

**Figure 4**—Cumulative absorption of aceclidine (3-acetoxyquinuclidine) into the anterior chamber of the rabbit eye.

function of the time of drug detection in the anterior chamber. Statistical analysis of the significance of the means between the times for onset of salivation resulting from corneal or conjunctival absorption was found to be insignificant at the 95% level. It has been assumed (2) that salivation is an index of corneal penetration of I. This assumption is not warranted from the observations reported here. Support for the lack of correlation is found in

Table I (corneal absorption) where it can be seen that drug in the anterior chamber can precede salivation from 2 to 35 min. It is conceivable that pharmacological assay with sensitivities considerably greater than reported here would show the different symptomatic relationships to be significant. The drawback in either chemical or pharmacological assay was the subjectivity involved in defining the onset of symptoms as a function of drug intake. For example, observation of salivation was partially subjective since the end result and not the initial action was observed.

In these experiments, there was no evidence for deacetylation of I to II. Therefore, as would be predicted, the intact drug (I) penetrates primarily through the cornea into the anterior chamber where it can act to influence intraocular pressure. The experiments indicated that the scleral conjunctival membrane was not a major absorbing surface for I into the anterior chamber.

#### SUMMARY

Aceclidine (I), after topical administration, was detected in the anterior chamber. The penetration was primarily, if not exclusively, through the cornea and not the conjunctiva. In a sensitive GLC assay, only I was detected. There was no evidence of hydrolysis to the corresponding 3-quinuclidinol (II).

#### REFERENCES

- (1) L. H. Sternbach and S. Kaiser, *J. Amer. Chem. Soc.*, **74**, 2215(1952).
- (2) W. T. Lieberman and I. H. Leopold, *Amer. J. Ophthalmol.*, **64**, 405(1967).

#### ACKNOWLEDGMENTS AND ADDRESSES

Received July 16, 1973, from the *Science and Technology Division, Alcon Laboratories, Inc., Fort Worth, TX 76101*

Accepted for publication December 17, 1973.

\* To whom inquiries should be directed.

## Effect of Washing on Physicochemical Properties of Aluminum Hydroxide Gel

ROBERT H. GREEN and STANLEY L. HEM<sup>x</sup>

**Abstract** □ The negative electrophoretic mobility of aluminum hydroxide gel approaches zero logarithmically as the gel is washed and is related to the elution of chloride ion. Chloride ion is eluted at a constant rate and appears to be associated with the gel by a single mechanism. The viscosity of the gel increases with increased washing.

**Keyphrases** □ Aluminum hydroxide gel—effect of washing on physicochemical properties, loss of electrophoretic mobility, elution of chloride ion □ Gels, aluminum hydroxide—effect of washing on physicochemical properties, loss of electrophoretic mobility, elution of chloride ion □ Electrophoresis—loss of mobility of aluminum hydroxide gel, effect of washing, elution of chloride ion

An important step in the preparation of aluminum hydroxide gel is washing the gel free of reactants and soluble components following precipitation. The USP (1) places a limit on the chloride and sulfate content of aluminum hydroxide gel. The effect of

washing on the physicochemical properties of aluminum hydroxide gel has not been extensively reported, although precipitation factors such as pH (2), temperature (3, 4), and order of addition and concentration of reactants (4–6) have been studied. The effect of washing on such dosage form-related properties as electrophoretic mobility and viscosity is examined in this report.

#### EXPERIMENTAL

**Materials**—All chemicals used were either official or reagent grade.

**Preparation of Aluminum Hydroxide Gel**—Aluminum hydroxide was prepared by the reaction of aluminum chloride, sodium carbonate USP, and sodium bicarbonate USP at pH 6.5 (2). Doubly distilled water was used for both precipitation and washing. Fractions of the wash water were collected for conductivity and chloride determinations. The extent of washing is expressed as the volumes of wash water eluted per volume of finished gel.

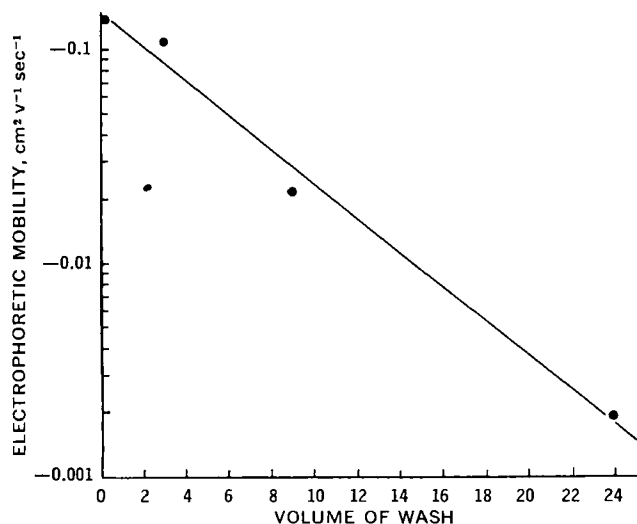


Figure 1—Effect of washing on electrophoretic mobility.

Thus, 1 liter of wash water eluted from 1 liter of gel is 1 volume.

**Analytical Procedures**—The aluminum oxide content of each aluminum hydroxide gel was determined by ethylenediaminetetraacetic acid titration (1).

The electrophoretic mobility was determined using an electrophoretic mass-transport analyzer<sup>1</sup> with the collection chamber containing the anode. The electrode was replaced whenever pitting was observed. The suitability of this instrument for the determination of the electrophoretic mobility of aluminum hydroxide gel was demonstrated by performing four replicate determinations of a gel having a mean electrophoretic mobility of  $-0.173$  (cm/sec)/(v/cm). The standard deviation was  $\pm 0.006$ . Six replicates of a second gel had a mean electrophoretic mobility of  $-0.133$  (cm/sec)/(v/cm) and a standard deviation of  $\pm 0.006$ . The precision in both trials was within  $\pm 5\%$  SD.

The conductivity of the wash water was determined by using the electrophoretic mass-transport analyzer<sup>1</sup> as a Wheatstone bridge. The conductivity cell constant was  $1.1760$  cm<sup>-1</sup>.

The concentration of chloride ion in each fraction of wash water was determined directly with a chloride-selective electrode<sup>2</sup> cali-

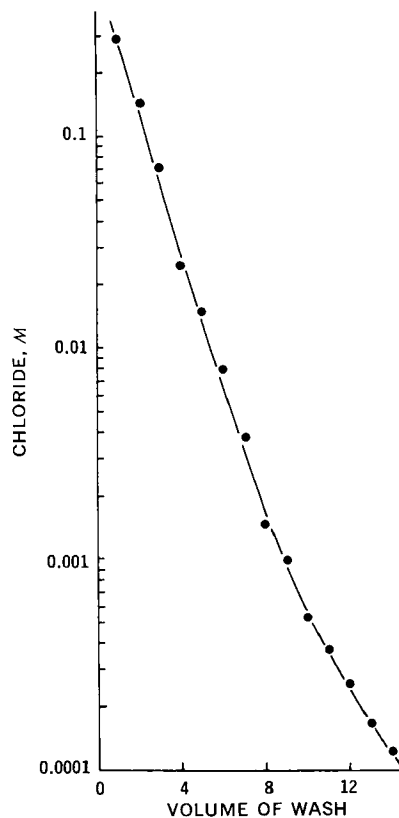


Figure 3—Chloride content of wash water

brated with a sodium chloride standardizing solution. A pH meter<sup>3</sup> was used to measure the voltages developed.

A portion of each gel was adjusted in volume to contain 5% Al<sub>2</sub>O<sub>3</sub>, and the viscosity of this sample was measured using a viscometer<sup>4</sup>. The reported results were determined using spindle 4 at 10 rpm.

## RESULTS AND DISCUSSION

The electrophoretic mobility of aluminum hydroxide gel is negative, but the negative charge diminishes logarithmically as the gel is washed (Fig. 1). The electrophoretic mobility of the gel de-

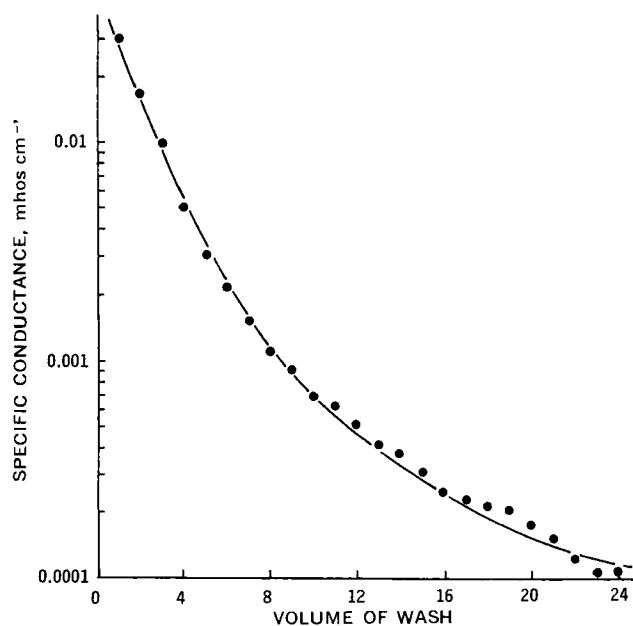


Figure 2—Specific conductance of wash water.

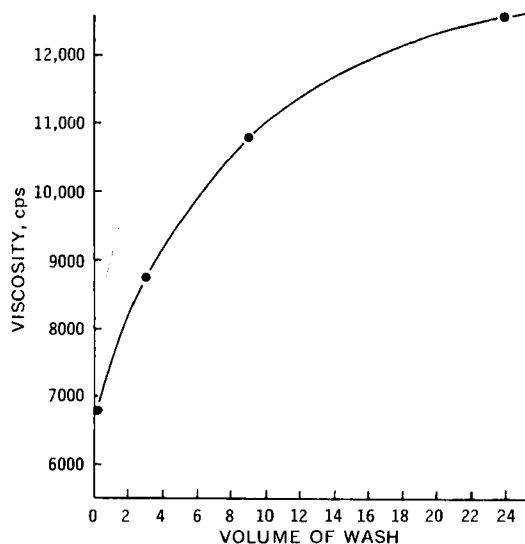


Figure 4—Effect of washing on viscosity.

<sup>1</sup> Model MIC 1201, Numec Instruments and Controls Corp., Monroeville, Pa.

<sup>2</sup> Model 94-17, Orion Research Inc., Cambridge, Mass.

<sup>3</sup> Model NX, Sargent-Welch Scientific Co., Skokie, Ill.

<sup>4</sup> Brookfield model RVT, Brookfield Engineering Labs., Stoughton, Mass.

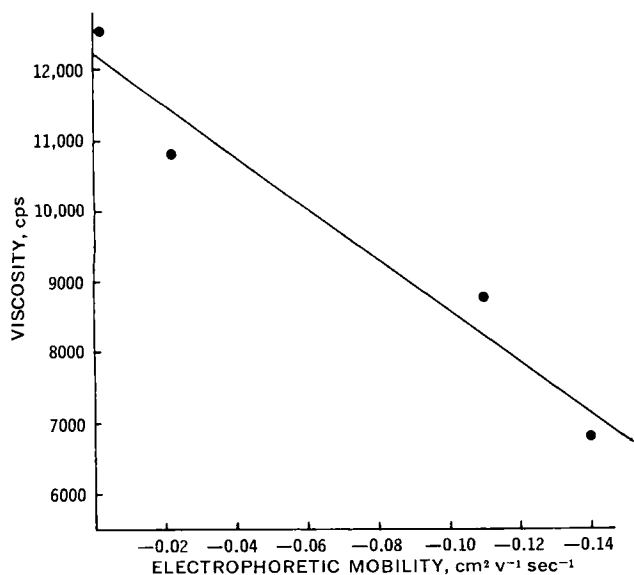


Figure 5—Relationship between electrophoretic mobility and viscosity.

creased from  $-0.140$  (cm/sec)/(v/cm) to essentially zero as the gel was washed with 24 volumes of water. This decrease in electrophoretic mobility is due to the removal of water-soluble components as demonstrated by the decrease in specific conductance of the wash water (Fig. 2). The specific conductance reached a low, essentially constant value after 22 volumes of wash water had been eluted.

The loss of the gel's negative electrophoretic mobility during washing suggests that chloride ion present at the time of precipitation may be responsible for the negative surface charge. This is confirmed by determining the concentration of chloride ion in the wash water. Figure 3 shows that chloride ion was present in the wash water in decreasing amounts during washing. Chloride ion was eluted at a constant rate of  $0.76$  volume<sup>-1</sup> during the first 8 volumes of wash, during which the chloride-ion content of the wash water decreased from  $3.0 \times 10^{-1}$  to  $1.5 \times 10^{-3}$  M. Further elution of chloride ion occurred more slowly as the chloride content of the wash water fell to  $1 \times 10^{-4}$  M, the lower limit of sensitivity for the chloride-selective electrode, during the 15th volume

of wash. The sum of the chloride ion present in the first 15 volumes of wash water plus the amount present in the initial draining totals 2.11 moles. This amount accounts for virtually all of the 2.25 moles of chloride ion contributed by the aluminum chloride. The removal of chloride ion from the gel was demonstrated further by dissolving 10 g of the gel that had been washed with 24 volumes of water in 1.5 ml of nitric acid and 20 ml of doubly distilled water. No precipitate formed when several drops of 0.1 N silver nitrate were added.

The decrease in electrophoretic mobility during washing thus appears to be directly related to the elution of chloride ion. The constant rate of elution suggests that chloride ion is associated with the gel by a single mechanism which allows the chloride ion to be completely eluted.

The viscosity of the gel is also related to the degree of washing. The viscosity increases as the gel is washed, but the viscosity appears to be reaching a limiting value as chloride ion is eluted and the electrophoretic mobility approaches zero (Fig. 4). The increased viscosity is inversely related to electrophoretic mobility (Fig. 5) and may be due to greater interaction occurring between colloidal gel particles possessing low surface charge.

The washing operation is an important part of the preparation of aluminum hydroxide gel because properties such as electrophoretic mobility and viscosity, which are significant in the design of suspension dosage forms, are directly related to washing.

#### REFERENCES

- (1) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 26.
- (2) S. L. Hem, E. J. Russo, S. M. Bahal, and R. S. Levi, *J. Pharm. Sci.*, **59**, 317(1970).
- (3) D. Cismaru, J. Iordachescu, G. Georgescu, and V. Cristescu, *Rev. Roum. Chim.*, **10**, 803(1965).
- (4) J. A. Lewis and C. A. Taylor, *J. Appl. Chem.*, **8**, 223(1958).
- (5) P. H. Hsu and T. F. Bates, *Miner. Mag.*, **33**, 749(1964).
- (6) H. Nogami and T. Nagai, *Chem. Pharm. Bull.*, **10**, 741(1962).

#### ACKNOWLEDGMENTS AND ADDRESSES

Received October 25, 1973, from the Industrial and Physical Pharmacy Department, Purdue University, West Lafayette, IN 47907

Accepted for publication December 12, 1973.

\* To whom inquiries should be directed.

## Improvements in the Synthesis of Pentylene-tetrazol-10-<sup>14</sup>C

J. W. DIRKSEN\*, G. S. BORN\*, W. V. KESSLER, and S. M. SHAW

**Abstract** □ Improvements in the synthesis of pentylene-tetrazol-10-<sup>14</sup>C from hydrazoic acid and cyclohexanone-1-<sup>14</sup>C are reported. Purification was accomplished by crystallization. Chemical purity was determined by GLC and TLC. The radiochemical purity was determined by TLC and autoradiography. The specific activity was found by liquid scintillation counting. A more efficient syn-

thesis was obtained by improvements in the cold bath, the extraction procedures, and the crystallization procedure. The latter change increased the effectiveness of the purification procedure.

**Keyphrases** □ Pentylene-tetrazol, radiolabeled (10-<sup>14</sup>C)—improvements in synthesis □ Radiolabeled compounds—improved synthesis of pentylene-tetrazol-10-<sup>14</sup>C

Pentylene-tetrazol has been synthesized in a number of ways. One of the most productive and yet simple synthesis developed (1) involves reacting cyclohexa-

none with hydrazoic acid. Modifications of this method have been utilized to produce pentylene-tetrazol-5,9-<sup>14</sup>C (2) and pentylene-tetrazol-10-<sup>14</sup>C (3).