Table II—Capsules

Lubricant, mg./capsule	Mean Capsule Weight, mg.[a]	Disintegration Time, min.[b]	Dissolution, % in 10 min.[b]	*CV*, %
1.0 Magnesium lauryl sulfate	472.0	4	97	2.4
0.5 Magnesium lauryl sulfate	489.7	4	—	3.6
0.25 Magnesium lauryl sulfate	473.7	4	—	5.1
1.0 Magnesium stearate	468	>270	15	2.2
0.5 Magnesium stearate	491.7	120	—	3.6
0.25 Magnesium stearate	469.3	50	—	3.0
None	471.0	7	—	3.9
2.5 Sodium lauryl sulfate	477.9	4	—	5.5

[a] Twenty capsules were taken at regular intervals at each of two stations, and 20 capsules were taken at random from a completed batch. Variance estimates from the sets of 20 capsules tended to be quite homogeneous and were, accordingly, pooled for each lubricant–amount combination. [b] NF XIII Method II with six capsules in 600 ml. of 0.3% HCl was used for disintegration and dissolution.

compressed on a tablet machine[1] equipped with capsule shape punches.

Table I shows that: (*a*) magnesium lauryl sulfate and magnesium stearate were equivalent because there were no significant tablet weight variability differences between any pair of the five combinations; (*b*) variability for either concentration of sodium lauryl sulfate was significantly higher than for all amounts of the magnesium salts, except in one case where 0.5% sodium lauryl sulfate was more variable than 0.125% magnesium stearate, but the difference was not significant at the 0.05 level; (*c*) weight variation varied inversely with lubricant content; and (*d*) several other agents were not effective lubricants at the 0.5% concentration.

A similar granulation was run on the rotary tablet machine[2] equipped with 0.79 × 0.79-cm. (0.31 × 0.31-in.) punches. Statistical analyses showed: (*a*) magnesium lauryl sulfate (0.25%) was equivalent in variability to magnesium stearate (0.5%); (*b*) magnesium lauryl sulfate (0.25%) was significantly less variable than sodium lauryl sulfate (0.5%); and (*c*) magnesium stearate (0.5%) was significantly less variable than sodium lauryl sulfate (0.5%).

Lubricant performance in the rotary tablet machine was also evaluated in a direct compression mix containing lactose[3] and starch. The results were: (*a*) magnesium stearate (0.5%) was significantly less variable than magnesium lauryl sulfate (2.0%); (*b*) magnesium lauryl sulfate (2.0%) was significantly less variable than sodium lauryl sulfate (2%); and (*c*) magnesium stearate (0.5%) was significantly less variable than sodium lauryl sulfate (2%).

Relative lubricating properties of magnesium lauryl sulfate and magnesium stearate were also determined by comparing capsule weight variations of mixes filled on an automatic capsule-filling machine[4]. Each capsule contained lithium carbonate (300 mg.), spray-dried lactose (90 mg.), and lubricant.

Table II shows that: (*a*) magnesium lauryl sulfate and magnesium stearate were equivalent at 1.0 and 0.5 mg./capsule concentrations; (*b*) magnesium stearate gave less weight variability than magnesium lauryl sulfate at 0.25 mg./capsule concentration; and (*c*) weight variation varied inversely with lubricant content. Note in Table II that the capsules with 1 mg. magnesium lauryl sulfate disintegrated rapidly and the contents dissolved rapidly ($T_{50\%}$ dissolved = 2.7 min.) but the capsules with 1 mg. magnesium stearate did not ($T_{50\%}$ dissolved = 48 min.).

In three of four formulations, magnesium lauryl sulfate was equivalent to magnesium stearate as a lubricant. It was better than sodium lauryl sulfate. Thus, these data indicate that magnesium lauryl sulfate possesses the lubricating properties of magnesium stearate but without its waterproofing liability.

While the safety of magnesium lauryl sulfate for use in pharmaceuticals remains to be established, we anticipate that it is as safe as sodium lauryl sulfate. Full details will be published later.

[1] Stokes model F.
[2] Stokes B-2.
[3] Fast-Flo.
[4] Zanasi model LZ 164.

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Solid-State Ophthalmic Dosage Systems in Effecting Prolonged Release of Pilocarpine in the Cul-De-Sac

Keyphrases □ Ophthalmic prolonged-acting dosage forms—pilocarpine alginate flakes, cul-de-sac deposition, compared to pilocarpine hydrochloride solutions □ Miosis—prolonged-acting pilocarpine alginate flakes □ Timed-release dosage forms, ophthalmic—pilocarpine alginate flakes, compared to pilocarpine hydrochloride solutions

Sir:

In the area of oral prolonged-acting pharmaceuticals, polyuronic acids have been described (1–3) as suitable carriers for the preparation of slightly soluble salt complexes. In this respect, we previously cited (4) the advantages to solid dose cul-de-sac deposition over that of conventional liquid installation for prolonging the duration of a desired pupillary response.

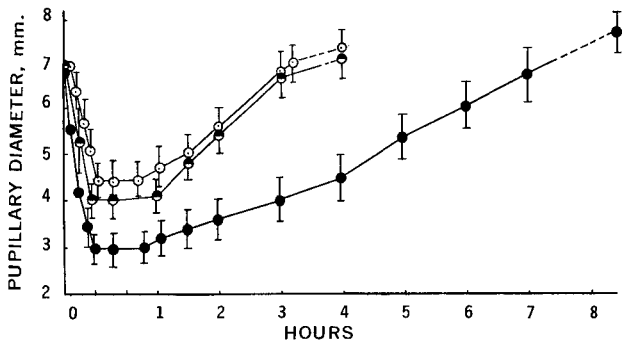

Figure 1—*Miotic responses from liquid and solid dose cul-de-sac treatments. Key: ⊙ pilocarpine alginate solution, 3.34%; ◓, pilocarpine hydrochloride, 2% (methylcellulose); ●, pilocarpine alginate flake, 4.9 mg. Broken lines signify rebound activity. Bars represent standard deviation,* N = *10–14.*

Our present findings show that the 1,4-β,D-mannuronic acid, commonly known as alginic acid, salt of pilocarpine when administered as an ophthalmic disk by this route provides a significantly greater miotic response than is obtained from pilocarpine solutions.

Ophthalmic flakes were prepared by dissolving pilocarpine alginate[1] powder (7% w/v) in sterile water for injection, with the aid of mechanical mixing. The solution was delivered into flat-bottom petri vessels and subjected to evaporation under reduced pressure at 30° in a thermostated water bath assembly. When the colloidal solution exhibited a semisolid consistency, the mass was sectioned into circular flakes (0.3-mm. thickness, 3–7-mm. diameter, 3.1–7.8 mg.) by means of various size trephines and dried to the point of solidification. Following additional drying for 24 hr. at room temperature, the ensuing transparent disks were removed and stored in light-resistant containers. Elemental analysis, on an anhydrous basis (loss on drying 2.94%), showed C = 49.65%, H = 6.39%, O = 38.14%, and N = 6.51%, corresponding to an alkaloid content of 48.54%. (Theoretical[2]: C = 50.76, H = 6.47, O = 35.81, and N = 6.96.)

Pilocarpine alginate, 3.34% (w/v), and pilocarpine hydrochloride, 2.00% (w/v), in the presence of methylcellulose 4000 cps., required to adjust the viscosity of the latter to that of the alginate (72 cps., Brookfield, LVT, 25°) solution, were prepared from sterile Sørensen phosphate buffer stock solutions mixed in varying proportions to give a final pH of 6.14 and adjusted for tonicity with sodium chloride.

Miotic studies were conducted using albino, 4–5-kg., male rabbits. The animals were allowed to equilibrate under constant conditions of illumination for 24 hr. prior to commencing treatment with either solid or liquid doses.

Each solution was delivered from a micrometer syringe (0.075 ml.) into the lower cul-de-sac of one eye, and its vehicle was used as the control in the other eye. With the solid dose studies, flakes were deposited into the lower sac with the aid of forceps after being soaked for 30 sec. in isotonic sodium chloride to allow the disk to assume a semiplastic consistency and reduce the degree of initial contact irritation. Alginic acid flakes, similarly prepared, were used as controls. The size of each pupil was measured immediately before the test drug was applied with an Optiker-Ryser pupillary gauge fixed at a distance of 15.2 cm. (6 in.) from the globe.

Pupillary responses (Fig. 1) indicate that, in the liquid state, pilocarpine alginate exhibits essentially comparable miotic activity as pilocarpine hydrochloride following single-dose treatment. No pupillary constriction was noted in both liquid and solid dose control eyes. The results derived from solid pilocarpine alginate deposition show the magnitude of maximum pupil size constriction to be enhanced, with duration of miosis significantly increased over that of both liquid dosage systems. Restoration of normal pupillary diameter for the solid-state dose is observed to occur between 7 and 8 hr. in contrast to about 3.5 hr. for the ophthalmic solutions.

These results indicate that availability of pilocarpine in the cul-de-sac from solid doses may be more uniform as a consequence of diminished diffusion through the gel matrix where the drug is held in reserve, in contrast to liquid dosage forms where the dose is immediately released in the conjunctival fluids. The present observations suggest that the use of solid ophthalmic dosages in the treatment of glaucoma may be more effective, requiring less frequent administration of drug to produce a prolonged physiological activity.

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[1] Tilden-Yates Laboratories, Inc.

[2] Estimated as a percent composition based on an empirical formula of $(C_6H_8O_6 \cdot H_2O)_n$ and $C_{11}H_{16}N_2O_2$ for alginic acid and pilocarpine, respectively.

Anthraquinone, a New Chemical Oxidation Product of Amitriptyline

Keyphrases □ Amitriptyline oxidation, permanganate—identification of dibenzosuberone and anthraquinone as products □ Dibenzosuberone and anthraquinone—identification as oxidation products of amitriptyline □ Anthraquinone and dibenzosuberone—identification as oxidation products of amitriptyline

Sir:

Wallace and Dahl (1) described a quantitative UV spectrophotometric procedure for the determination of amitriptyline (I) and nortriptyline as well as their prin-