# Heterogeneous Systems II: Influence of Partitioning and Molecular Interactions on *In Vitro* Biologic Activity of Preservatives in Emulsions

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**Abstract** □ The preservative activity of *p*-hydroxybenzoic acid esters (parabens) in the presence of a polysorbate 80–sorbitan monooleate water system was found to be related to the concentration of the free or unbound paraben. Prediction of required preservative concentration for an emulsified system from a knowledge of oil–water partition coefficients and preservative-macromolecules binding data is illustrated. It was demonstrated by an *in vitro* microbiological procedure and using a glass dialysis cell that the fungistatic activity against *Aspergillus niger* of methyl- and propylparaben in emulsified systems was primarily a function of the free paraben concentration in the aqueous phase.

**Keyphrases** □ *p*-Hydroxybenzoic acid esters activity—partitioning, molecular interaction, effects □ Biological activity—emulsion preservatives *in vitro* □ Emulsions, effect—preservatives □ Inhibition determination—dialysis cell

Biological activity of antimicrobial agents in a heterogeneous system such as an emulsion is much more complex than in a simple aqueous medium. These agents, under the classification of preservatives, are incorporated in emulsified systems—medicinal, cosmetic, pharmaceutical, and nonpharmaceutical emulsions; ointments, creams, *etc.*—to protect against deterioration from bacterial and fungal attack. During the past 2 decades, pharmaceutical and cosmetic industries have recognized an increasing number of failures of the preservative to protect against microbial spoilage. This period coincides with the time during which nonionic emulsifiers, those containing polyoxyethylene groups and others, have become increasingly popular. A multiplicity of factors governs the efficacy of a preservative in the final formulation, and some notable reviews on the subject have appeared in the literature (1–5).

Emulsion and cream formulations contain a variety of ingredients which collectively form excellent substrates for microbial growth (6, 7). Under some conditions, fixed oils, fats (6, 7), hydrocarbon oils (8), the emulsifier (9), or the preservative (10) may be metabolized by certain microorganisms.

Previous investigations (11–16) have shown that many of the more commonly used preservatives in pharmaceutical and cosmetic emulsions are adsorbed to, bound to, or solubilized by nonionic emulsifiers in aqueous solution. The bound or solubilized (12) preservative in such a system has been shown to be devoid of antimicrobial activity (13, 15, 17, 18). In emulsified systems an additional factor, partitioning of the preservative between the oil and water phases, must be considered for the effective preservation of the entire formulation.

It is generally recognized that emulsified preparations containing different oil phases require higher concentration of preservatives (19) than normally used. The activity of some phenols in a two-phase system, liquid petrolatum–water, has been studied by Bean *et al.* (20). Recently, Anderson and Chow reported on the distribution and activity of benzoic acid in oil–water systems, emulsified with 0.1% polyoxyethylene lauryl ether[1] (21); the antifungal activity of benzoic acid was related to its concentration in aqueous phase.

As pointed out by Atkins (22), the problem of deterioration of cosmetic emulsion systems during storage, due to either mold formation or bacterial growth, is confined mainly to oil-in-water emulsions; it is rarely a problem with water-in-oil emulsions, the reason being that most troublesome organisms require an aqueous medium for favorable growth. In a water-in-oil emulsion, the water is surrounded by an inhospitable oil phase and this is not conducive to growth. The less common organisms which can infect the oil phase apparently do not cause product decomposition or spoilage, so that, even if they exist, their presence is not suspected (22). The most important factors affecting the activity of preservatives in oil-in-water emulsions containing nonionic emulsifying agents are those governing the availability of the preservatives in the aqueous phase. In such a system the preservative would partition into the oil phase and would also interact with the nonionic emulsifiers, thus reducing the activity of the preservative. The principal aim of this investigation was to show how the partition coefficient and binding data can readily and satisfactorily be used to determine the effective concentration in aqueous phase of methyl- and propylparaben in typical oil-in-water emulsions containing polysorbate 80[2] and sorbitan monooleate[3] (or polysorbate 20[4] and sorbitan monolaurate[5]) as emulsifying agents. It will also be demonstrated by an *in vitro* microbiological procedure that the activity of the preservatives is related to their concentrations in the aqueous phase. Selection of the oils was based on their varying oil–water partition coefficients (23).

## THEORY

The theory behind the partitioning of a preservative in an oil–water system has been described in Part I (23). The equilibria con-

[1] Brij 35, marketed by Atlas Chemical Industries, Inc., Wilmington, Del.

[2] Polyoxyethylene (20) sorbitan monooleate, marketed as Tween 80 by Atlas Chemical Industries, Canada, Ltd., Brantford, Ontario.

[3] Span 80, marketed by Atlas Chemical Industries, Canada, Ltd., Brantford, Ontario.

[4] Polyoxyethylene sorbitan monolaurate, marketed as Tween 20 by Atlas Chemical Industries, Canada, Ltd., Brantford, Ontario.

[5] Span 20, marketed by Atlas Chemical Industries, Canada, Ltd., Brantford, Ontario.

trolling the partitioning of a preservative between two phases and its binding to surfactant have also been discussed (2,12,13,15).

When a preservative distributes between oil and aqueous phases, the transfer is governed by its distribution coefficient or partition coefficient, $D$ (23), as follows:

$$C_{oil} = DC_{H_2O} \quad \text{(Eq. 1)}$$

where $C_{oil}$ and $C_{H_2O}$ are the preservative concentrations in oil and water phases at equilibrium. Assuming that the amount in the aqueous phase is active and if some transfers to the oil phase, sufficient additional preservative should be provided to maintain the required concentration in the water. Thus the total preservative, $C_{ts}$, to be added to a two-phase system can be calculated by knowing the usual concentration required in the aqueous phase ($C_{H_2O}$), and knowing the volume of each phase ($V_{oil}$ and $V_{H_2O}$) and the distribution coefficient:

$$\text{total preservative} = C_{H_2O}V_{H_2O} + C_{oil}V_{oil} \quad \text{(Eq. 2)}$$

Substituting the value of $C_{oil}$ from Eq. 1:

$$C_{ts} = C_{H_2O}V_{H_2O} + DC_{H_2O}V_{oil} \quad \text{(Eq. 3)}$$

If the preservative binds to the emulsifier in aqueous solution, the total preservative in water can be given by the following equation as described elsewhere (13, 15):

$$C_{t_{H_2O}} = RC_{H_2O} \quad \text{(Eq. 4)}$$

where $C_{tH_2O}$ and $C_{H_2O}$ are the concentrations of total (free + bound or solubilized) and free preservative in water, and $R$ is the binding or solubilization constant as explained previously (13,15). The total preservative in this study was taken as the free plus the amount bound to or solubilized by the polysorbate–sorbitan ester dispersion.

If the failure of a preservative in a system consisting of oil and water phases emulsified with nonionic surfactants can be attributed to the partitioning as well as the binding of the preservative, the total quantity of the preservative which is theoretically needed for preservation, $C_{ts}$, can be computed by combining Eqs. 3 and 4 as represented by the following equation:

$$C_{ts} = C_{H_2O}(RV_{H_2O} + DV_{oil}) \quad \text{(Eq. 5)}$$

In the present work it was assumed that the minimum inhibitory concentration of paraben in the absence of surfactants and oil corresponds to the concentration of free paraben.

## MATERIALS

The oil phases and preservatives were the same as employed in earlier papers (15, 23). Polysorbate 80, polysorbate 20, sorbitan monooleate, and sorbitan monolaurate were commercial samples.

## EXPERIMENTAL PROCEDURES

**Determination of Interaction between Preservative and Nonionic Surfactants**—Equilibrium dialysis method using a cellophane membrane[6] was employed to determine this interaction, and the general approach and experimental procedure for this part have been detailed in previous communications (12, 24). Preliminary experimentation showed that this membrane (23) was impermeable to sorbitan monooleate. It was found previously to be impermeable to polysorbate 80 (16) and to the oils (23) used in this study. The general procedure was the same as that described earlier (24) with the following exception. A 10-ml. portion of aqueous polysorbate–sorbitan ester dispersion was pipeted into one of the compartments of the dialysis cell (24) and an equal volume of paraben solution was placed into the opposite compartment. In order to increase the total paraben content of the system, it was necessary in some cases to dissolve additional paraben in the dispersion. Overnight agitation of the assembled cells was sufficient for attainment of equilibrium. Any sorption of the parabens by the membrane and dialysis cells was found to be insignificant (25) under experimental conditions.

[6] Fisher Scientific Co.

Table I—$R$ Values Based on the Interaction Between Parabens and Macromolecules at 30°

| Paraben | Macromolecules: Proportion | % | HLB | $R$[a] |
|---|---|---|---|---|
| **Polysorbate 20–Sorbitan Monolaurate** | | | | |
| Methyl | 92:8 | 5 | 16.0 | 3.84 |
| Propyl | 92:8 | 5 | 16.0 | 16.6 |
| **Polysorbate 80–Sorbitan Monooleate** | | | | |
| Methyl | 70:30 | 5 | 11.8 | 3.44 |
| Methyl | 70:30 | 4 | 11.8 | 3.03 |
| Methyl | 58:42 | 5 | 10.5 | 3.15 |
| Propyl | 70:30 | 5 | 11.8 | 14.5 |
| Propyl | 58:42 | 5 | 10.5 | 15.5 |

[a] Each $R$ value represents an average of five to eight determinations.

After equilibration, an aliquot was removed from the nonmacromolecule side of the membrane and the concentration of the preservative was ascertained spectrophotometrically (16). Since the quantity of paraben added to the system was known, the amount on the macromolecule side was readily calculated by simple subtraction and the difference was taken as the amount bound or solubilized (12) by the macromolecules.

**Preparation of Emulsion**—The emulsions were prepared according to the formula 25% oil, 5% w/v emulsifier (4% in the case of castor oil), and sufficient distilled water or culture medium (as described in the following section) to make 100 ml. Because of high partitioning of propylparaben into almond oil and due to its high binding with the emulsifiers, 10% almond oil was used for microbiological work involving propylparaben–almond oil emulsion system. The emulsifier concentrations were selected to give the most stable emulsion with a minimum concentration of the emulsifying agents. Appropriate amounts of polysorbate 80 and sorbitan monooleate were blended to give the HLB (hydrophile–lipophile balance) values of: 10.5 for mineral oil, 16 for oleic acid, and 11.8 for almond oil and castor oil. Preliminary experiments using the procedure described in the literature (26) gave the above HLB values yielding the most stable emulsions. Polysorbate 80 was dissolved in warm aqueous phase, and sorbitan monooleate was dissolved in warm oil phase; both the phases were blended and passed 2–3 times through a hand homogenizer.

**Microbiological Procedures**—*Aspergillus niger*[7] was selected as the principal microbe, and the synthetic culture medium used in this study was the same as described elsewhere (15).

*Procedure for Dispersions*—The minimum inhibitory concentrations (MIC) for methyl- and propylparaben were determined in the presence of dispersions of polysorbate 80 and sorbitan monooleate (or polysorbate 20 and sorbitan monolaurate) in culture medium. The emulsifiers were blended and aqueous dispersion was passed twice through a hand homogenizer. The binding data in terms of $R$ values (total preservative/free preservative) as presented in Table I were used to predict the inhibitory concentration for the surfactant dispersions. The method of prediction and the general procedure have been described earlier (15). The growth of *A. niger* was observed for a 2-week period in the form of mycelial hyphae which were readily visible on the surface in the test tube.

*Procedure for Emulsions*—A convenient method for approximating the free preservative or the preservative in the aqueous phase in an emulsified system is an equilibrium dialysis technique which utilizes a membrane that permits the free passage of the preservative but is impermeable to the emulsifier and the oil. At equilibrium the activity of the preservative would be identical on both sides of the membrane; for reasonably dilute solutions, it may be assumed that the concentration of the free preservative on both sides of the membrane will be essentially equal. Thus, by placing an emulsion on one side of the membrane and determining the concentration of the free preservative on the opposite side, it is possible to approximate the concentration of free preservative in equilibrium with the emulsifier and the oil phase. Assumption is made that the

[7] UAMH No. 1456, Provincial Laboratory of Public Health, Edmonton. Stock culture was grown on slants of potato dextrose agar.

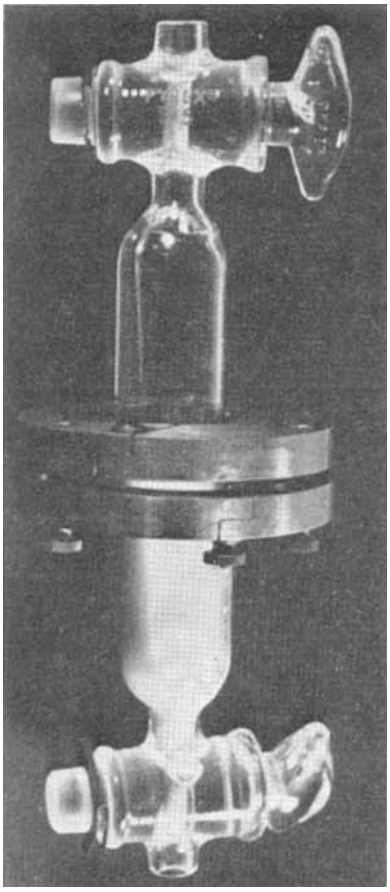

**Figure 1**—*Assembled dialysis cell containing emulsion in one compartment and culture medium in the other, separated by a cellophane membrane.*

biologic activity of the preservative would parallel the concentration of free preservative.

A glass dialysis cell was constructed for growth studies; it consisted of two halves, each with a capacity of about 30 ml. Each half was prepared by fusing a 6-mm. ground-glass stopcock with the cylindrical end of a flat flange.[8] To assemble the unit, a cellophane membrane was placed between the two halves and secured with the aid of a brass bracket. The assembled dialysis cell is portrayed in Fig. 1. Twenty milliliters of an appropriate concentration (0.065% methylparaben or 0.020% propylparaben) of the paraben in the culture medium was pipeted into one of the compartments. It should be noted that these concentrations correspond to the MIC of these agents for *A. niger* in the culture medium. The entire unit was sterilized by autoclaving at 15 lb. pressure for 15 min. (15). During sterilization, it was necessary to place the dialysis cell in a slant position with both ends kept open to avoid the rupture of the membrane due to pressure buildup at autoclaving temperature. The cell was allowed to attain room temperature with aseptic precautions and the compartment containing preservative solution was closed. Four such dialysis cells were prepared. A predicted inhibitory concentration of the preservative in the emulsion was computed using Eq. 5 and from the knowledge of binding and partition coefficient (23) data. A required amount of the preservative was dissolved in the emulsion. Three additional concentrations of the agent were prepared, one of which was lower and two higher than the above value (15). A 20-ml. sample of the emulsion was pipeted into the empty compartment of the dialysis cell. The unit was closed and equilibrated by overnight agitation at 30°.

The nonemulsion side of the dialysis cell was inoculated with two loopfuls of a spore suspension (15) of *A. niger*. The cells were incubated at 30°, and the growth in the form of mycelial hyphae was observed visually each day for a total period of 2 weeks. In some

[8] Quickfit FG 25.

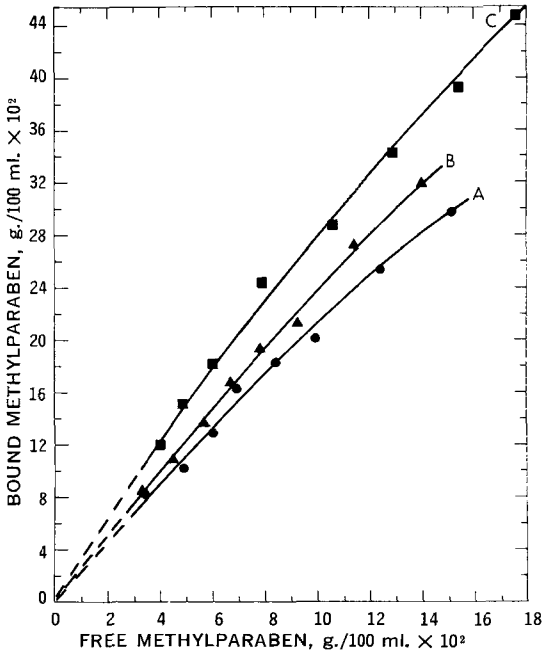


**Figure 2**—*Adsorption isotherms based on the interaction of methylparaben with 5% aqueous dispersion of surfactants. Key:* A, *polysorbate 80–sorbitan monooleate (58:42), HLB, 10.5;* B, *polysorbate 80–sorbitan monooleate (70:30), HLB, 11.8; and* C, *polysorbate 20–sorbitan monolaurate (92:8), HLB, 16.0.*

cases there was a marked separation of the emulsion during incubation. This separation was prevented by agitation of the cells in a water bath at 30° during the 2-week period. Preliminary tests showed that the membrane was impermeable to *A. niger*, to any other organism which might be present in the emulsion, and to the emulsion itself. At the end of this experiment, a 1-ml. aliquot was moved from the nonemulsion side of the cell and the paraben content analyzed spectrophotometrically. The exact paraben concentration in the emulsion was then calculated.

## RESULTS AND DISCUSSION

**Interaction of Parabens with Surfactants**—The interactions of methyl- and propylparaben with a dispersion of polysorbate 80 and

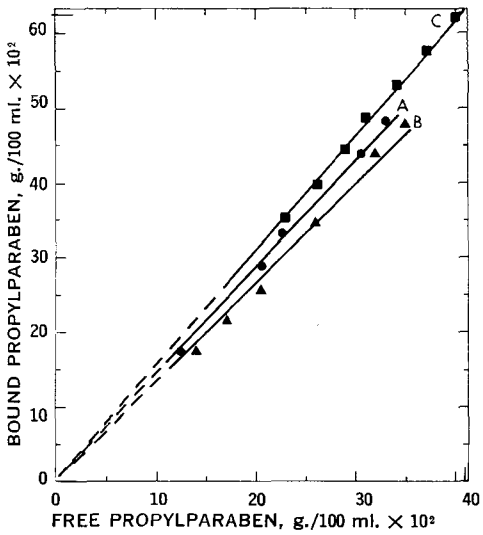


**Figure 3**—*Adsorption isotherms based on the interaction of propylparaben with 5% dispersion of surfactants. Key:* A, B, *and* C *as defined in Fig. 2.*

sorbitan monooleate (or polysorbate 20 and sorbitan monolaurate) are shown in Figs. 2 and 3. These plots represent typical adsorption isotherms and similar isotherms for a methylparaben–polysorbate system have been reported (12). More useful data for the formulation work are presented in Table I. The ratio, $R$, of total/free paraben over the concentration range studied as shown in Figs. 2 and 3 is fairly constant. The results also demonstrate that varying proportions of the emulsifiers show a difference in the extent of binding. The $R$ values can easily be obtained from these figures and the average of these values in each case was computed. The average $R$ values are listed in Table I and have been found to be useful in computing the free preservative for a definite concentration of a macromolecule (15).

**Inactivation by Surfactants Related to Binding**—It has been established that parabens are inactivated in the presence of polysorbate 80 in aqueous solution due to binding or solubilization (12–15). A correlation between the predicted and experimental inhibitory concentrations of methyl- and propylparaben in the presence of 5% dispersion containing various proportions of polysorbate 80 and sorbitan monooleate (or polysorbate 20 and sorbitan monolaurate) is illustrated in Fig. 4. The proportion and the concentrations of the surfactants correspond to the HLB values and the concentrations used in the emulsions for microbiological work. The figure also shows the MIC of the parabens in the absence of the surfactants for the purpose of comparison.

As is evident, there is a significant inactivation of the parabens due to solubilization or binding by the surfactant dispersion. It can be noticed that the magnitude of inactivation increases from methyl- to propylparaben. This is reasonable since propylparaben is bound by the surfactants to a greater extent than methylparaben as shown in Figs. 3 and 4 and Table I ($R$ values).

**Correlation of the Binding and Partitioning Data with Inhibitory Concentrations**—Figure 5 depicts a comparison of the experimental inhibitory concentrations of methyl- and propylparaben for emulsified systems and the concentrations predicted (using Eq. 5) from a knowledge of MIC in culture medium, the partitioning data, and the binding data. The results show that there is a reasonably good agreement between the predicted and experimental values. The difference in these values can be attributed to small variations in the partition coefficients and $R$ values.

There are two factors responsible for the biologic availability of the antimicrobial agent in the emulsified system, namely the binding to the emulsifier and the partitioning into the oil. If one compares the magnitude of inactivation in Fig. 4 with that in Fig. 5, it is observed that for mineral oil emulsion the inactivation is due solely to the surfactants. This is to be expected since both methylparaben and propylparaben have mineral oil–water partition coefficient values lower than 1 (23). This might also explain the observed lower MIC values for both methyl- and propylparaben in

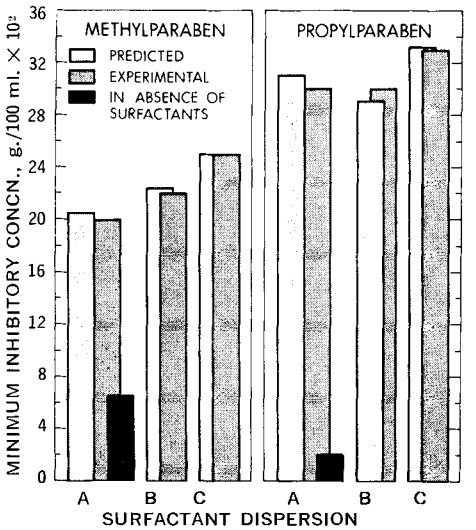


**Figure 4**—*Comparison of predicted and experimental minimum inhibitory concentrations of parabens in the presence of 5% aqueous dispersion of surfactants. For comparison, the figure also shows the minimum inhibitory concentrations of the parabens in the absence of the surfactants. Key: A, B, and C as defined in Fig. 2.*

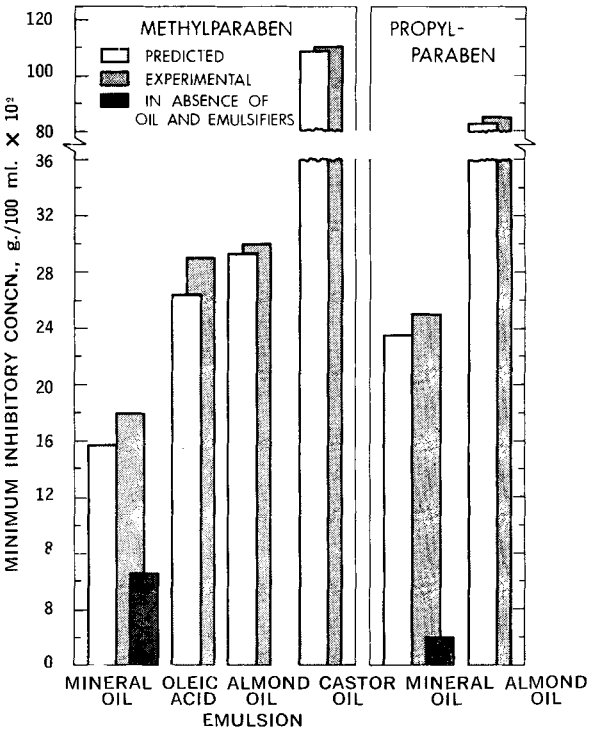


**Figure 5**—*Comparison of predicted and experimental minimum inhibitory concentrations of parabens in emulsified systems. Concentrations of oils and emulsifiers were 25% and 5% with the following exception: castor oil emulsion contained 4% total emulsifiers, and almond oil emulsion in the case of propylparaben consisted of 10% of the oil.*

the case of mineral oil emulsions (Fig. 5) than those in the aqueous dispersion of the surfactants (Fig. 4).

The magnitude of inactivation of the parabens increased from oleic acid to almond oil to castor oil emulsion, primarily due to the increase in the partition coefficients of these oils. In Part I, the authors reported the oil–water partition coefficients for these oils as 4.4, 7.6, and 58, respectively. From the partitioning data, one would expect a greater difference in the MIC values of oleic acid and almond oil emulsions. However, this difference was reduced due to the higher binding capacity of the emulsifiers (Table I) in the case of oleic acid than those in almond oil emulsion. The greatest inactivation was observed in the case of castor oil emulsion because of the very high partitioning of methylparaben in this oil.

The degrees of binding and partitioning for propylparaben (23) are greater than those of methylparaben. Thus propylparaben was inactivated to a greater extent than methylparaben.

Although emulsions containing nonionic agents can be effectively preserved, there may be some practical limitations. The amount of preservative in emulsified systems with oil of high partition coefficient, and especially when the emulsifier has a high binding tendency, may affect the stability of the product or may be in the range to cause contact dermatitis (27) or may be prohibitive economically. Preliminary work indicated that the stability of emulsions containing nonionic surfactants which have a complexing tendency for parabens was seriously affected with increase in the concentration of paraben (28). Nevertheless, the knowledge of partitioning and binding data should permit evaluation in a product development laboratory so that the most efficient preservative is selected for a particular system. For example, it was found that the almond oil–water partition coefficients of methylparaben and sorbic acid were 7.5 and 3.3. Of the two preservatives, the nonionic emusifier has less affinity for sorbic acid (15). Sorbic acid would be preferred as a preservative for vegetable oil emulsions, although pH of the system must be considered. Furthermore, as suggested by Riegelman (29), rather than using 5–10% of nonionic surfactants as the emulsifier, it would be advisable to attempt to formulate the emulsion with a much lower concentration of emulsifying agent and to attempt to stabilize the system with another agent with less affinity for the preservative.

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# Kinetics of Hydrous Aluminum Oxide Conversion in Mixtures of Amorphous Alumina Gels of Various Acid Reactivities


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**Abstract** □ Mixtures of two amorphous alumina gels of different acid reactivity change physically and chemically upon aging until a constant state is reached. The gels, when individually aged, retain their initial properties. The end-point appearance, viscosity, X-ray diffraction pattern, DTA thermogram, acid-insoluble fraction, and acid reactivity of the mixture are identical to those of the gel having the lower acid reactivity. The change in properties appears to be due to the conversion of the gel having the higher reactivity into the less reactive form. The rate of conversion is first-order, temperature-dependent, and directly dependent on the initial concentration of the less reactive gel.



**Keyphrases** □ Hydrous aluminum oxide conversion—kinetics □ Alumina gels, amorphous, effect—$Al_2O_3$ conversion □ X-ray diffraction—identity □ Calorimetry—anlysis, gels


The physical and chemical properties of hydrous aluminum oxide depend on the nature of the reactants used in its formation (1, 2), the pH and temperature of its precipitation (3–5), and the conditions under which it is aged (6, 7). The effects of mixing alumina gels of different physical and chemical properties have not been reported. Preliminary experiments in the authors' laboratories have indicated that when amorphous alumina gels of various acid reactivities are mixed, there are changes in the physical and chemical properties of the mixtures during aging. The purpose of the present study was to examine these changes in greater depth.

## EXPERIMENTAL

**Source of Gels**—One alumina gel was prepared by the reaction of aluminum chloride with sodium carbonate and sodium bicarbonate at 25° and pH 5.8, according to the procedure of Papée *et al.* (8), and washed with deionized water until the concentration of chloride ion in the filtrate, as determined by the Volhard method (9), was less than 0.1%. This gel (I) possessed the full theoretical acid reactivity in terms of its $Al_2O_3$ content. Gels with reactivity less