds by varying the pH of the drug-containing vehicle applied to the skin.

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# Adsorption of Phosphate by Aluminum Hydroxycarbonate


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**Abstract** □ Phosphate is specifically adsorbed by aluminum hydroxycarbonate by anion ligand exchange. IR analysis indicated that phosphate exchanged with specifically adsorbed carbonate. Adsorption is favored by low pH and is inversely related to particle size. Adsorption of phosphate decreases the rate of acid neutralization of aluminum hydroxycarbonate. The results are applied to the treatment of hyperphosphatemia and hypophosphatemia.



**Keyphrases** □ Adsorption—phosphate by aluminum hydroxycarbonate □ Aluminum hydroxycarbonate— adsorption of phosphate


The adsorption of phosphate species by aluminum hydroxide is important, as aluminum hydroxide-containing antacids have been implicated in hypophosphatemia. In contrast, aluminum hydroxide is used as a phosphorus-binding agent in hyperphosphatemia. The interaction of phosphate species with crystalline forms of aluminum hydroxide has been extensively studied due to the wide occurrence of aluminum hydroxide in the soil and the extensive use of phosphorus-containing fertilizers. However, little is known about the interaction of phosphate species with amorphous aluminum hydroxycarbonate, the acid-reactive form of aluminum hydroxide containing specifically adsorbed carbonate which is used in antacids. The purpose of this study was to determine the mechanism of adsorption of phosphate species by aluminum hydroxycarbonate, with emphasis on possible adsorption of phosphate on surface carbonate sites.

## BACKGROUND

The binding of phosphorus by aluminum hydroxide in the gastrointestinal tract during antacid therapy was first noted 40 years ago (1, 2). Since that time, it has been confirmed in numerous studies that aluminum hydroxide may reduce the intestinal absorption of phosphate (3–13). Clinical symptoms of phosphorus depletion syndrome parallel serum phosphorus levels and are most likely to be observed in patients who combine aluminum hydroxide antacid therapy with a low dietary phosphorus intake (14, 15). This observation is especially pertinent to critically ill patients who receive only parenteral nutrition and who also require antacid therapy to prevent upper GI bleeding (16).


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