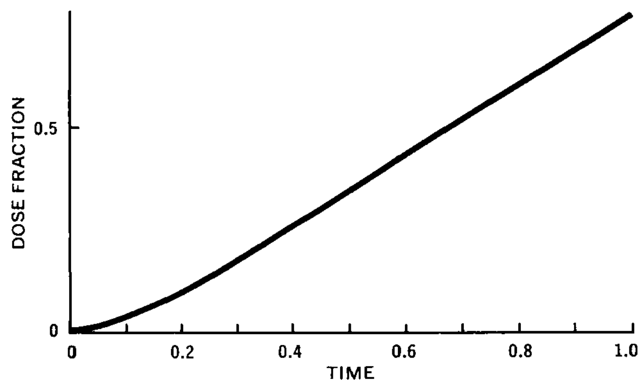

Figure 3—*Dose fraction in Compartment 3 as a function of time.*

partment model, even though K is nonsymmetric. Let $\mathbf{p}_i$ be the real eigenvector of K associated with λ_i, where $P = (\mathbf{p}_1, \mathbf{p}_2, \ldots, \mathbf{p}_n)$ and P^{-1} is the inverse of P. Then the solution of Eq. 2 can be written:

$$\mathbf{x} = PDP^{-1}\mathbf{x}_0 = \sum_{i=1}^{n} b_i \mathbf{p}_i \exp(\lambda_i t) \qquad \text{(Eq. 27)}$$

where $b = P^{-1}\mathbf{x}_0$. Thus, Eq. 24 can be written in terms of scalar exponentials, but the notation is cumbersome.

To evaluate $\mathbf{x}$ for plotting, let $G = \exp(KT)$, where T is a sufficiently small increment of time, say 0.1 in this example. Calculate G once and for all by using Eq. 13 to get:

$$G = \begin{pmatrix} .3679 & .0000 & 0. \\ .5966 & .9048 & 0. \\ .0355 & .0952 & 1. \end{pmatrix} \qquad \text{(Eq. 28)}$$

or by using the eigenvalues of K:

$$\Lambda = \begin{pmatrix} -10. & 0. & 0. \\ 0. & -1. & 0. \\ 0. & 0. & 0. \end{pmatrix} \qquad \text{(Eq. 29)}$$

and the eigenvectors of K:

$$P = \begin{pmatrix} 1.0000 & 0. & 0. \\ -1.1111 & 1. & 0. \\ 0.1111 & -1. & 1. \end{pmatrix} \qquad \text{(Eq. 30)}$$

in Eq. 27. Thus, at time $t = T$, we have:

$$\mathbf{x}(T) = G\mathbf{x}_0 \qquad \text{(Eq. 31)}$$

At $t = 2T$, we have:

$$\mathbf{x}(2T) = G\mathbf{x}(T) \qquad \text{(Eq. 32)}$$

the interpretation being that $\mathbf{x}(T)$ itself is a new set of initial conditions to use in calculating $\mathbf{x}(2T)$. Thus:

$$\mathbf{x}(3T) = G\mathbf{x}(2T) \qquad \text{(Eq. 33)}$$

which gives the values of $\mathbf{x}$ at $t = 0.3$ in the example. Now, similarly calculate $\mathbf{x}(4T)$, which gives the values of $\mathbf{x}$ at $t = 0.4$ but just before the first maintenance dose is given. Now let an asterisk denote the values of $\mathbf{x}$ immediately after the first maintenance dose is given. Then clearly:

$$\mathbf{x}^*(4T) = \mathbf{x}(4T) + (.3, .0, .0)' \qquad \text{(Eq. 34)}$$

where the prime denotes the vector transpose. Then:

$$\mathbf{x}(5T) = G\mathbf{x}^*(4T) \qquad \text{(Eq. 35)}$$

With this approach, it is clear that we can write easily the equations for nonuniform multiple dosing into each compartment, so that in general we have:

$$\mathbf{x}[(n + 1)T] = G\mathbf{x}^*(nT) \qquad \text{(Eq. 36)}$$

As a check, we used the Continuous System Modeling Program (6) to integrate Eq. 20 numerically with the arguments of the example. The output plots are shown in Figs. 1–3. Plots of the solution of Eq. 20 can also be obtained by use of an analog computer, provided that one has a multiple-dose generator as described by Howell (7).

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Quantitation, Elimination, and Discussion of Decomposition Product Interference in *N*-Acetyl-*p*-aminophenol Colorimetry

Keyphrases □ *N*-Acetyl-*p*-aminophenol—direct colorimetric analysis, decomposition product interference examined □ Colorimetry—analysis, *N*-acetyl-*p*-aminophenol, degradation product interference examined

To the Editor:

Direct colorimetric assay of *N*-acetyl-*p*-aminophenol (I) has been effected by reaction of I with nitrous acid under mild conditions to form 2-nitro-4-acetamidophenol. This reaction was elucidated by Le Perdriel *et al.* (1), who measured the orange-red color of the phenolate ion; Inamdar and Kaji (2), working separately, assayed using the yellow of the unionized phenol.

Chafetz *et al.* (3) compared these methods with their modified technique employing an entirely aqueous system. Because these methods require only the successive addition of reagents, Daly *et al.* (4) adapted the latter technique to an automated assay apparatus, resulting in excellent recovery data with commercial formulations.

The assay of Le Perdriel *et al.* (1) resulted in good

selectivity for I; no interference was incurred by most structurally similar drugs except salicylamide (3). However, Le Perdriel *et al.* noted that when I was aged, results in excess of theory were obtained at a point where some 50% of I had degraded. This problem was strongly emphasized by Shearer *et al.* (5) who, using the Chafetz *et al.* (3) method, claimed that a minimum of 25% contribution to the absorbance was observed when an equivalent molar concentration of *p*-aminophenol was tested.

Because of the limited and confusing documentation of the true extent of interference perpetrated by the degradation products of I, the purposes of this study were to document this degree of interference and to discuss the limit of applicability of the Le Perdriel *et al.* assay *per se*.

The degree of interference or the ability of the Le Perdriel *et al.* assay method to determine I selectively in the presence of increasing percentages of the breakdown products of I is shown in Fig. 1. The assay method closely paralleled the method of Le Perdriel *et al.* An ethanolic solution of I was treated with the following reagents: 0.5 ml of 50% (v/v) hydrochloric acid and then 1 ml of a 10% (w/v) sodium nitrite solution. A reaction time of 15 min was allowed before the samples were adjusted to 10 ml with 5% (w/v) anhydrous sodium carbonate solution. The absorbance was read at 440 nm using a similarly treated 2-ml alcohol sample as the blank.

The error shown in Fig. 1 can be eliminated by using the ion-exchange separation of Koshy and Lach (6). This method involved separation of I from its degradation products using a narrow bore column[1] previously washed with 10% hydrochloric acid, distilled water, and alcohol, in that order. A flow rate of 5–10 drops/min was allowed until the sample passed to the upper level of the resin, at which time the alcohol elution flow rate was increased to approximately 20 drops/min. The eluate was collected until exactly 100 ml was obtained.

Two absorbance readings were found essential for proper determination of I after column separation. The first was measurement of the color developed, and the second was measurement of the absorbance of the small proportion of noncolumn-held yellow-brown oxidative products of *p*-aminophenol in a similar dilution with nitrite omitted. Both solutions were read using the same blank at 440 nm. Subtraction of the second from the first yielded, with 95% confidence, an assay value of 99.3 ± 0.8% of the quantity of I present up to the tried value of 67.51% simulated degradation.

The degree of interference depicted in Fig. 1, resulting from breakdown products of I in the Le Perdriel *et al.* determination of I, suggests less interference than was referred to by Shearer *et al.* (5) yet seemingly complies with the qualitative evidence of Le Perdriel *et al.* (1).

With data as to the degree of interference perpetuated by the breakdown products of I now available,

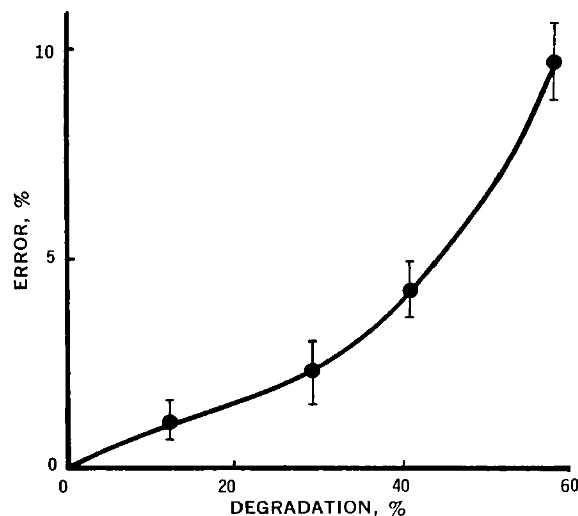

Figure 1—*Percent degradation of* N-*acetyl*-p-*aminophenol versus error in* N-*acetyl*-p-*aminophenol determination. The 95% confidence limits about mean values* (n = 4) *are shown.*

quantitative determination of I by the Le Perdriel *et al.* method may be reviewed objectively.

Consider the determination of the kinetic picture of the degradation of I. To determine effectively the order of a reaction, 90% of the reaction of the initial species should be followed. Because of the eventual growth in percentage of degradants as the reaction proceeds, the unacceptable interference (Fig. 1) of these degradation products will necessarily dictate column elution before the Le Perdriel *et al.* method *per se* may be quantitatively used.

From a practical formulation viewpoint, the concern is with 10% or less degradation. If a formulation results in a greater than 10% potency loss during a shorter period than is desirable, reformulation is necessary. The method of Le Perdriel *et al.* (1) in this instance, without column separation, would be virtually unequalled in its simplicity and quantitative potentialities, since an error determination of 1% (Fig. 1) is well within the limits of analytical error.

Thus, knowledge of the error in analysis in the presence of breakdown products (Fig. 1) is essential for the rational use of the Le Perdriel *et al.* 2-nitro-4-acetamidophenol determination of I.

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[1] Amberlite IR-120.

Role of Carbonate in Aluminum Hydroxide Gel Established by Raman and IR Analyses

Keyphrases □ Carbonate—role in aluminum hydroxide gel, Raman and IR analyses □ Aluminum hydroxide gel—role of carbonate, Raman and IR analyses □ Raman spectroscopy—association of carbonate and aluminum in aluminum hydroxide gel □ IR spectroscopy—association of carbonate and aluminum in aluminum hydroxide gel

To the Editor:

Aluminum hydroxide gel has been recognized as an effective antacid by the Food and Drug Administration (FDA) (1) and is included in USP XVIII (2). However, FDA makes no attempt to describe the structure of aluminum hydroxide gel. The USP states that aluminum hydroxide gel contains the equivalent of 3.6–4.4% of aluminum oxide in the form of aluminum hydroxide and hydrated oxide. This statement does not fully describe aluminum hydroxide gel, since a number of reports (3–6) have concluded that anions present during precipitation are incorporated in the gel structure and act to stabilize the gel. Carbonate ion is the most effective in stabilizing the gel (3). For this reason, reactive aluminum hydroxide gels usually contain carbonate. In this communication, we report that Raman and IR spectroscopy clearly demonstrate that an association exists between carbonate and aluminum in aluminum hydroxide gel. Thus, carbonate is an integral part of reactive aluminum hydroxide gel and is not simply present in solution or as a void-filling occluded ion.

The Raman spectrum of carbonate ion in solution was compared to the Raman spectrum[1] of aluminum hydroxide gel and to a crystalline sodium aluminum hydroxy carbonate gel. The aluminum hydroxide gel was prepared, following a previously described procedure (3), by the addition of a solution of aluminum chloride to a solution of sodium carbonate and sodium bicarbonate until pH 6.5 was reached. The aluminum hydroxide gel was amorphous by X-ray diffraction, contained the equivalent of 3.2% Al_2O_3, and was fully reactive as measured by the acid-consuming capacity test (2). The amount of carbonate in the gel was determined by the gasometric determination of carbon dioxide (7). The gel evolved 1.4% CO_2.

A crystalline sodium aluminum hydroxy carbonate gel containing 6.9% $NaAl(OH)_2CO_3$, which is equivalent to 2.4% Al_2O_3, was evaluated by Raman and IR spectroscopy. The crystalline gel contained the equivalent of 2.8% CO_2 and possessed X-ray diffraction bands at 5.67, 3.38, 2.784, 2.601, 2.151, 1.988, and 1.728 Å, which identify the gel as dawsonite (8).

The Raman spectrum of carbonate ion in solution (9) has a very strong band at 1063 cm^{-1}, weak bands at 1415 and 680 cm^{-1}, and an inactive band at 880 cm^{-1}. The Raman spectrum of the amorphous aluminum hydroxide gel has a broad band ranging from 1060 to 1174 cm^{-1} with the maximum at 1120 cm^{-1}. The crystalline sodium aluminum hydroxy carbonate has a sharp band at 1090 cm^{-1}.

The change in the band at 1063 cm^{-1} from a sharp peak for carbonate ion in solution to a broad band centered at 1120 cm^{-1} in the amorphous gel indicates that varying degrees of interaction are occurring between the oxygens of the carbonate ion and aluminum in the gel. These interactions destroy the symmetry possessed by the carbonate ion in solution, and the loss of symmetry causes a shift in the peak position. In aluminum hydroxide gel, numerous degrees of association are possible due to the amorphous nature of the gel. Therefore, the carbonate peak appears as a broad band reflecting the varying degrees of association of carbonate with aluminum.

In crystalline sodium aluminum hydroxy carbonate, a sharp peak appears at 1090 cm^{-1}. This shift indicates that the symmetry of carbonate ion is destroyed due to the association of carbonate with aluminum. However, the carbonate is associated with the aluminum in only one environment, as indicated by the sharp peak.

The IR spectra also indicate that definite association exists between carbonate and aluminum in aluminum hydroxide gel. Because of interference by strong water bands in the 1400–1700-cm^{-1} region, the IR spectra[2] were run as air-dried films of the gels on a zinc sulfide[3] window.

The IR spectrum of sodium carbonate has bands at 1450, 880, and 720 cm^{-1} (10). In aluminum hydroxide gel, bands associated with carbonate occur at 1525, 1415, 1100, and 850 cm^{-1}. The band at 1450 cm^{-1} for sodium carbonate has split into two bands, 1525 and 1415 cm^{-1}, in aluminum hydroxide gel. Nakamoto (10) and Healy and White (11, 12) showed that when carbonate ion coordinates to a metal, the ν_3 vibration splits into two bands. The magnitude of the splitting has been shown to be dependent on whether a uni- or a bidentate complex forms.

Carbonate bands occur at 1580, 1390, 1080, and 840 cm^{-1} in the crystalline sodium aluminum hydroxy carbonate. The carbonate band occurring at 1450 cm^{-1} for sodium carbonate has again split, but the magnitude of the split is 190 cm^{-1} for the crystalline gel in comparison to 110 cm^{-1} for the amorphous gel (Fig. 1). The magnitude of the split of this carbonate band may be useful in predicting the acid reactivity of aluminum hydroxide gel.

In addition to the splitting of the degenerate vibration, the appearance of the inactive band at 1100 cm^{-1} in the amorphous gel and 1080 cm^{-1} in the crystalline gel is also typical of a substantial lowering of symmetry due to association between carbonate and aluminum (12).

Thus, it is concluded that Raman and IR spectroscopy are useful tools for studying the role of anions in stabilizing aluminum hydroxide gel. Raman spectroscopy is especially useful because water does not interfere and the gels can be run in their natural condi-

[1] Raman spectra were run on a Spex RAMALOG 4, courtesy of Spex Industries, Metuchen, N.J.

[2] Model 421, Perkin-Elmer Corp., Norwalk, Conn.

[3] Irtran 2, Eastman Kodak, Rochester, N.Y.