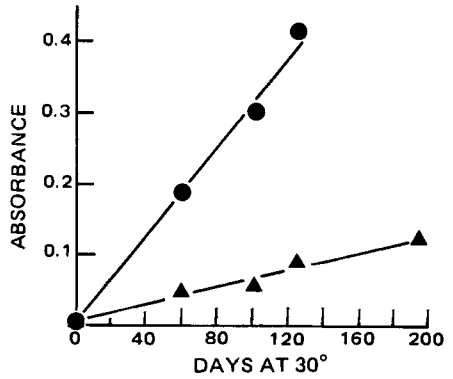



**Figure 3**—*Discoloration of 0.5% neomycin solutions with (●) and without (▲) edetate disodium during storage at 30°.*

solutions with and without I. Thereafter, the rate was slightly greater in the solution containing I (data not shown).

The fall in neomycin concentration and the associated discoloration of the solutions during storage at 30° are shown in Figs. 2 and 3. The data illustrated are for 10 ml of solution in amber ophthalmic dropper bottles. Solutions stored in ampuls at 30° gave qualitatively similar results, but the extent of degradation was somewhat less, due possibly to the smaller proportion of air to liquid in the ampuls. During prolonged storage, II was more stable in the absence rather than the presence of I. This pattern was reflected in the discoloration of the solutions.

Ethylenediaminetetraacetic acid or its disodium salt were observed previously to increase the degradation rate of epinephrine (11), physostigmine (12), and isoproterenol (13), which, like neomycin, all possess basic nitrogen groups in the molecule. With epinephrine (11) and isoproterenol (13), the diminished stability occurred at 37 and 60°, respectively, when ethylenediaminetetraacetic acid was present together with ferric ions at neutral pH values, although the mechanisms responsible for this effect have not been explained adequately. In the experimental system used in the present study, iron was not present other than as a contaminant of other chemicals or if it leached from glass. Furthermore, the same qualitative effects of edetate disodium inclusion were observed regardless of the neomycin batch, buffer concentration, color of the glass container, and presence or absence of phenylmercuric nitrate as a preservative.

The reported results show that inclusion of edetate disodium in neomycin ophthalmic formulations is likely to reduce the stability of the antibiotic during long-term storage at room temperatures. This effect is particularly important if the antibiotic solution is sterilized by filtration because the data indicate that the destabilization is operative even during the early storage period and that the initial protective effect observed at high temperatures is eliminated.

## REFERENCES

(1) Y. Kitano, N. Saegusa, S. Namikawa, E. Yoshikawa, and H. Kono, Japanese pat. 77, 31820 (Mar. 10, 1977).

(2) E. H. Girgis and A. A. Kassem, *J. Drug. Res.*, **5**, 189 (1973).

(3) M. C. Scrutton, *FEBS Lett.*, **78** (2), 216 (1977).

(4) R. M. Simone and R. P. Popino, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 275 (1955).

(5) "British Pharmaceutical Codex," Pharmaceutical Press, London, England, 1973.

(6) "Australian Pharmaceutical Formulary and Handbook," Australasian Pharmaceutical Publishing Co., Melbourne, Australia, 1974.

(7) S. Makino, E. Hayashi, and K. Okamura, Japanese pat. 6247 ('60) (June 1, 1960).

(8) Y. Okami, in "Handbook on Microbiology Vol. III," A. I. Laskin and H. A. Lechevalier, Eds., C.R.C. Press, Cleveland, Ohio, 1973, p. 758.

(9) N. A. Hodges and J. Singh, *J. Pharm. Pharmacol.*, **30**, 737 (1978).

(10) "British Pharmacopoeia 1973," Her Majesty's Stationery Office, London, England, 1973, p. 241.

(11) S. Green, A. Mazur, and E. Shorr, *J. Biol. Chem.*, **220**, 237 (1956).

(12) J. Mørch, "Proceedings of the 17th Congress on Pharmaceutical Sciences," Leiden, The Netherlands, 1957; through T. D. Whittet, *Pharm. Acta Helv.*, **34**, 489 (1959).

(13) J. A. Clements, K. Hasson, and G. Smith, *J. Pharm. Pharmacol.*, **32**, 50P (1980).

# Physicochemical Properties of Magnesium Salicylate

**A. S. ALAM *x and D. GREGORIADES**

Received July 17, 1980, from the *Department of Preclinical Research, Rohm and Haas Company, Spring House, PA 19477.* Accepted for publication January 28, 1981. *Present address: American Critical Care, McGaw Park, IL 60085.

**Abstract** □ Magnesium salicylate tetrahydrate is a nonhygroscopic, crystalline powder, whereas anhydrous magnesium salicylate is amorphous and very hygroscopic. Magnesium salicylate tetrahydrate tablets formulated with gelatin as a binder showed a dissolution half-life ($t_{1/2}$) of 12 min, whereas a formulation using pregelatinized starch as a binder showed a $t_{1/2}$ of 33 min. The optimum level of calcium stearate in the formulation was determined by the oscilloscope tracings of compressional and ejectional forces from an instrumented rotary tableting machine. Increasing the level of calcium stearate from 1 to 1.5 and 2% resulted in dissolution $t_{1/2}$ values of 12, 18, and 21 min, respectively, and a higher incidence of softer tablets and capping.

**Keyphrases** □ Magnesium salicylate—physicochemical properties, tableted tetrahydrate and anhydrous forms, effect of calcium stearate on dissolution rate □ Calcium stearate—effect on dissolution rate of tableted magnesium salicylate □ Dissolution—effect of calcium stearate on magnesium salicylate tablets □ Analgesics—magnesium salicylate tablets, effect of calcium stearate on dissolution

Magnesium salicylate is a white powder with analgesic, antipyretic, and anti-inflammatory properties similar to those of aspirin (1). Although magnesium salicylate or combinations of magnesium salicylate with other analgesics have been widely used in various diseases, the physicochemical properties of magnesium salicylate are not well characterized. This study characterized the physicochemical properties of magnesium salicylate and determined the effect of several excipients on the dissolution rate from tablet formulations.

## EXPERIMENTAL

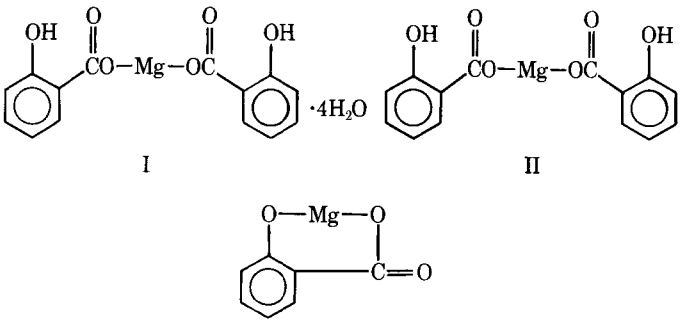
**Materials**—Magnesium salicylate tetrahydrate, anhydrous magnesium salicylate, lactose monohydrate, gelatin, pregelatinized starch, FD&C Red No. 3 aluminum lake, and calcium stearate were used for tablet preparations.

**Thermogravimetric Analysis**—Profiles of the tetrahydrate and anhydrous forms were obtained under nitrogen with a heating rate of 20°/min.

**X-Ray Diffraction**—Profiles of the tetrahydrate and anhydrous forms were determined using nickel-filtered radiation with a copper target, a range of 500, and time constant 5.

**Equilibrium Moisture Content**—Sulfuric acid–distilled water admixtures were prepared for the relative humidity chambers; 20, 40, 60,

0022-3549/81/0800-0961$01.00/0



I II III

and 80% relative humidities (RH) were obtained (2). The tetrahydrate and anhydrous forms were dried at 105°/4 hr/76 cm vac-vented, weighed into aluminum dishes, and placed in the humidity chambers at ambient room temperature. The dishes were weighed after 1, 2, and 3 weeks.

**Tablet Preparation**—Formulation A was prepared by granulating magnesium salicylate tetrahydrate, lactose, and colorant with 41% aqueous gelatin solution. Formulation B was prepared by adding water to the powder mix of magnesium salicylate tetrahydrate, lactose, pregelatinized starch, and colorant. The granulations were dried, sized in a hammermill, lubricated with calcium stearate, and compressed to a 1.83 × 0.74-cm capsule-shaped tablet on an instrumented rotary machine.

**Dissolution**—Tablet dissolution was determined by placing one tablet in the rotating-basket apparatus immersed in 900 ml of distilled water (3). The basket was rotated at 100 rpm. At 10, 20, 30, 60, and 120 min, a 1-ml sample was withdrawn, filtered through a 0.45-$\mu$m membrane filter, and diluted to 10 ml with distilled water; an aliquot was taken for UV absorbance at 296 nm. The amount dissolved was determined, and the cummulative percentage dissolved was calculated based on assayed values. Six individual tablets were run for each product. A NONLIN program (4) was used to calculate the apparent dissolution rate ($k_d$). The dissolution half-life ($t_{1/2}$) was determined by:

$$t_{1/2} = \frac{0.693}{k_d} \qquad \text{(Eq. 1)}$$

## RESULTS AND DISCUSSION

Magnesium salicylate tetrahydrate did not gain any moisture as reflected by the weights after 1, 2, and 3 weeks of storage of samples at 20, 40, 60, and 80% RH. Although the moisture gain for the 40% RH sample was higher, it was not significant. Anhydrous magnesium salicylate gained 1.7, 5.1, 12.2, and 21.5% of its weight, respectively, in these humidity chambers (Table I). Moisture equilibration was reached within 1 week of exposure in each chamber.

**Table I—Moisture Uptake (Percent) by Magnesium Salicylate Tetrahydrate and Anhydrous Magnesium Salicylate at Various Relative Humidity Storage**

| Product | Weeks | Relative Humidity 20% | 40% | 60% | 80% |
|---|---|---|---|---|---|
| Magnesium salicylate tetrahydrate | 1 | 0.05 | 0.03 | 0.08 | 0.06 |
| | 2 | 0.07 | 0.40 | 0.05 | 0.03 |
| | 3 | 0.06 | 0.90 | 0.60 | 0.04 |
| Anhydrous magnesium salicylate | 1 | 1.70 | 4.70 | 11.50 | 21.50 |
| | 2 | 1.70 | 4.80 | 11.90 | 21.80 |
| | 3 | 1.70 | 5.10 | 12.20 | 21.50 |

**Table II—Dissolution Profile[a] of Magnesium Salicylate Tetrahydrate Tablets**

| Formulation | $k_d \pm SD$, min$^{-1}$ | $t_{1/2} \pm SD$, min |
|---|---|---|
| A, 1% calcium stearate | 0.057 ± 0.012 | 12 ± 2.4 |
| A, 1.5% calcium stearate | 0.038 ± 0.007 | 18 ± 3.2 |
| A, 2% calcium stearate | 0.033 ± 0.007 | 21 ± 3.7 |
| B, 1% calcium stearate | 0.021 ± 0.003 | 33 ± 8.8 |

[a] USP apparatus, 100 rpm in distilled water, mean ± $SD$ of six tablets.

The thermogravimetric profile of magnesium salicylate tetrahydrate (I) showed a 20% weight loss between 75 and 200° (II) and a 35% weight loss between 200 and 350° (III), followed by a plateau region between 350 and 475°. Based on molecular weights and weight losses, the postulated products are as shown in Structures I–III.

X-ray diffraction results showed magnesium salicylate tetrahydrate to be crystalline, whereas anhydrous magnesium salicylate was amorphous. Based on these results, magnesium salicylate tetrahydrate was selected for tablet formulation.

Tablet dissolution data are shown in Table II. Although Formulations A and B were compressed to the same size, weight, thickness, and hardness, with equivalent compressional forces, the dissolution rates were different by as much as threefold. The $t_{1/2}$ values for Formulations A and B were 12 and 33 min, respectively. In both cases, the tablets did not disintegrate, and magnesium salicylate dissolved directly from the tablet matrix. It is postulated that the gelling properties of starch decreased the dissolution rate, whereas gelatin made the drug particles more hydrophilic; thus, the dissolution rate was increased (5).

The optimum calcium stearate level for Formulation A was determined by monitoring the oscilloscope tracings of compressional and ejectional forces during tableting (6). At 1% calcium stearate, tableting proceeded smoothly at the rate of 1500–1700 tablets/min, which was the maximum speed for the tablet machine. However, as the concentration of calcium stearate was increased to 1.5 and 2%, the resulting tablets became softer and showed a higher incidence of capping. Since calcium stearate is a hydrophobic lubricant, the $t_{1/2}$ value was affected adversely with the higher concentrations of lubricant. The dissolution $t_{1/2}$ values from Formulation A tablets containing 1, 1.5, and 2% calcium stearate were 12, 18, and 21 min, respectively.

## REFERENCES


(1) A. E. Swinyard, in "Remington's Pharmaceutical Sciences," 15th ed., Mack Publishing Co., Easton, Pa., 1975, p. 1050.

(2) A. S. Alam and E. L. Parrott, *J. Pharm. Sci.*, **61**, 265 (1972).

(3) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, p. 651.

(4) W. J. Dixon, "Biomedical Computer Programs," University of California Press, Berkeley, Calif., 1975.

(5) S. Solvang and P. Finholt, *J. Pharm. Sci.*, **59**, 49 (1970).

(6) E. L. Knoechel, C. C. Sperry, and C. J. Lintner, *ibid.*, **56**, 116 (1967).


## ACKNOWLEDGMENTS


The authors thank Mr. H. Lindemeyer and Mr. J. Graham for analytical services, Mr. J. Ritts for computer analysis, and Dr. T. G. Brown, Jr., and Dr. W. E. Goode for interest and support.