# Semisolid Oleaginous Ointment Bases for Ophthalmic Use

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**Abstract** □ A high molecular weight nonemulsifiable polymer, a fused micronized silica, and sodium stearate were each evaluated for their gel-forming characteristics with hexadecyl alcohol and other liquid vehicles. Selected formulations of these were studied as possible oleaginous, semisolid bases for use as ophthalmic ointments over 0 to 50° and compared to two commonly used ointment bases for physical characteristics and drug release.

**Keyphrases** □ Ointment bases for ophthalmic use—formulation of semisolid oleaginous, water-free bases, physical properties and pilocarpine hydrochloride release □ Ophthalmic ointment bases—formulation of semisolid oleaginous, water-free bases, physical properties and pilocarpine hydrochloride release □ Oleaginous semisolids—evaluated for use as ophthalmic ointment bases, physical properties and pilocarpine hydrochloride release

Little research has been done on ophthalmic ointment bases. Until recently, if a water-free, oleaginous base was desired, petrolatum was the base most frequently employed. Because petrolatum is of natural origin, however, it may be expected to vary with its source and its method of refinement (1). Due to this variability, a base with a more uniform consistency would be desirable. Also, under cold weather conditions, petrolatum base ointments are difficult to extrude from an ointment tube and, when instilled into the eye by application to the lower eyelid, they exhibit poor release of the medicament (2). Water-removable or water-containing bases sometimes are not desirable carriers of medicaments unstable in the presence of water; at freezing temperatures, the water may crystallize, causing separation of the vehicle into two phases.

Recently the gelling of various nonpolar solvents from new pharmaceutical materials has brought about many applications for oleaginous-type bases (3). The versatility and applicability of recent pharmaceutical materials have provided many new opportunities for the formulation of oleaginous bases. The stability of these bases has been improved as has, in some cases, their activity due to the increased release of an incorporated medicament of the base.

In this study, a high molecular weight nonemulsifiable polymer[1], a food grade sodium stearate, and a fused micronized silica[2], when gelled with different nonpolar solvents, were investigated as to their possible effectiveness for use as oleaginous ophthalmic ointment bases. An evaluation of their physical properties included a comparison with two commonly used oleaginous bases, petrolatum and a hydrocarbon oil and wax gel combination[3].

The objectives of this investigation were to formulate by reproducible methods and to evaluate several properties by different parameters water-free, oleaginous, water-insoluble, gel-type pharmaceutical bases which are spreadable or extrudable over 0–50°. The ingredients of the bases were chosen to be compatible with the eye and surrounding areas, although no attempt was made to perform an *in vivo* eye irritation study.

[1] Epolene C-10, Eastman Kodak.
[2] Cab-O-Sil, Cabot Corp.
[3] Plastibase, Squibb.

**Table I**—Description of Bases Employed

| Base Description | Percent | Method of Preparation |
|---|---|---|
| 1. White petrolatum | | |
| 2. Hydrocarbon oil and wax gel combination[a] | | |
| 3. Micronized fumed silica[b] | 12.0 | A |
| Stearyl alcohol USP | 2.0 | |
| Hexadecyl alcohol[c] | 86.0 | |
| 4. Nonemulsifiable polymer, mol. wt. 8003[d] | 10.0 | B |
| Light mineral oil USP | 90.0 | |
| 5. Sodium stearate, food grade | 10.0 | C |
| Hexadecyl alcohol[c] | 90.0 | |

[a] Plastibase, Squibb. [b] Cab-O-Sil, Cabot Corp. [c] Enjay Corp. [d] Epolene C-10, Eastman Kodak.

## EXPERIMENTAL

**Preparation of Ointment Bases**—New materials introduced as gelling agents in different vehicles were investigated in preliminary studies to determine if the gelled products would be applicable for evaluation as ophthalmic ointment bases. The bases (Table I) were chosen as a result of their apparent stability over 1 month at 0–50°.

*Method A*—The liquid vehicle was placed in a beaker and heated to 90° on a water bath while stirred[4] at medium speed. The matrix polymer or solid was then added with continued stirring and heating until either a homogeneous dispersion or gelation resulted. The resulting semisolid was then allowed to cool to room temperature.

*Method B*—The vehicle was heated to 110–120° on a hot plate. The matrix and any modifiers were added to the vehicle with moderate stirring until thoroughly dispersed or dissolved. The mixture was then shock cooled by pouring it as a thin-layered film over precooled aluminum foil stretched on an acetone–ice bath at approximately −5° until gelation resulted.

*Method C*—The matrix and any modifiers were suspended or dissolved in a small amount of hot (85–90°) distilled water. This mixture was then added to the previously heated vehicle in an evaporating dish, and the vehicle–mixture combination was heated until *all* water was removed by evaporation. The resulting material, after being allowed to cool to room temperature, was levigated thoroughly with a spatula until a smooth semisolid formed.

**Softness Point**—Determination of the temperature at which the base became soft was accomplished by immersing three-quarters of a 10-ml beaker containing approximately 3.0 g of the base to be tested in a controlled-temperature water bath. A 1.1-g stainless steel ball bearing was then placed on the surface of the base. When the ball bearing became completely covered with the

[4] With a Lightnin' Mixer, Model F.

**Table II**—Water Numbers of Bases Stored in Type I Glass Containers at Different Time Intervals at Selected Temperatures

| Base | Weeks[a] | Storage Temperature 0° | 30° | 40° | 50° |
|---|---|---|---|---|---|
| 1 | 0[a] | 17.0[b] | 17.0 | 17.0 | 17.0 |
| | 2 | 19.0 | 15.0 | 12.6 | 16.2 |
| | 4 | 16.9 | 15.4 | 13.5 | 15.4 |
| | 12 | 16.7 | 15.6 | 21.0 | 16.4 |
| | 24 | 15.0 | 22.0 | 20.0 | 18.0 |
| 2 | 0 | 24.8 | 24.8 | 24.8 | 24.8 |
| | 2 | 20.6 | 20.7 | 20.7 | 19.2 |
| | 4 | 18.6 | 17.2 | 14.5 | 20.6 |
| | 12 | 18.7 | 18.6 | 15.0 | 16.8 |
| | 24 | 20.0 | 20.9 | 16.7 | 16.7 |
| 3 | 0 | 76.8 | 76.8 | 76.8 | 76.8 |
| | 2 | 33.6 | 78.0 | 68.0 | 77.8 |
| | 4 | 32.8 | 64.5 | 54.5 | 72.0 |
| | 12 | 35.0 | 41.7 | 37.3 | 20.0 |
| | 24 | 49.2 | 39.2 | 37.2 | 20.0 |
| 4 | 0 | 21.0 | 21.0 | 21.0 | 21.0 |
| | 2 | 18.5 | 16.4 | 19.2 | 20.8 |
| | 4 | 16.3 | 16.3 | 18.1 | 16.8 |
| | 12 | 16.7 | 16.1 | 23.8 | 16.9 |
| | 24 | 18.5 | 17.1 | 20.1 | 20.6 |
| 5 | 0 | 42.6 | 42.6 | 42.6 | 42.6 |
| | 2 | 46.6 | 40.8 | 47.8 | 43.8 |
| | 4 | 48.7 | 45.9 | 48.0 | 38.8 |
| | 12 | 48.9 | 50.0 | 49.0 | 32.3 |
| | 24 | 50.1 | 50.0 | 54.0 | 34.1 |

[a] Zero time is defined as the 24-hr period necessary to prepare and to test the ointment base initially. [b] All values have an allowable variance of ±3.

ointment from increasing the temperature of the water bath, the temperature was then recorded as the base's softness point.

**Water Absorption**—In this study, a "water number" was used as a parameter for the percentage of water absorbed by a given base. The percentage of water absorption was determined similarly to a method described by Halpern and Zopf (4). The base was first weighed to the nearest 0.01 g and placed in an evaporating dish; then the ointment-containing dish was heated on a hot plate to a temperature at which the particular base became very soft. Distilled water was added in increments of 0.5 ml and thoroughly mixed in the base. The base was then removed from the heat source and allowed to cool to room temperature. This process was continued until the water extruded from the base after cooling. The quantity of water absorbed per amount of base was used to calculate the water number according to Eq. 1:

$$\text{water number} = \frac{\text{milliliters of water absorbed}}{\text{grams of base used}} \quad \text{(Eq. 1)}$$

**Viscosity Determination**—Viscosity studies of the bases over a 6-month period were conducted using a rotational viscometer[5]. Yield values before and after storage over 6 months were determined by a viscometer[6], and the shearing stress was applied by a weight hanger with various slotted weights. The bases were stored in Pyrex beakers tightly sealed[7] at 0, 30, 40, and 50°. To observe any changes in flow rates of each base over the specified time, rheograms of shearing stress *versus* rate of shear at the different temperatures were plotted.

**Release Rate Observations**—To compare the release rates of the different bases after storage, a frequently employed ophthalmic drug (pilocarpine hydrochloride) was incorporated into the ointment. This incorporation was accomplished by levigating the finely powdered pilocarpine hydrochloride USP[8], 4%, into approximately 30.0 g of base. Each ointment base with the incorporated drug was then suspended in a dissolution apparatus, and the quantity of the drug released from the base into the normal saline dissolution medium was assayed on a grating spectrophotometer[9] by analyzing 5-ml aliquots of the normal saline dissolution medium at the specified intervals. A standard curve was constructed using five different concentrations of pilocarpine hydrochloride in normal saline. Absorbances of these solutions were determined at 216 nm. A plot of concentration *versus* absorbance was then made to establish a linear relationship in conformity with Beer's law.

The dissolution apparatus consisted of placing the drug-incorporated ointment in one side of a disposable laboratory petri dish, 100 × 15 mm, and inverting and suspending it in 800 ml of normal saline solution (0.9%), using a stainless steel sieve[10] affixed to the open end to prevent the ointment from falling out of the container. A water bath held at 30°, surrounding the container of normal saline, kept the saline dissolution medium at constant temperature.

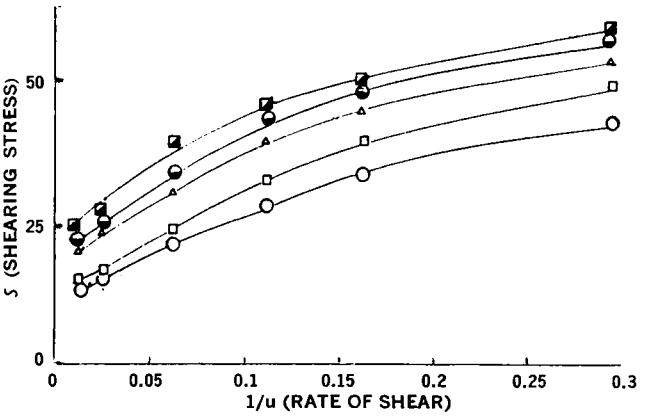


**Figure 1**—*Characteristic rheogram for Base 4 at different storage times at 40°. Curves represent relative flow patterns from initially prepared sample and are not indicative of exact viscosity values. Key:* ○, $S_0$ *(initial reading);* □, $S_1$ *(2 weeks of storage);* △, $S_2$ *(4 weeks of storage);* ◒, $S_3$ *(12 weeks of storage); and* ◪, $S_4$ *(24 weeks of storage).*

## RESULTS AND DISCUSSION

This investigation was conducted to develop an oleaginous water-free ointment base intended for ophthalmic use that would maintain its consistency over 0–50°. Three experimental bases (Bases 3, 4, and 5, Table I) were chosen from a large number of exploratory bases because of their apparent physical stability over 0–50°. Quantities of these experimental bases were manufactured and compared to two standard bases (Bases 1 and 2) in relation to possible changes in viscosity over 6 months, drug release studies over 1 month, and water absorption and softness temperature alterations over 6 months. All bases were stored at 0, 30, 40, and 50° in Type I glass vials and Pyrex-type containers to observe any alterations in these physical characteristics.

Water numbers were calculated to give an indication of the aqueous absorptivity of the various bases and of release of the drug from the base. Their initial values decreased in the following order: Base 3 < Base 5 < Base 2 < Base 4 < Base 1. Base 3 decreased its water-absorbing capacity significantly after initial storage at 40 and 50°. All of the remaining bases increased or maintained their water absorptivity after storage at all temperatures (Table II). The increase in water absorption of Bases 1, 2, and 4 appeared independent of the temperature at which the base was stored. It is possible that the base may have slightly altered its physical molecular arrangement upon standing at various temperatures or some impurity in the base might have caused a slight emulsification. The tendency of emulsification then could have increased water absorption by the base yielding higher values after an extended time.

The initial softness temperatures or points of the various bases stored in Type I glass vial containers decreased in the following order: Base 5 < Base 2 < Base 4 < Base 1 < Base 3. After 6

[5] Haake Rotovisco (67-369) with a six-bladed star-shaped paddle (FL-10).
[6] Stormer.
[7] With Parafilm (American Can Co.) and aluminum foil.
[8] S. B. Penick.
[9] Beckman model DG-GT.
[10] Fisher No. 4-6.

**Table III**—Release of Pilocarpine Hydrochloride from Freshly Prepared Bases at Selected Time Intervals

| Base | Concentration (moles/liter) × $10^{-5}$ (Cumulative Percent Extracted) | | | | | |
|---|---|---|---|---|---|---|
| | Hours | | | | | |
| | 0.25 | 0.50 | 1.00 | 3.00 | 6.00 | 12.00 |
| 1 | 1.00 (0.140) | 1.00 (0.140) | 1.30 (0.183) | 1.50 (0.212) | 1.50 (0.212) | 1.80 (0.254) |
| 2 | 3.10 (0.459) | 3.20 (0.474) | 4.00 (0.592) | 4.10 (0.607) | 4.40 (0.651) | 5.00 (0.740) |
| 3 | 39.00 (5.790) | 80.00 (11.880) | 160.00 (23.760) | 300.00 (44.550) | 350.00 (51.970) | 500.00 (74.242) |
| 4 | 12.50 (1.672) | 13.00 (1.740) | 13.50 (1.809) | 13.50 (1.809) | 14.00 (1.874) | 15.00 (2.008) |
| 5 | 34.00 (5.049) | 40.00 (5.939) | 45.00 (6.685) | 60.00 (8.909) | 80.00 (11.879) | 120.00 (17.818) |

**Table IV**—Release of Pilocarpine Hydrochloride from Different Bases at Selected Time Intervals after 1 Month of Storage at 30°

| Base | Concentration (moles/liter) × $10^{-5}$ (Cumulative Percent Extracted) | | | | | |
|---|---|---|---|---|---|---|
| | Hours | | | | | |
| | 0.25 | 0.50 | 1.00 | 3.00 | 6.00 | 12.00 |
| 1 | 1.50 (0.210) | 1.70 (0.238) | 1.80 (0.252) | 2.00 (0.280) | 2.20 (0.308) | 2.40 (0.336) |
| 2 | 3.50 (0.490) | 4.00 (0.560) | 4.00 (0.560) | 4.50 (0.630) | 4.70 (0.658) | 5.00 (0.770) |
| 3 | 20.00 (3.182) | 28.00 (4.455) | 35.00 (5.568) | 50.00 (7.955) | 120.00 (19.091) | 380.00 (60.455) |
| 4 | 7.00 (1.039) | 9.00 (1.364) | 10.00 (1.485) | 10.00 (1.485) | 12.00 (1.782) | 14.00 (2.079) |
| 5 | 60.00 (9.671) | 80.00 (12.895) | 100.00 (16.118) | 120.00 (19.342) | 130.00 (20.954) | 180.00 (29.013) |

months of storage at various temperatures, Base 3 increased its initial softness temperature and Bases 1, 2, and 4 decreased their softness point. An increase or decrease of the softness temperature of a base was independent of the storage temperature. The time of storage, however, was significant. An increase or decrease from the original softness value of the base always occurred after a minimum of 1 month of storage in any container. This may have been due to a "settling" phenomenon of the base giving more rigidity or compactness after no disturbance of the base occurred (as in its production, packaging, *etc.*). From the data available, however, it was not possible to explain the increase in softness values of Base 3 after storage.

Viscosity rheograms were constructed for the various bases stored at 0, 30, 40, and 50° for 6 months from rotational viscometer measurements to show possible alterations in flow behavior upon storage of the ointment. All bases showed a plastic flow behavior with various yield values measured with a viscometer. The gelled matrix-type bases, 2 and 4, showed insignificant changes in flow characteristics, altering little from their initial stress *(S)* values after storage at the selected temperature (Fig. 1). The remaining bases increased their stress values significantly after storage at all temperatures, with 0° readings showing the greatest increases from the initial readings.

The flow behavior was not considered significant in any case; no base was unspreadable or unmanagable to work with after storage. Base 5, after storage for more than 1 week, lacked spreadability and became too wax-like and hard to construct a rheogram.

Incorporated pilocarpine hydrochloride released from the bases into a normal saline solution had the following order of release: Base 3 > Base 5 > Base 4 > Base 2 > Base 1 (Tables III and IV). A dissolution model was developed to describe *in vitro* the release that may occur if the ointment is instilled into the eye *via* application to the lower eyelid. Bases 3 and 5 showed the best release of the bases although Base 3 started to disintegrate in the dissolution medium after 6 hr of exposure. Bases 4 and 2 released between 1 and 2% of their medicament after the conclusion (12 hr) of dissolution. Base 1 showed an increased release of the drug after 1 month of storage at 30 and 50°, but a decrease occurred at 0° after the same storage period.

Of the bases investigated using the experimental parameters, Base 4 had the most overall desirable properties. However, this investigation was limited to a study of certain *in vitro* parameters that may be used to develop and select a desirable ophthalmic ointment base. *In vivo* irritation studies of the bases on eye surfaces would be the next useful step in determining which of the bases studied may be applicable for further testing.

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## ACKNOWLEDGMENTS AND ADDRESSES

Received August 13, 1973, from the *College of Pharmacy, University of Florida, Gainesville, FL 32601*

Accepted for publication October 11, 1973.

Abstracted in part from a dissertation submitted by R. W. Jurgens, Jr., to the University of Florida in partial fulfillment of the Doctor of Philosophy degree requirements.

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