Aluminum Chlorohydrate II: Physicochemical Properties

DIRK L. TEAGARDEN *, JOHN F. RADAVICH §, JOE L. WHITE ‡, and STANLEY L. HEM *x

Received October 3, 1980, from the **Department of Industrial and Physical Pharmacy, the ‡Department of Agronomy, and the §School of Materials Engineering, Purdue University, West Lafayette, IN 47907.* Accepted for publication December 8, 1980.

Abstract □ Determination of the chloride content of aluminum chlorohydrate by a chloride-selective electrode indicated that $\gamma_{Cl^-} \rightarrow 1$. IR analysis demonstrated that chloride was exchanged readily by nitrate and that the IR bands of the anion were not perturbed significantly. Thus, chloride is believed to act as a counterion. A high positive charge is predicted based on the critical coagulation concentration of aluminum chlorohydrate and the stability of aluminum chlorohydrate to attack by protons, as demonstrated by pH-stat titration. Potentiometric titration with sodium hydroxide showed adsorption of hydroxyl anions initially, but a higher pH than expected was observed at the end-point. This behavior is consistent with the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex, which would adsorb hydroxyl anions initially and in which the central tetrahedral aluminum is shielded from the added hydroxyl anions. The reaction rate with ferron (8-hydroxy-7-iodo-5-quinolinesulfonic acid) suggests that the major species in aluminum chlorohydrate is a large aluminum polycation. A platey morphology for lyophilized, air-dried, and spray-dried aluminum chlorohydrate was observed by scanning electron microscopy. The platey appearance is consistent with the structure of $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ since the spherical nature and high uneven charge of the complex make stacking difficult.

Keyphrases □ Aluminum chlorohydrate—physicochemical properties determined by IR spectroscopy and pH-stat and potentiometric titrations □ Spectroscopy, IR—analysis, aluminum chlorohydrate, physicochemical properties determined □ Potentiometric titration—aluminum chlorohydrate, physicochemical properties determined, IR spectroscopy and pH-stat titration □ Critical coagulation concentration—aluminum chlorohydrate, physicochemical properties determined using IR spectroscopy and pH-stat and potentiometric titrations

X-ray diffraction and IR and ^{27}Al-NMR spectroscopy recently showed that aluminum chlorohydrate is composed of a central aluminum in tetrahedral configuration surrounded by 12 aluminum atoms, each in an octahedral configuration (1). The complex, $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$, is essentially spherical with the +7 charge equally distributed on the surface. Seven chloride ions are believed to be associated with the complex as counterions. The objectives of this study were to examine the physicochemical properties of aluminum chlorohydrate and to determine if these properties are related to the recently proposed structure.

EXPERIMENTAL

Aluminum chlorohydrate was obtained commercially as a 50% (w/w) solution[1].

Aluminum was quantified by a chelatometric titration procedure (2). The chloride content was determined by both the modified Volhard technique (3) and a chloride-selective electrode[2]. The aluminum chlorohydrate solutions were diluted with potassium nitrate solutions prior to measurement by the chloride-selective electrode to produce a solution having 1×10^{-2}–1×10^{-4} *M* chloride and an ionic strength of ~0.1. The chloride concentration of aluminum chlorohydrate solutions that had been hydrolyzed by nitric acid also was determined by the modified Volhard method and by the chloride-selective electrode. Hydrolysis was accomplished by adding the quantity of nitric acid indicated in Table I and heating to 70° for 1 hr.

Chloride in aluminum chlorohydrate was replaced by nitrate; after air drying, the IR spectrum was determined in potassium bromide pellets. One hundred milliliters of 0.308 *M* silver nitrate was placed in a 400-ml beaker, and 90 ml of a diluted aluminum chlorohydrate solution (0.308 *M* in chloride) was added slowly. Silver chloride precipitated throughout the addition. The mixture was stirred for 15 min and centrifuged at 2500 rpm for 10 min. The precipitate was discarded, and the supernate was prepared for IR spectroscopy[3].

Table I—Chloride Content of Aluminum Chlorohydrate Determined by Volhard Method and Chloride-Selective Electrode

Nitrate Added, *M*	Volhard Method, *M*	Chloride-Selective Electrode, *M*
Potassium nitrate		
9.0×10^{-2}	2.3×10^{-3}	2.3×10^{-3}
9.9×10^{-2}	2.3×10^{-4}	2.3×10^{-4}
Nitric acid		
9.0×10^{-2}	2.3×10^{-3}	2.1×10^{-3}
9.9×10^{-2}	2.3×10^{-4}	2.3×10^{-4}

The charge of the aluminum chlorohydrate complex was determined by the method of Matijevic *et al.* (4), except that 0.69% sodium montmorillonite was used as the lyophobic colloid rather than silver iodide. Potassium chloride, calcium chloride, aluminum nitrate, and thorium nitrate were used to prepare a standard curve of the valence of the coagulating cation *versus* the ratio of the critical coagulation concentration of the cation to the critical coagulation concentration of potassium.

The potentiometric titration curve of aluminum chlorohydrate or aluminum chloride with sodium hydroxide was determined with an automated titrator[4]. The aluminum chloride solution was brought to a ratio of 2.5 (hydroxyl to aluminum) with sodium hydroxide before the recorder was activated so that both aluminum samples were titrated from a hydroxyl to aluminum ratio of 2.5 to 3.0.

The rate and extent of acid neutralization by aluminum chlorohydrate was determined at pH 1, 2, and 3 at 25° with an automated titrator[4].

The distribution of aluminum in aluminum chlorohydrate (*i.e.*, monomers, small polycations, and large polycations) was determined by

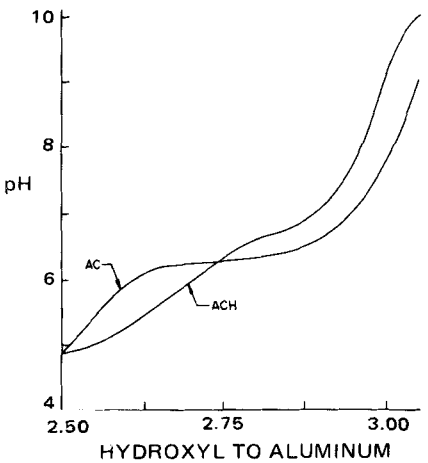

Figure 1—*Potentiometric titration of aluminum chlorohydrate (ACH) or aluminum chloride (AC) with sodium hydroxide.*

[1] Lot 8473, Wicken Products, Huguenot, N.Y.
[2] Model 94-17A, Orion Research, Cambridge, Mass.
[3] Model 180, Perkin-Elmer Corp., Norwalk, Conn.
[4] PHM 26, TTT 11, ABU 12 (2.5 ml), TTA 3, SBR 2, Radiometer, Copenhagen, Denmark.

0022-3549/81/0700-0762$01.00/0

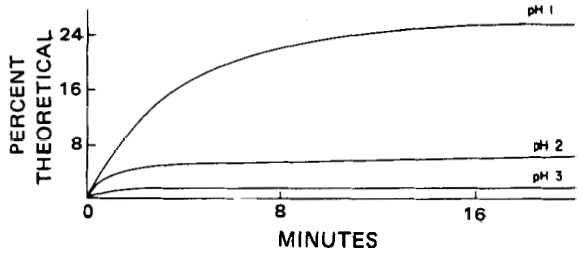

Figure 2—*A pH-stat titrigram of aluminum chlorohydrate at pH 1, 2, and 3.*

the ferron (8-hydroxy-7-iodo-5-quinolinesulfonic acid) test (5).

Scanning electron photomicrographs[5] of aluminum chlorohydrate were taken following air drying, spray drying, or lyophilization.

RESULTS AND DISCUSSION

Table I compares the chloride content of aluminum chlorohydrate solutions as determined by the Volhard titration and the chloride-selective electrode. The results by both methods were virtually identical. In addition, the chloride content was the same for intact and hydrolyzed aluminum chlorohydrate. Thus, the chloride activity coefficient of aluminum chlorohydrate must be close to 1, indicating that the chloride ion acts as a counterion. This finding is in contrast to the activity of chloride in chloride-containing aluminum hydroxide gel. The fact that the chloride content of chloride-containing aluminum hydroxide gel, as determined by a chloride-selective electrode, was less than that determined by the Volhard titration was attributed to the binding of the chloride ion to the aluminum hydroxy complex (6).

The degree of interaction of the anion with the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex could be studied by IR spectroscopy if the anion was IR active. Thus, aluminum chlorohydrate was treated with silver nitrate to attempt to replace the IR inactive chloride with IR active nitrate. Nitrate anion was chosen because it is the same approximate size and charge as chloride, and it is symmetrical so that any perturbations due to interaction with the aluminum complex would cause a shift in the IR spectrum. The IR spectrum was not affected by the replacement of chloride by nitrate except for the appearance of bands at 1380 and 830 cm^{-1}. Both bands correspond to the bands for nitrate in sodium nitrate, indicating that the anion in aluminum chlorohydrate is readily exchangeable. Furthermore, the IR bands of sodium nitrate at 1358 and 836 cm^{-1} show little interaction of the anion with the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex (7). Thus, the activity of the chloride ion and the IR spectrum of aluminum nitrohydrate indicate that the anion is not part of the aluminum complex but rather functions as a counterion. This behavior is consistent with the structure of the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex.

Table II shows that the critical coagulation concentration of aluminum chlorohydrate was less than thorium. The regression equation for the known cations (charge = 0.12 CCC/CCC_{K+} + 0.97)[6] had a R^2 value of 0.990 and predicted a valence of 5.6 for aluminum chlorohydrate. This valence is the average of all species present in the aluminum chlorohydrate solution. In addition, the valence of highly charged cations may be greater than that determined by the critical coagulation concentration method because interionic distances increase rapidly with dilution (8). Therefore, the valence of aluminum chlorohydrate as determined by the critical coagulation concentration method is consistent with the high charge of the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex.

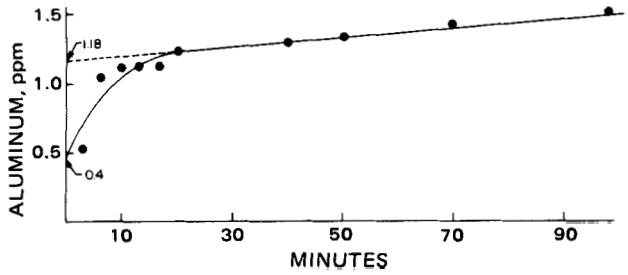

Figure 3—*Rate of reaction of a solution of aluminum chlorohydrate containing 9.87 ppm of aluminum with ferron.*

[5] Super III A, International Scientific Products, Mountain View, Calif.

[6] CCC/CCC_{K+} is the ratio of the critical coagulation concentration of the cation to the critical coagulation concentration of potassium.

Table II—Critical Coagulation Concentration (CCC) of Aluminum Chlorohydrate in Comparison to Known Cations

Ion	Charge	CCC, N	CCC/CCC_{K+}
Potassium	1	6.25×10^{-3}	1.00
Calcium	2	8.73×10^{-4}	7.16
Aluminum	3	3.5×10^{-4}	17.85
Thorium	4	2.5×10^{-4}	25.00
Aluminum chlorohydrate	Unknown	1.62×10^{-4}	38.58

The titrigrams of aluminum chloride (following the addition of sodium hydroxide to produce a hydroxyl to aluminum ratio of 2.5) and of aluminum chlorohydrate are shown in Fig. 1. The pH of the aluminum chlorohydrate solution did not increase as rapidly as the aluminum chloride solution, indicating that the added hydroxyl concentration was being adsorbed by the aluminum chlorohydrate. The evenly distributed positive charge of the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex would be expected to adsorb hydroxyl anions. Furthermore, the pH at the end-point (hydroxyl to aluminum ratio of 3) was higher for aluminum chlorohydrate. This finding suggests that more hydroxyl anions are in solution in the aluminum chlorohydrate solution, possibly because the tetrahedral aluminum in the center of the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex is inaccessible to the added hydroxyl anions.

The reactivity of aluminum chlorohydrate to proton attack was investigated by pH-stat titration. Hydroxyl anions are released into solution if aluminum chlorohydrate breaks up under proton attack. As can be seen in Fig. 2, aluminum chlorohydrate is very stable to proton attack. Even at pH 1, only ~25% of the total hydroxyl anions in aluminum chlorohydrate were neutralized. The fact that protons do not readily attack the complex further indicates that aluminum chlorohydrate is positively charged. In addition, the charge is predicted to be high and evenly distributed to shield the hydroxyl anions of the complex from proton attack.

Based on the reaction rate with ferron, the distribution of aluminum species in aluminum chlorohydrate can be classified as 4% monomeric aluminum, 8% small polycations, and 88% large polycations (Fig. 3). The fact that the major species in aluminum chlorohydrate reacts slowly with ferron also is consistent with the structure of the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex.

The morphology of aluminum chlorohydrate that had been air dried,

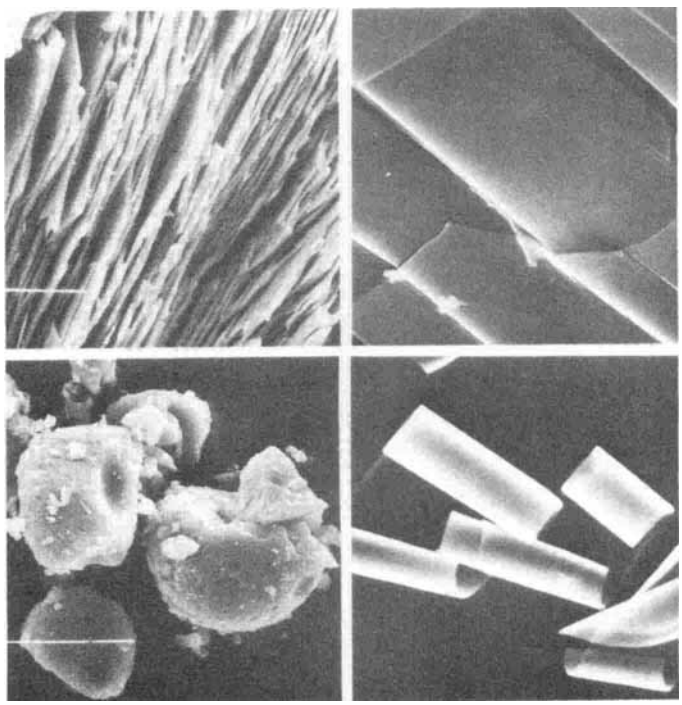

Figure 4—*Scanning electron photomicrographs of aluminum chlorohydrate. Key: upper left, lyophilized, 700×, line of 50 μm; upper right, lyophilized, 5000×; lower left, spray dried, 2000×, line of 5 μm; and lower right, air dried, 10,000×.*

lyophilized, or spray dried was examined by scanning electron microscopy (Fig. 4). All samples showed a platey structure, although it was most evident in the lyophilized sample. The spray-dried sample showed spherical particles that are inherent to spray drying. However, the spheres were made up of thin plates. The air-dried samples formed scroll-like sheets due to the more rapid rate of water loss from the top surface during drying. Johansson (9), in proposing the $Al_{13}O_4(OH)_{24}(H_2O)_{12}^{7+}$ complex, noted the formation of plate-like crystals during the study of a basic aluminum sulfate that was built up from the same kind of aluminum–oxygen complexes. It is suggested that the high uneven charge on the spherical units minimize contact with adjacent units so that a planar configuration provides the most favorable spatial and electrostatic arrangement.

REFERENCES

(1) D. L. Teagarden, J. F. Kozlowski, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **70**, 758 (1981).

(2) "The United States Pharmacopeia," 20th rev., United States Pharmacopeial Convention, Rockville, Md., 1980, p. 456.

(3) I. M. Kolthoff, "Quantitative Analysis," 4th ed., Macmillan, London, England, 1969, p. 799.

(4) E. Matijevic, K. G. Mathai, R. H. Ottewill, and M. Kerker, *J. Phys. Chem.*, **65**, 826 (1961).

(5) R. W. Smith, in "Advances in Chemistry," vol. 106, R. F. Gould, Ed., American Chemical Society, Washington, D.C., 1971, p. 250.

(6) S. L. Nail, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **65**, 1188 (1976).

(7) C. J. Serna, J. L. White, and S. L. Hem, *Soil Sci. Soc. Am. J.*, **41**, 1009 (1977).

(8) E. Matijevic, D. Broadhurst, and M. Kerker, *J. Phys. Chem.*, **63**, 1552 (1959).

(9) G. Johansson, *Acta Chem. Scand.*, **14**, 771 (1960).

ACKNOWLEDGMENTS

This report is Journal Paper 8255, Purdue University Agricultural Experiment Station, West Lafayette, IN 47907.

Automated Dissolution Testing of Combination Drug Product Using High-Pressure Liquid Chromatography

DALE ERIC WURSTER ˣ, WILLIAM A. WARGIN, and MARTIN DeBERARDINIS, Jr.

Received July 24, 1980, from the *School of Pharmacy, University of North Carolina, Chapel Hill, NC 27514.* Accepted for publication December 8, 1980.

Abstract □ An automated high-pressure liquid chromatographic (HPLC) system compatible with any standard tablet dissolution apparatus was developed. This system allowed the individual drug concentrations within a product to be determined simultaneously, even when the drugs had similar structures and UV spectra. This automated system permitted unattended sampling and concentration determination at predetermined time intervals. The dissolution medium was pumped continuously through a fixed-volume, microprocessor-controlled injector and returned to the USP rotating-basket dissolution apparatus. No corrections for the changing dissolution medium volume were necessary since each injection onto a reversed-phase HPLC column consumed just 10 μl of medium. Dissolution tests were performed on three brands of trisulfapyrimidines tablets. Sample injections were made automatically at 5.1-min intervals for ~2 hr. Dissolution profiles were determined for each drug in each product. Statistically significant differences were found in the mean concentration–time values between drugs within a drug product and between drug products.

Keyphrases □ High-pressure liquid chromatography—with automated dissolution testing of a combination drug product □ Dissolution—automated high-pressure liquid chromatography, combination drug product □ Combination drugs—dissolution testing using automated high-pressure liquid chromatography □ Trisulfapyrimidines—combination drug product, dissolution testing using automated high-pressure liquid chromatography

Automated procedures for dissolution testing of pharmaceuticals have been of interest since such procedures are labor saving and increase analytical reproducibility. These automated procedures usually involve pumping the dissolution medium directly through a flowcell mounted in a UV spectrophotometer (1–6). An inherent problem with such an arrangement is the lack of drug specificity. If two or more drugs in a drug product have similar UV spectra, this procedure is useless.

In view of the number of combination products on the market, an automated technique is needed that allows each drug in a product to be quantitated individually during a dissolution run.

BACKGROUND

High-pressure liquid chromatography (HPLC) is a versatile analytical technique that combines the specificity of chromatography with the sensitivity of refractive index, UV, fluorescence, or electrochemical detection. Optimal retention times for the separation of active ingredients and dosage form excipients may be obtained by appropriately varying the mobile phase composition, pH, and/or flow rate. Changing the chromatographic temperature and utilization of gradient elution also are viable options. Other than filtration, aqueous samples require no special preparation prior to injection onto a reversed-phase HPLC column.

While various components of an HPLC system have been used to automate drug analysis procedures (3, 7) during dissolution, the actual chromatographic process has been included only in a manual (8) or semiautomated (7) procedure.

This report describes a totally automated HPLC method that has been used successfully to characterize the dissolution profile of each drug entity in a trisulfapyrimidines USP tablet. Completely unattended dissolution analysis is possible using this technique.

EXPERIMENTAL

A USP rotating-basket dissolution apparatus, a dissolution stirrer drive[1], and a water bath[2] were used. The basket was rotated at 150 rpm, and the temperature of the dissolution medium (0.1 *N* HCl) was 37.0 ± 0.1°. A pump[3] circulated the dissolution medium through a fixed-volume (10-μl loop) microprocessor[4]-controlled injector[5] and returned the me-

[1] Model 53, Hanson Research Corp., Northridge, CA 91234.

[2] Precision Scientific, Chicago, Ill.

[3] Milton Roy Mini-Pump, Laboratory Data Control, Riviera Beach, FL 33404.

[4] Model 740 Control Module, Micromeritics, Norcross, GA 30093. (Depending on the interfacing procedure, the Micromeritics model 753 ternary solvent mixer may also be required.)

[5] Model 735 with model 725 automatic injector valve, Micromeritics, Norcross, GA 30093.

0022-3549/81/0700-0764$01.00/0