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Research Article

Dehydration Kinetics of Prostaglandin E_1 in a Lipid Emulsion

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The overall dehydration kinetics of prostaglandin E_1 (PGE_1) in a lipid emulsion at 35°C were found to fit a model whereby the $k_{apparent}$ measured at each pH is simply the sum of the product of the fraction of the PGE_1 at the interface, f_i, and the rate constant at the interface, k_i, plus the product of the fraction of the PGE_1 in the aqueous phase, f_{aq}, and the rate constant in the aqueous phase, k_{aq}. The values for f_i and f_{aq} were reported earlier as a function of pH at 35°C. The k_{aq} and $k_{apparent}$ were experimentally determined as a function of pH at 35°C. The k_i was indirectly determined from the stability data in the emulsion. Microscopic rate constants for dehydration of PGE_1 in the aqueous phase and interface at 35°C were estimated from the experimental data. Based on the kinetic evaluation performed, it appears that the dehydration kinetics might be manipulated by the addition of charged surface active agents.

KEY WORDS: lipid emulsion; kinetics; prostaglandin E_1; interface.

INTRODUCTION

Oil-in-water emulsion formulations of prostaglandin E_1 (PGE_1) are of considerable interest due to recent observations that such formulations of PGE_1 appear to exhibit marked increases in biological activity and reduced side effects in comparison with parenteral solutions of the drug (1–5). Because a lipid emulsion formulation is feasible only if adequate chemical stability of the relatively labile PGE_1 can be attained, the chemical stability of PGE_1 in lipid emulsion systems is an important issue. This report compares the rate constants for the degradation of PGE_1 in aqueous solutions and in a lipid emulsion formulation as a function of pH. The kinetic data generated in this work and previously reported data for the partitioning behavior of PGE_1 as a function of pH in the same lipid emulsion systems (6) are combined to describe the reactivity of interfacially bound PGE_1 as a function of pH. Finally, based on the changes in reactivity observed for interfacially bound PGE_1, formulation strategies to improve the chemical stability of PGE_1 in lipid emulsions are suggested.

MATERIALS AND METHODS

Materials

All compounds were used as received from the supplier: prostaglandin E_1 (The Upjohn Company), soybean oil (Croda Inc.), soybean phosphatide NC 95 (American Lecithin Co.), glycerin USP (Proctor and Gamble), sodium phosphate monobasic (J. T. Baker), glycine (Mallinckrodt), trichloroacetic acid (Mallinckrodt), sodium citrate (Pfizer), and tromethamine (Fisher Scientific), absolute ethanol (U.S. Industrial Co.), hydrochloric acid (Scientific Products), sodium hydroxide (Mallinckrodt), acetonitrile (Burdick and Jackson), potassium chloride (Mallinckrodt), and disodium EDTA (Dow Chemical). All other chemicals were reagent grade.

Aqueous Solution Kinetic Studies

Solutions of PGE_1 at 60 μg/ml and at various pH values were prepared by placing 100 μl of a 100 mg/ml ethanol solution of PGE_1 into 160 ml of 0.002 *M* buffer. Buffers used included trichloroacetic acid (pH 1.0), glycine (pH 1.5–3.0 and 10.0–11.0), citrate (pH 3.5–6.5), and tromethamine (pH 7.0–8.5). The acceptable pH range for each buffer was ±0.02 pH unit. These solutions were incubated in a 35°C water bath (Model EX-300, Neslab, Portsmouth, N.H.). Samples which were buffered at pH 9 or less were removed at various time intervals and assayed for prostaglandin A_1 (PGA_1) by high-performance liquid chromatography (HPLC). Rate constants were calculated using initial rate methods. Samples buffered at pH values greater than pH 9 were monitored by HPLC for PGE_1 disappearance with time. None of the samples drifted in pH value greater than 0.05 pH unit from the beginning to the end of the kinetic experiment.

Solutions of PGE_1 with variable buffer concentrations and ionic strengths were prepared at pH 7.5 similar to the method described above. Potassium chloride was used to adjust the ionic strength of 0.002, 0.005, and 0.010 *M* Tris buffers to 0.01. A solution of 60 μg/ml at pH 7.5 with 0.01% disodium EDTA was prepared similar to the method described above. Kinetic evaluations for these solutions were also identical to that reported earlier.

Emulsion Kinetic Studies

Approximately 30 ml of a 10% soybean oil-in-water

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emulsion containing 200 μg/ml PGE_1 prepared as previously described (6) was placed into a vessel jacketed to 35°C. A Ross electrode (Orion Research Inc., Boston, Mass.) was inserted into the emulsion sample and the pH was controlled with a pH stat (Models PHM-62 pH meter, TTT-60 titrator, ABU-13 autoburette, Radiometer, Copenhagen, Denmark) which added dilute acid or base to maintain the set pH. Samples at each pH were removed from the vessel at the start of the experiment and at various time intervals thereafter and assayed for PGA_1 by HPLC. The initial samples were also assayed for PGE_1 by HPLC. Kinetic evaluations were conducted in the pH range of 3 to 9. Kinetic analyses were performed by the initial rate technique.

Chromatography

A modular high-performance liquid chromatographic system consisting of a constant pump (Altex Model 110A, Beckman Instruments, Fullerton, Calif.), an automated sample injector (WISP Model 710B, Waters Associates, Millford, Mass.), a variable wavelength detector (Model 783, Kratos, Westwood, N.J.), and an integrator (Data Module Model 730, Waters Associates) was operated at ambient temperature. PGE_1 and PGA_1 were detected at 200 and 218 nm, respectively. The column used was a 25-cm stainless-steel (4.6-mm i.d.) 5-μm Brownlee Spheri-5 RP-18 (Santa Clara, Calif.) along with a 5-cm guard column of the same material with a 10-μm particle size. The mobile phase consisted of acetonitrile:0.002 *M* phosphate buffer (pH 3.0). The ratio of organic to aqueous phase was 37:63 (v/v) and 50:50 (v/v) for the PGE_1 and PGA_1 mobile phases, respectively. The flow rates were 1.0 ml/min for the PGE_1 assay and 1.5 ml/min for the PGA_1 assay. Both aqueous and emulsion samples were injected "as is." Peak shape and retention times were identical to those of external standards.

Particle Size Measurement

The particle size of the emulsion was measured with a photon correlation particle size analyzer (Nicomp Model 200, Pacific Scientific, Silver Spring, Md.).

RESULTS AND DISCUSSION

In a previous publication (6), the distribution of PGE_1 in a lipid emulsion was treated using a three-phase model consisting of the oil and water phases and an interfacial phase. This model was simplified to a two-phase model based on experimental data showing that the majority of PGE_1 (>99%) resides either at the interface or in the aqueous phase. The degradation of PGE_1 in such a system should therefore reflect the fractional amount of drug in each phase and the rate constants for decomposition in each phase. Therefore, the $k_{apparent}$ measured at each pH is simply the sum of the product of the fraction of the PGE_1 at the interface, f_i, and the rate constant at the interface, k_i, plus the product of the fraction of the PGE_1 in the aqueous phase, f_{aq}, and the rate constant in the aqueous phase, k_{aq}, as shown below:

$$k_{apparent} = f_i k_i + f_{aq} k_{aq} \quad (1)$$

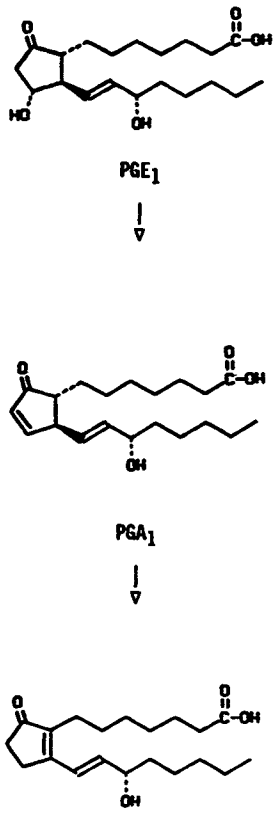
In order to describe properly the kinetic mechanisms for PGE_1 degradation in lipid emulsion systems, the various constants in Eq. (1) must be determined. f_i and f_{aq} depend on the state of ionization of PGE_1 and, therefore, are pH dependent. Values for f_i and f_{aq} as a function of pH at 35°C were reported earlier (6). The rate constants k_{aq} and k_i are also expected to be complex functions of pH due to the different reactivities of the neutral and anionic PGE_1 species and the likelihood that, in addition to uncatalyzed mechanisms, both acid- and base-catalyzed routes of degradation may occur. The rate constants for PGE_1 degradation in aqueous solution can be measured directly as a function of pH, while the interfacial rate constants must be obtained indirectly from stability data in emulsions.

Aqueous Solution Kinetics

Monkhouse *et al.* (7) described the decomposition of PGE_1 in aqueous solutions at various temperatures and over a pH range of 1–10. In acidic environments, the major degradative pathway for PGE_1 is acid-catalyzed dehydration to PGA_1. In alkaline solutions, PGE_1 undergoes sequential dehydration to PGA_1 followed by isomerization to prostaglandin B_1 (PGB_1) as illustrated in Scheme I. The log *k* versus pH profile reported by Monkhouse *et al.* for PGE_1 was linear between pH 4 and pH 10 but with a slope significantly less than one, suggesting that more than simple specific hydroxyl-ion catalysis is involved. Contrary to these findings, the decomposition of PGE_2 in alkaline solutions is first order with respect to hydroxide ion (8). The degradation of PGE_1 should parallel that of PGE_2, however, as similar mechanisms are believed to be involved (9). Because of the uncertainties surrounding the existing pH–rate data for PGE_1 and the absence of data at 35°C, such data were generated in this study.

At pH values below 9, first-order rate constants for the dehydration of PGE_1 at 35°C were determined by monitoring the initial rate of PGA_1 formation. Plots of the concentration of PGA_1 formed versus time produce slopes which are equal to the product of the degradation rate constant and the initial PGE_1 concentration provided that the amount of PGE_1 degradation which occurs during the kinetic study is small (<5%). At pH values greater than 9 the rate constants were more easily determined from the disappearance of PGE_1 with time due to the higher reaction rates and the increased significance of isomerization of PGA_1 to PGB_1. A 60 μg/ml PGE_1 concentration, which was close to the saturation solubility of PGE_1 at low pH, was chosen for the aqueous solution kinetic studies to obtain the maximum possible assay sensitivity. Preliminary work indicated that PGE_1 degradation was not affected by changes in PGE_1 concentration within the concentration range examined.

Figure 1 illustrates typical kinetic data collected at pH values less than pH 9.0 for the formation of PGA_1 versus time. Linear regression of the data yielded excellent fits, with coefficients of determination greater than 0.98. First-order rate constants for the dehydration of PGE_1 to PGA_1 were determined by dividing the slope of each line by the initial PGE_1 concentration (approximately 60 μg/ml). Figure 2 illustrates the kinetic data for the disappearance of PGE_1 collected at pH 10 through pH 11. Dehydration rate constants were determined from the slopes of these plots. The



Scheme I

rate constants obtained at each pH are listed in Table I along with their 95% confidence limits.

The pH–rate profile generated from the kinetic data is shown in Fig. 3. The squares represent the experimental rate constant determined at 35°C at each pH. The relationship between the observed rate constant in aqueous solution, k_{aq}, and pH can be expressed by the following equation:

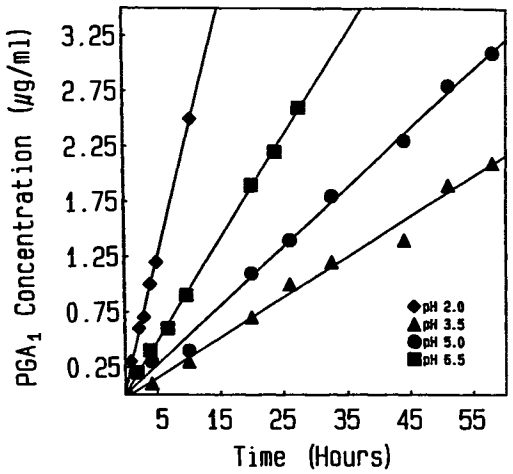


Fig. 1. Examples of initial rate kinetic data for the dehydration of PGE_1 in aqueous solution at 35°C.

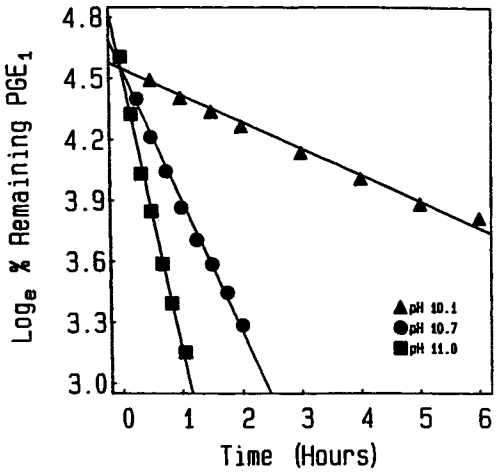


Fig. 2. First-order kinetic data for the dehydration of PGE_1 in aqueous solution at high pH at 35°C.

$$k_{aq} = k_{H^+}[H^+](1 - \alpha) + k_{H_2O}(1 - \alpha) + k'_{H_2O}(\alpha) + k_{OH^-}[OH^-](\alpha) + k_\sigma(\sigma) \quad (2)$$

where k_{H^+} is the rate constant for specific acid-catalyzed dehydration, k_{H_2O} and k'_{H_2O} are the rate constants for solvent-catalyzed dehydration of the nonionized and ionized species, respectively, k_{OH^-} is the rate constant for hydroxide ion-catalyzed dehydration, and k_σ is the rate constant for dehydration of the enolate-activated complex as described by Lee *et al.* (10). α and $1 - \alpha$ are the fractions of ionized and nonionized PGE_1, respectively. σ is the fraction of PGE_1 activated complexes in the enolate form. σ is calculated according to the following equation:

$$\sigma = K_a'/(K_a' + H^+) \quad (3)$$

where K_a' is the acid dissociation constant for the enol-activated complex. The curve shown in Fig. 3 represents the fit of the above model to the experimental data, which appears to be excellent. The parameter values obtained in the nonlinear regression are listed in Table II.

Originally attempts were made to fit the data according to the degradation model suggested by Thompson *et al.* (8) and Stehle (9) for the degradation of PGE_2. This model did not include the term for the ionization of the enol transition state. The fit using this model was quite poor in the pH range 6–8. Therefore, studies of the effect of the buffer concentration, ionic strength, and presence of metal chelators at a pH in this range (pH 7.5) on the reaction kinetics were initiated. The results of these studies are reported in Table III. The data suggest that buffer effects are negligible at a concentration of 0.002 *M*. Also, the data demonstrate that the ionic strength does not affect the kinetics in the ionic strength range of the experiments. (The total ionic strength was purposely kept low in order that these data could be used in the evaluation of the lipid emulsion kinetics. Low ionic strengths were necessary in the emulsions to maintain adequate physical stability). Finally, the possibility that the deviations were due to catalytic effects of trace metal impurities was ruled out since the addition of 0.01% disodium EDTA had no effect on the rate constants in this pH range.

Table I. Rate Constants for the Dehydration of PGE_1 at Various pH's at 35°C

Environment	pH	Rate constant at 35°C (hr^{-1}) ± 95% CI[a]
Aqueous	1.1	$(2.4 \pm 0.1) \times 10^{-2}$
Aqueous	1.5	$(1.2 \pm 0.1) \times 10^{-2}$
Aqueous	2.0	$(3.9 \pm 0.2) \times 10^{-3}$
Aqueous	2.5	$(1.6 \pm 0.3) \times 10^{-3}$
Aqueous	3.0	$(7.6 \pm 0.4) \times 10^{-4}$
Aqueous	3.5	$(6.1 \pm 0.4) \times 10^{-4}$
Aqueous	4.0	$(6.4 \pm 0.5) \times 10^{-4}$
Aqueous	4.5	$(7.4 \pm 0.4) \times 10^{-4}$
Aqueous	5.0	$(9.0 \pm 0.4) \times 10^{-4}$
Aqueous	5.5	$(1.0 \pm 0.1) \times 10^{-3}$
Aqueous	6.0	$(1.2 \pm 0.1) \times 10^{-3}$
Aqueous	6.5	$(1.6 \pm 0.1) \times 10^{-3}$
Aqueous	7.0	$(2.4 \pm 0.1) \times 10^{-3}$
Aqueous	7.5	$(3.3 \pm 0.1) \times 10^{-3}$
Aqueous	8.0	$(4.6 \pm 0.6) \times 10^{-3}$
Aqueous	8.5	$(6.6 \pm 0.6) \times 10^{-3}$
Aqueous	10.1	$(1.3 \pm 0.1) \times 10^{-1}$
Aqueous	10.7	$(6.5 \pm 0.4) \times 10^{-1}$
Aqueous	11.0	$(1.4 \pm 0.1) \times 10^{0}$
Emulsion	3.0	$(1.9 \pm 0.3) \times 10^{-2}$
Emulsion	3.5	$(3.5 \pm 0.4) \times 10^{-3}$
Emulsion	4.0	$(1.6 \pm 0.1) \times 10^{-3}$
Emulsion	4.5	$(6.0 \pm 0.6) \times 10^{-4}$
Emulsion	5.0	$(3.7 \pm 0.3) \times 10^{-4}$
Emulsion	5.5	$(5.0 \pm 1.5) \times 10^{-4}$
Emulsion	6.0	$(6.3 \pm 0.5) \times 10^{-4}$
Emulsion	6.5	$(9.7 \pm 1.6) \times 10^{-4}$
Emulsion	7.0	$(1.4 \pm 0.1) \times 10^{-3}$
Emulsion	8.0	$(2.9 \pm 2.1) \times 10^{-3}$
Emulsion	9.0	$(9.5 \pm 0.2) \times 10^{-3}$

[a] Univariate 95% confidence interval (CI) calculated using MINSQ, Micromath, Salt Lake City.

The fit of the data in the pH 6–8 range is markedly improved by assuming that dehydration proceeds through an enol-activated complex as first proposed by Lee *et al.* (10) in their studies of the dehydration of a methyl ester of a PGE_1 analogue. Their model described the use of an acid dissociation constant in a phenomenological model even though no apparent ionizable group was present. The kinetic pK_a observed was attributed to the ionization of the enol in the transition state. From their data a pK_a of 7.2 was estimated for the ionization of the PGE_1 enol-activated complex at 35°C. This pK_a was assumed in the curve shown in Fig. 3.

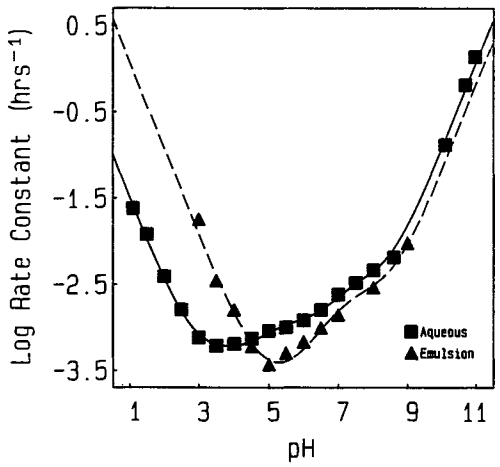


Fig. 3. Kinetic profile of the dehydration of PGE_1 as a function of pH at 35°C for aqueous solutions and lipid emulsions of PGE_1.

Table II. Parameter Values for the Dehydration Kinetics of PGE_1 at 35°C

Environment	Parameter	Rate constant ± 95% CI[a]
Aqueous	k_{H^+}	$(3.2 \pm 0.4) \times 10^{-1}$ $(1 \cdot hr^{-1} \cdot mol^{-1})$
Aqueous	k_{H_2O}	$(5.1 \pm 0.8) \times 10^{-4}$ (hr^{-1})
Aqueous	k'_{H_2O}	$(1.1 \pm 0.2) \times 10^{-3}$ (hr^{-1})
Aqueous	k_{OH^-}	$(5.6 \pm 0.7) \times 10^{2}$ $(1 \cdot hr^{-1} \cdot mol^{-1})$
Aqueous	k_σ	$(2.5 \pm 0.7) \times 10^{-3}$ (hr^{-1})
Interface	$k^i_{H^+}$	$(1.2 \pm 0.4) \times 10^{1}$ $(1 \cdot hr^{-1} \cdot mol^{-1})$
Interface	$k^i_{H_2O}$	$(2.7 \pm 1.4) \times 10^{-4}$ (hr^{-1})
Interface	$k'^i_{H_2O}$	$(1.7 \pm 1.1) \times 10^{-3}$ (hr^{-1})
Interface	$k^i_{OH^-}$	$(6.5 \pm 39.3) \times 10^{1}$ $(1 \cdot hr^{-1} \cdot mol^{-1})$

[a] Univariate 95% confidence interval (CI) calculated using MINSQ, Micromath, Salt Lake City.

It is evident from a comparison of the rate constants in the pH 3.5–4 range with those obtained at pH 5–5.5 that ionization of the carboxylic acid side chain also influences the rate of dehydration, even though it is substantially removed from the site of degradation. Thus, both ionization reactions were included in the model.

Emulsion Kinetics

A 200 μg/ml PGE_1 concentration was selected for the lipid emulsion experiments in order to increase the assay sensitivity of the degradation product PGA_1. Due to their adverse effect on the physical stability of the emulsion, buffers could not be used for pH control during the kinetic evaluations. The pH was therefore controlled with a pH-stat. Due to physical stability constraints, kinetic data could reliably be obtained only in the pH range of 3 to 9. Particle size determinations by photon correlation spectroscopy at the beginning and end of the kinetic studies indicated that no significant changes occurred in the particle size of the emulsion droplets. Particle size changes were typically less than 0.006 μm for emulsion droplets which averaged approximately 0.15 μm. The initial rate of formation of PGA_1 was

Table III. Effect of the Buffer Concentration, Ionic Strength, and Metal Chelator on the Dehydration Rate Constant of PGE_1 at pH 7.5 and 35°C

Tris conc. (*M*)	Ionic strength	Rate constant (hr^{-1}) ± 95% CI[a]
0.002	0.002	$(3.3 \pm 0.1) \times 10^{-3}$
0.002	0.010	$(3.2 \pm 0.3) \times 10^{-3}$
0.005	0.010	$(3.0 \pm 0.5) \times 10^{-3}$
0.010	0.010	$(2.7 \pm 0.6) \times 10^{-3}$
0.002[b]	0.002	$(3.5 \pm 0.1) \times 10^{-3}$

[a] Univariate 95% confidence interval (CI) calculated using MINSQ, Micromath, Salt Lake City.
[b] Plus 0.01% disodium EDTA.

used to generate rate constants, $k_{apparent}$, as a function of pH as described previously for the aqueous solution kinetic studies. Typical kinetic data for the formation of PGA_1 with time in the emulsion are shown in Fig. 4. The first-order rate constants for dehydration of PGE_1 in the lipid emulsion at various pH values are listed in Table I. These data are plotted in Fig. 3 along with the pH profile obtained in aqueous solution. Most remarkable in comparing the lipid emulsion data with the stability data in aqueous solutions is the increased reactivity in the lipid emulsion at low pH, where the dominant degradation mechanism is specific acid catalysis.

The changes in the pH–rate profile observed upon formulation of PGE_1 in a lipid emulsion are consistent with Eq. (1), which takes into account the pH-dependent partitioning of PGE_1 between the aqueous phase and the lipid–water interface and the altered microscopic reaction rate constants of interfacially bound PGE_1. The interfacial contribution to $k_{apparent}$ in Eq. (1), $f_i k_i$, is expected to vary with pH due to the differing affinities of the nonionized and ionized forms of PGE_1 for the interfacial phase, the differing reactivities of the nonionized and ionized species, and the likelihood for specific acid and specific base catalysis of the dehydration of interfacially bound PGE_1. The pH dependence of $f_i k_i$ is expressed in Eq. (4).

$$f_i k_i = k^i_{H^+}[H^+](1 - \beta) + k^i_{H_2O}(1 - \beta) + k'^i_{H_2O}(\beta) + k^i_{OH^-}[OH^-](\beta) \quad (4)$$

where $k^i_{H^+}$ is the interfacial rate constant for specific acid-catalyzed dehydration of the nonionized species, $k^i_{H_2O}$ and $k'^i_{H_2O}$ are the interfacial rate constants for solvent catalyzed dehydration of the nonionized and ionized species, respectively, and $k^i_{OH^-}$ is the rate constant for hydroxide ion-catalyzed dehydration of the interfacially bound PGE_1 anion. β and $1 - \beta$ are the fractions of ionized and nonionized PGE_1 at the interface, respectively.

Figure 5 illustrates the pH-dependent phase distribution of the various PGE_1 species in the emulsion reported in an earlier study (6), from which f_{aq} and f_i values (or α and β values) can be obtained at any pH. Table IV contains the various constants used to calculate the pH-dependent phase distribution shown in Fig. 5. Rearrangement of Eq. (1) and substitution of the experimentally determined constants enable calculation of the k_i as a function of pH, from which the microscopic rate constants in Eq. (4) can be obtained. The parameter values obtained from nonlinear regression are listed in Table II. The calculated pH profile for the degradation of PGE_1 in the lipid emulsion, obtained using the rate constants listed in Table II, is shown in Fig. 3. The fit of the actual data points to the calculated curve appears to be quite good.

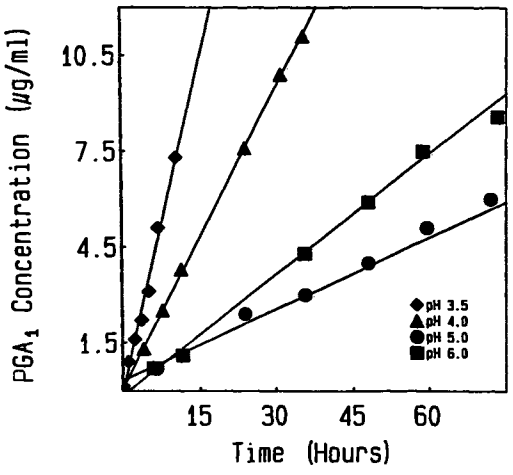


Fig. 4. Examples of initial rate kinetic data for the dehydration of PGE_1 in a lipid emulsion at 35°C.

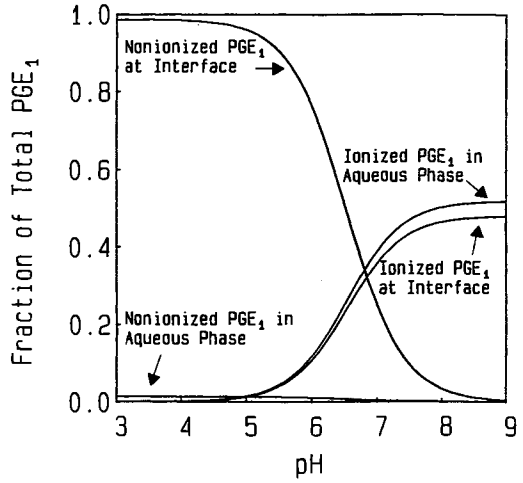


Fig. 5. Calculated distribution of ionized and nonionized PGE_1 species in the interfacial and aqueous phases in the 200-µg/ml lipid emulsion as a function of pH at 35°C.

At a pH of 6 and below, as seen in Fig. 5, PGE_1 resides largely at the interface. The greater than 30-fold increase in the acid-catalyzed dehydration rate constant when PGE_1 is localized at the lipid–water interface is attributed to a higher effective concentration of hydrogen ions in the interfacial region due to the negative surface charge of the emulsion droplets (11). This phenomenon resembles the catalysis of bimolecular reactions frequently observed in micellar systems in which the reactants are concentrated into the small volume of the Stern layer (12,13). Anionic micelles tend to

Table IV. Constants Used in Calculating the Distribution of Various PGE_1 Species in the Emulsion at 35°C

V_w	Aqueous phase volume = 87.3% (v/v) of total volume
V_o	Oil phase volume = 10.8% (v/v) of total volume
V_i	Interfacial volume = 1.9% (v/v) of total volume
pK_a	−log of the acid dissociation constant for PGE_1 in the aqueous phase = 4.95
pK_a^i	−log of the acid dissociation constant for PGE_1 at the interface = 6.84
K_d^0	Distribution coefficient for the neutral form of PGE_1 between the interface and the aqueous phase 3481 ± 1158[a]
K_d^-	Distribution coefficient for the ionized form of PGE_1 between the interface and the aqueous phase = 45.3 ± 7.5[a]

[a] Univariate 95% CI calculated using MINSQ, Micromath, Salt Lake City.

concentrate hydrogen ions in the Stern layer (14), resulting in catalysis of reactions involving hydrogen ions. Compared to the aqueous stability, at higher pH values the stability of PGE_1 in the lipid emulsion systems would be improved only twofold because the binding of PGE_1 anion to the interface is approximately 50% (Fig. 5).

Previous studies of the distribution of PGE_1 in the lipid emulsion as a function of pH (6) indicated that the pK_a of PGE_1 is increased nearly 2 units [from 4.95 to 6.84 (Table IV)] upon interfacial binding. An upward shift in the pK_a of the interfacially bound enol-activated complex would also be expected due to the negative surface charge of the emulsion droplets and the lower effective dielectric constant of the local environment at the interface. Thus, ionization of interfacially bound enol was neglected in the treatment of the emulsion kinetics between pH 3 and pH 9.

Despite interfacial catalysis of the acid-catalyzed dehydration of PGE_1, formulation in a lipid emulsion results in an overall improvement in the stability of PGE_1 at the pH of maximum stability due to a modest decrease in the rate constant for the water-catalyzed reaction of PGE_1 free acid. Further improvement in the stability of PGE_1 would appear to be possible if the acid-catalyzed reaction could be further suppressed. Cho and Allen (15) have previously demonstrated that prostacycline, which undergoes specific acid-catalyzed degradation, could be stabilized by incorporation into cationic micelles. Their data indicated that the increased stability was a result of the charge repulsion between the cationic micelle and the hydrogen ions and the incorporation of prostacycline into the hydrophobic core of the micelle. The addition of a cationic surfactant to the lipid emulsion under investigation herein would be expected to bring about a positive surface charge. Due to charge repulsion, the concentration of hydrogen ions at the interface would be reduced in such a system, leading to a marked reduction in the acid-catalyzed degradation rate. The effect of excipients such as cationic surfactants on the chemical stability of PGE_1 in the lipid emulsion will be addressed in a subsequent report.

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