Temperature-Dependent Effect of Edetate Disodium on Neomycin Stability

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Abstract □ When heated at temperatures in excess of 100°, the stability of neomycin in aqueous ophthalmic formulations was improved by the addition of edetate disodium (0.01%). As the exposure temperature was reduced, the degree of stability enhancement diminished until the effect was reversed, and addition of edetate disodium was detrimental to neomycin stability in solutions stored at 30°.

Keyphrases □ Neomycin—stability in ophthalmic solutions containing edetate disodium □ Edetate disodium—temperature-dependent effect on neomycin stability □ Stability—neomycin in solutions containing edetate disodium

Edetate disodium (I) has been used to restrict metal-catalyzed oxidation of various drugs including several antibiotics (1–3). Neomycin (II), in common with other aminoglycoside antibiotics, is susceptible to atmospheric oxidation (4), and I has been recommended for inclusion in various neomycin preparations described in national formularies (5, 6). The factual basis for this recommendation is obscure, because few reports directly described the effects of I on the stability of II, although I has been included in formulations of fradiomycin (7), the principal components of which are neomycins B and C (8). The foregoing, together with observations during work on neomycin stability (9) that suggested I was of doubtful value in stabilizing neomycin at room temperatures, prompted the present study.

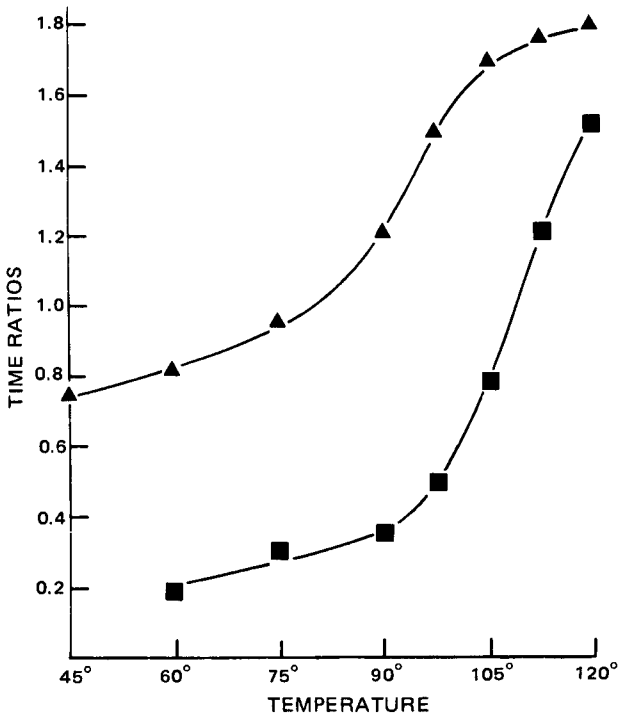

Figure 1—*Effect of heating temperature on the ratio of times required to achieve 15% (▲) or 50% (■) neomycin degradation in the presence and absence of edetate disodium.*

EXPERIMENTAL

All reagents, apparatus, and procedures were described previously (9). The prepared 0.2 and 0.5% neomycin sulfate ophthalmic solutions contained 0.7% $Na_2HPO_4 \cdot 12H_2O$, 0.7% $NaH_2PO_4 \cdot 2H_2O$, and 0.002% phenylmercuric nitrate; 0.01% edetate disodium was included as required.

Initially, 3.5 ml of 0.2% neomycin solutions with and without I were sealed in neutral glass ampuls of nominal 5-ml capacity, leaving ~2 ml of airspace. The ampuls were heated by immersion in an oil bath at 120°, removed at suitable intervals, and rapidly cooled, and the contents were assayed. Plots of log percentage residual neomycin against time were constructed for solutions with and without I. Loss of neomycin did not consistently follow either zero- or first-order kinetics, and it was not possible to represent decomposition by a rate constant. For this reason, the effect of I inclusion was recorded as the ratio of times required to achieve either 15 or 50% neomycin loss in the presence and absence of I. This procedure was adopted also for 0.2% neomycin solutions heated between 45 and 112°.

The 0.5% neomycin solutions with and without edetate disodium were prepared to investigate the effect of changing the ratio of I to II and also to examine the stability of II at 100°, the temperature recommended for the BP process of heating with a bactericide (10). The solutions also were stored at 30°, and the stability of II was monitored.

Discoloration of solutions was recorded as absorbance at 450 nm.

RESULTS AND DISCUSSION

The relationship between heating temperatures and the benefit resulting from inclusion of edetate disodium in the formulation is shown in Fig. 1. The beneficial effect, in terms of the time required for 50% neomycin loss, declined as the exposure temperature was reduced from 120 to 110°. Thereafter, the benefit was eliminated, and lowering the temperature further resulted in a progressively severe detrimental effect. A similar relationship was observed when a 15% fall in neomycin concentration was considered, but the advantage of edetate disodium inclusion was retained down to 80°. Thus, at temperatures between 80 and 110°, I afforded protection to II during the initial heating, but the reverse situation arose on prolonged exposure. In the 0.2% neomycin solutions, insufficient degradation occurred for values to be plotted at temperatures lower than 45 and 60° for 15 and 50% loss, respectively.

In the 0.5% neomycin solutions heated at 100°, the degradation rates down to ~70% of the initial concentration were almost identical in the

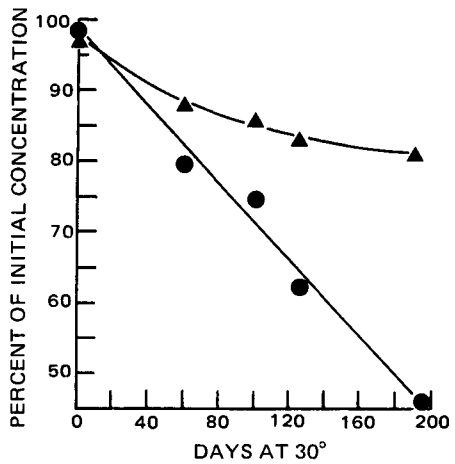

Figure 2—*Stability of 0.5% neomycin solutions with (●) and without (▲) edetate disodium during storage at 30°.*

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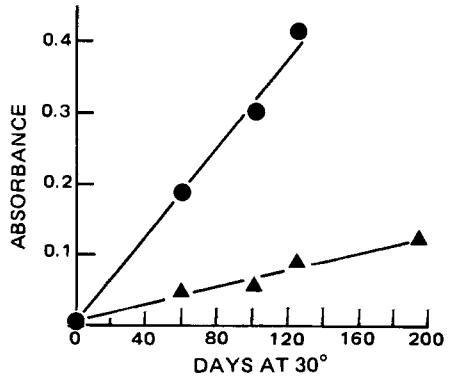

Figure 3—*Discoloration of 0.5% neomycin solutions with (●) and without (▲) edetate disodium during storage at 30°.*

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.

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Physicochemical Properties of Magnesium Salicylate

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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,

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