Physical and Chemical Characteristics of Water-Soluble, Semisolid, Anhydrous Bases for Possible Ophthalmic Use

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Abstract □ Following a preliminary review of pertinent literature citations, a total of 84 semisolid, water-soluble, anhydrous bases for possible ophthalmic use was formulated. Of these 84 exploratory bases, five were designated evaluatory bases for further study on the basis of apparent pH and/or desirable physical spreadability characteristics over the temperature range of 0–50°. Four of the five bases were further characterized by rotational viscometer studies, and an organogel was selected on the basis of several of its listed attributes as the best attempt in this investigation to formulate the type of semisolid base desired for possible ophthalmic use.

Keyphrases □ Semisolid bases—formulated, evaluated for use as potential ophthalmic ointments, pH and viscosity considerations □ Ophthalmic ointments, potential—formulation, evaluation of semisolid, water-soluble, anhydrous bases, pH and viscosity considerations □ Organogels—formulated for use as possible ophthalmic ointments

In USP XVIII (1), four classes of ointment or semisolid bases are recognized on the basis of physical characteristics: hydrocarbon or grease-type bases, absorption bases, water-removable bases, and water-soluble bases. Although polyethylene glycol ointment USP is the only official nonaqueous, water-soluble base, the more recent organogel-type bases comprise a little investigated supplement to these classes.

In the past, a hydrocarbon-type base was the most frequent choice when an anhydrous base was required; however, the nonaqueous organogels may offer advantages over the hydrocarbons and other traditional bases because of some of the following undesirable attributes of the latter bases:

1. Spreadability or extrudability over only a narrow incidence of temperatures.
2. Irritation to eyes and mucous membranes.
3. Inability to release effectively active medicinal ingredients.
4. Incompatibility with body tissue at site of application.
5. Instability of active ingredient(s) in base, *e.g.*, physical separation and/or chemical decomposition upon storage, especially because of improper pH, oxidation-reduction reaction, hydrolysis, *etc.*
6. Lack of cosmetic or esthetic appeal, *e.g.*, greasiness or stickiness, which could result in improper application of the base by the patient.
7. Lack of a completely dependable sterilization method.
8. Difficulty in removal of contaminating particulate matter from the base because of inherent physical, chemical, and/or viscosity characteristics.

The purpose of this investigation was to formulate, by reproducible methods, semisolid, anhydrous, water-soluble bases spreadable and/or extrudable over the general temperature range of 0–50° and with an apparent acidic pH. Furthermore, the bases should be: (*a*) compatible with a variety of drugs for ophthalmic use, *e.g.*, antibiotics, alkaloids, dimercaprol, and corticosteroids; (*b*) clinically nonirritating to the eyes; and (*c*) able to release medicinal agents in a desirable therapeutic manner.

DISCUSSION

A gel (2) is a solid or semisolid system of two or more ingredients, including a matrix that encloses and is interpenetrated by a liquid vehicle. Gels that are formed by aggregates or floccules of small particles represent two-phase systems; upon standing, they may exist as semisolids but, upon stirring or agitation, they liquefy and thus are termed thixotropic or shear thinning. Gels may also consist of entangled and/or matted strands of long-chain polymeric macromolecules, which may be joined by van der Waals forces and may align in a parallel-type sequence to maintain a gel matrix within a vehicle. These gels of macromolecules are usually one-phase systems and may be termed organogels.

The main disadvantage of certain anhydrous organogel-type systems is a tendency toward syneresis, which was defined (3) as: "The spontaneous separation of an initially homogeneous colloid system into two phases, a coherent gel and a liquid. The liquid is actually a dilute solution whose composition depends on the original gel. When the liquid appears, the gel contracts, but there is no net change in volume."

USP XVIII (4) requires only that ophthalmic bases be free from contamination with viable microorganisms and palpable particulate matter, that they be nonirritating, that they permit effective release of medicinal agents, and that they maintain the activity of the agents for a reasonable time during storage.

Unfortunately, the ophthalmic applications and characteristics of water-soluble, anhydrous, organogel-type bases have not received much study. However, cosmetic applications are numerous and at least one topical base (5) containing the antifungal agent tolnaftate[1] exists. Moreover, some industrial pharmacists recently recommended use of the polyethylene glycol polymers in water-soluble ophthalmic bases and emphasized the importance of their cosmetic appeal with concomitant medicinal efficacy (6).

A variety of factors influence the ophthalmic use of drugs and/or semisolid bases. The primary site of drug action in the eye is the cornea. Although recent studies (7, 8) indicated precorneal tear film to be lipid in nature, most drugs probably penetrate to the cornea from semisolid bases with little influence from this thin precorneal tear film.

One study (9) involving rabbits indicated that particles greater than 50 μ in size are capable of causing significant mechanical eye irritation. Furthermore, application of excess amounts of hydrocarbon bases to postsurgical eyes resulted in the entry of visible globules of base into the anterior chamber, and in one case a globule of petrolatum persisted innocuously for 3 years (10, 11).

The pH values of normal human tears and of ophthalmic pharmaceuticals have received some attention; the pH of normal tears is about 7.4. Tears are reported to have a great buffer capacity and are able to alter almost immediately a drop of unbuffered solution between pH 3.5 and 10.5 to neutrality or slight alkalinity; for this reason, buffering of some ophthalmic products is not recommended by some authorities (12, 13). The importance of pH adjustment rather than buffering in some ophthalmic bases includes prevention of excess lacrimation (and subsequent drug loss from the eye) and maintenance of drug stability. As a general rule, most ophthalmic

[1] Tinactin Cream, Schering Corp., Bloomfield, N. J.

drugs are 100 times more stable at pH 5.0 than at pH 7.0, contingent upon dissociation characteristics of the compound and upon relative stability of the free base and cation (14).

Isotonicity is another factor of importance to ophthalmic products. Rosenberg (13) reported that tears directly in contact with the cornea are slightly hypertonic. A second source (15) indicated 0.93% rather than the classical 0.90% as the true NaCl equivalent of normal tears and suggested that irritation to the eyes occurred only when the NaCl equivalent extremes of less than 0.6% and more than 2.0% existed.

Nearly all eye irritation tests involve the use of animals, usually albino rabbits, and clinical observation of their eyes periodically following instillation of the test compound. The standard for these tests is the Draize eye irritation test (16). The Draize test, when compared with several other similar tests in a recent comprehensive study (17), indicated as high as 100% error for a given test compound between it and the test normally used by the participating laboratory. Thus, results such as these support the need to delineate between irritation such as definite physical damage (*e.g.*, lesions, tissue swelling, and excess erythema) to the eyes of animals and the transitory discomfort irritation experienced subjectively by humans.

Viscosity (18), *i.e.*, resistance to flow of a fluid under stress, has been directly related to both the diffusion rate of a drug from a semisolid base and the therapeutic efficacy of the drug in the base (19–21). However, one study (22) of some organogel-type bases made from carboxy vinyl polymers[2] and involving ocular absorption of several drugs from the bases showed no correlation between viscosity of the base and drug release. A second study (23) indicated no change in viscosity of some carboxy vinyl polymer gels after 4 weeks of exposure to sunlight or repeated autoclaving at 121° and 15 p.s.i. for 15 min.

NF XIII (24) suggested that medications including antibiotics may be more effective in water-soluble rather than in hydrocarbon-type bases. This contention was corroborated for some polyethylene glycol-type bases by some investigators (25, 26). One study (27) involving incorporation of sulfa drugs, coal tar, and ichthammol into semisolid carboxy vinyl polymer bases indicated good stability of the drugs in the bases. However, the disadvantage of complexation of certain drugs with polyethylene glycols was established in other studies (28, 29). Some researchers (23, 30) indicated contaminants within the polyethylene glycols and carboxy vinyl polymers as a source of drug and/or semisolid base degradation.

A final important factor in the ophthalmic use of semisolid bases is sterility. The cornea and anterior chamber of the eye offer an optimum environment for growth of many types of pathogenic microorganisms, since these tissues lack the immunological defenses ambient in the bloodstream (31). Therefore, there is a stringent requirement for sterility in the manufacture and product life of semisolid bases for ophthalmic use. Several different studies (22, 32–34) of the sterility of commercially prepared ophthalmic ointments each indicated that some portion of the sample population was contaminated with viable microorganisms.

EXPERIMENTAL[3]

Materials—Materials used in this investigation were selected on the basis of previous similar research[4] (35) and with consideration of water-solubility, official and unofficial reports of low incidence of eye irritation and/or acute toxicity, ability to form semisolid bases or organogels in selected combinations, and commercial availability. All materials were of USP grade unless otherwise specified.

Table I—Percent (Weight) of Materials and Methods of Preparation of Evaluatory Bases

Base	Matrix Solids	Percent	Vehicles	Percent	Method of Preparation
E-1	Micronized, fumed silica, M-5[a]	7.3	Glycerin	91.2	A
	Nonionic surfactant polyol, F68[b]	1.5			
E-2	Poly(methyl vinyl ether–maleic anhydride)-139[c]	2.6	Polyethylene glycol 200[d]	97.4	B
E-3	Carboxy vinyl polymer 940[e]	1.36	Polyethylene glycol 200	29.24	D
			Polyethylene glycol 400[f]	68.83	
			Polyoxyethylene (15) cocoamine[g]	0.57	
E-4[h]	Polyethylene glycol 4000[i]	16.0	Polyethylene glycol 400	24.0	C
			1,2,6-hexanetriol	60.0	
E-5	Carboxy vinyl polymer 940	1.50	Polyethylene glycol 200	38.40	D
			Polyethylene glycol 400	58.12	
			Polyoxyethylene (15) cocoamine	0.53	
			Hexadecyl[j] alcohol	1.44	

[a] Cab-O-Sil, M-5, Cabot Corp., New York, NY 10017 [b] Pluronic F68, Wyandotte Chemical Corp., Wyandotte, MI 48192 [c] Grantrex AN-139, GAF Corp., New York, NY 10020 [d] Carbowax 200, Union Carbide Corp., New York, NY 10017 [e] Carbopol 940, B.F. Goodrich Chemical Co., Cleveland, OH 44115 [f] Carbowax 400, Union Carbide Corp., New York, NY 10017 [g] Ethomeen C/25, Armour Industrial Chemical Co., Chicago, IL 60690 [h] Base E-4 was not formulated in sufficient quantity for viscometer studies because of lack of 1,2,6-hexanetriol, previously generously supplied as a sample. [i] Carbowax 4000, Union Carbide Corp., New York, NY 10017 [j] Cosmetic grade, Enjay Chemical Co.

Formulation and Evaluation of Bases—Initial investigation in this study involved formulation of approximately 100 g. of each of 84 exploratory bases produced by one of the following methods:

Method A—The liquid vehicle was heated to 90° on a water bath with stirring at medium speed. Then the matrix polymer (solid) was added with continued heating and stirring until either a homogeneous dispersion or gelation resulted.

Method B—The matrix polymer was added to the liquid vehicle with stirring at medium speed at 22–25° for 48 hr. Then the dispersion was heated carefully to 125° with stirring and maintained at 125° for 1 hr., after which a homogeneous gel resulted.

Method C—The liquid vehicle and polymer solids were combined with stirring at medium speed at 65° until homogeneously mixed. Heat was then removed and the mixture was allowed to congeal or thicken with continuous stirring until its temperature reached 30°.

Method D—The matrix polymer was added to the liquid vehicle(s) with stirring at medium speed at 22–25°; stirring was continued for 1–2 hr. until a homogeneous dispersion resulted. This dispersion was then heated to 85–95° with stirring at medium speed and neutralized with an appropriate amine to yield a collapsed or viscous organogel.

Each of the 84 exploratory bases was developed incrementally by the addition of small portions of matrix solids to the balance of the liquid vehicle(s). After each addition, the physical characteristics of each base were observed at 0, 30, and 50°, and increments of matrix ingredients were added until a desirable base resulted or the amount

[2] Various Carbopols, B. F. Goodrich Chemical Co., Cleveland, Ohio.

[3] All liquids not measured in standard graduated cylinders were weighed on either an Ohaus "Dial-O-Gram" 1600 series balance (which reads to 0.1 g.) or a Mettler B-5 analytical balance. Bases were mixed in glass beakers of appropriate size using a model F "Lightnin' Mixer" equipped with a three-bladed marine-type impeller. Heat was provided by a Corning model PC-35 hot plate. Determinations of pH were conducted on a Corning model 10 pH meter with standard Corning electrodes; a Corning model PC-353 magnetic stirrer was used to mix all samples constantly for pH determinations. Samples of bases were placed into 90-ml. (3-oz.), general purpose (NP), amber glass ointment jars fitted with metal screw caps with waxed cardboard liners; they were stored in Thelco model 6M ovens adjusted to 30 and 50° and in a Herrick refrigerator adjusted to 0°. Viscosity studies were conducted on a Haake Rotovisko (model 67-369) rotational viscometer equipped with six-bladed star-shaped paddle (FL-10).

[4] At the University of Florida, College of Pharmacy.

Table II—Physical Characteristics of Evaluatory Bases at Selected Temperatures[a]

Base	0°	30°	50°
E-1	tr, sp, ss	c, f, tk, sp, l	tr, f, tk, sp, l
E-2	tr, sp, ss	tr, sp, s	tr, sp, ss
E-3	tr, sp, ss	c, sp, ss	c, sp, ss
E-4	o, sp, ss	o, sp, ss	o, sp, ss
E-5	c, sp, ss	c, sp, ss	o, sp, ss

[a] Abbreviations are as follows: c, clear or transparent; f, flowing; tr, translucent; o, opaque; tk, thick; sp, spreadable; l, liquid (a base that flows to some extent at temperature specified); and ss, semisolid (a base that is spreadable and/or extrudable at temperature specified).

Table III—Apparent pH values for Diluted Evaluatory Bases

Base	pH of 10 g. Base Diluted to 50 ml. with Distilled Water[a]
E-1	5.4
E-2	3.3
E-3	4.4
E-5	4.2

[a] The pH of the distilled water used to dilute all samples was 7.0.

of solids approached 15% by weight (because of limited amounts of some ingredients) and a semisolid base did not result.

On the basis of physical characteristics at 0, 30, and 50° and of apparent pH, five of the 84 exploratory bases were designated evaluatory Bases E-1 through E-5. The formulas and physical characteristics of Bases E-1 through E-5 are listed in Tables I and II, respectively.

Determinations of apparent pH of the bases studied were conducted as follows. Exactly 10 g. of the base was diluted to 50 ml. with distilled water and thoroughly dispersed. The pH value of the dispersion was then observed. The pH values of E-1, E-2, E-3, and E-5 are listed in Table III. In an attempt to determine arbitrarily if these four bases were buffer-type systems, 10 g. of each was thoroughly dispersed in distilled water to make 100 ml. and this dispersion was titrated with 0.1 *N* NaOH solution until pH 7.0 was reached. The results of these titrations are listed in Table IV.

Viscosity studies[5] were conducted at 30° on 100-g. samples of E-1, E-2, E-3, and E-5 by immersing the star-shaped paddle to a standard depth in the sample, allowing it to remain in place for 1 min., and then engaging the clutch at a selected *U* value. Upon clutch engagement, the initial *S* value, S_0, was read; the viscometer was then allowed to operate for 2 min. until a second *S* value, S_2, was recorded. An undisturbed sample of each base was used for each separate determination at each given *U* value.

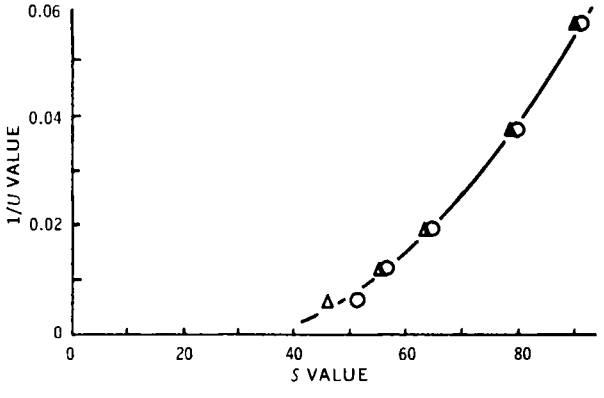

Figure 1—*Characteristic viscosity curve for Base E-5 at zero time and observed at 30°. Key:* ○, S_0; *and* △, S_2.

Table IV—Amount of 0.1 *N* NaOH Solution Required to Neutralize 10 g. of Base Diluted to 100 ml. with Distilled Water[a,b]

Base	pH of 10 g. Base Diluted to 100 ml.	Amount 0.1 *N* NaOH Required, ml.
E-1	6.1	0.1
E-2	3.5	11.9
E-3	4.0	—[c]
E-5	3.9	—[c]

[a] The pH of the distilled water used was 7.0. [b] All readings were taken at 30°. [c] Addition of approximately 2.5 ml. of 0.1 *N* NaOH solution yielded a thick, collapsed semisolid gel of pH 5.2, which thickened more with further addition of 0.1 *N* NaOH and prevented pH determination concurrent with titration by 0.1 *N* NaOH.

Following viscometer evaluations of each base at five different *U* values at zero time (0–96 hr. after formulation of the base), five tightly sealed samples of each base were stored in glass containers for 1 month in two ovens adjusted to 30 and 50°, respectively. Following this storage, viscometer studies on E-1, E-2, E-3, and E-5 were completed as previously described and at 30°.

RESULTS

The findings after storage of samples of Bases E-1, E-2, E-3, and E-5 at 30 and 50° for 1 month and subsequent viscosity studies and attempts to describe rheological[6] (36) characteristics of these bases are summarized as follows.

1. Storage of E-1 at 50° for 1 month resulted in syneresis of the normally thixotropic system; storage of E-1 at 30° for 1 month resulted in a viscous liquid-type system, which appeared nearly Newtonian in rheological behavior.

2. Storage of E-2 at 50° for 1 month resulted in a two-layered system (liquid upper phase and semisolid lower phase). Storage of E-2 at 30° for 1 month resulted in a homogeneous organogel system, which indicated development of some thixotropy.

3. Storage of E-3 at 50° for 1 month resulted in an apparent dilatent (shear-thickening) system, probably as a result of redispersion of microscopic transparent lumps of matrix polymer by the agitation of the viscometer paddle. Storage of E-3 at 30° for 1 month resulted in plots of S_0 and S_2 that were nearly coincidental and were very similar to plots for E-3 at zero time.

4. Storage of E-5 at 50° for 1 month resulted in an organogel containing some small dense lumps, whereas storage of this base at 30° for 1 month resulted in a thick homogeneous organogel. A comparison of plots of S_0 and S_2 in Fig. 1 with those in Figs. 2 and 3 indicates that storage of E-5 for 1 month at 30 and 50°, respectively, resulted in some thixotropy of the base. However, for given *U* values, plots of S_0 are in approximately the same position along the abscissas of all three figures; this suggests acceptable stability

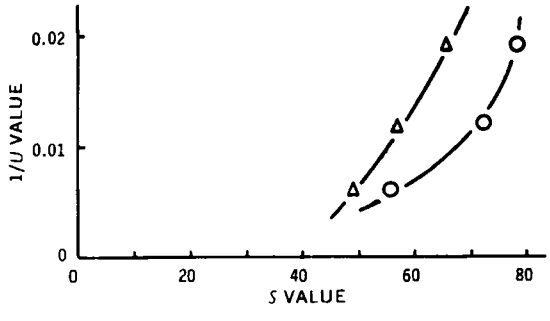

Figure 2—*Characteristic viscosity curve for Base E-5 after storage for 1 month at 30° and observed at 30°. Key:* ○, S_0; *and* △, S_2.

[5] The viscometer is fitted with an *S* scale of 0–100 arbitrary units, corresponding to shearing stress, and with a *U* scale of 10 arbitrary clutch values, corresponding to rates of shear. The viscometer is also equipped with a sensitivity switch adjustable for "fine" or "normal" and with a head setting switch with the settings 50 and 500 (the 500 setting is theoretically 10 times as sensitive as the 50 setting and is used for highly viscous samples).

[6] Rheology may be defined as the study of deformation of solids and flow of liquids.

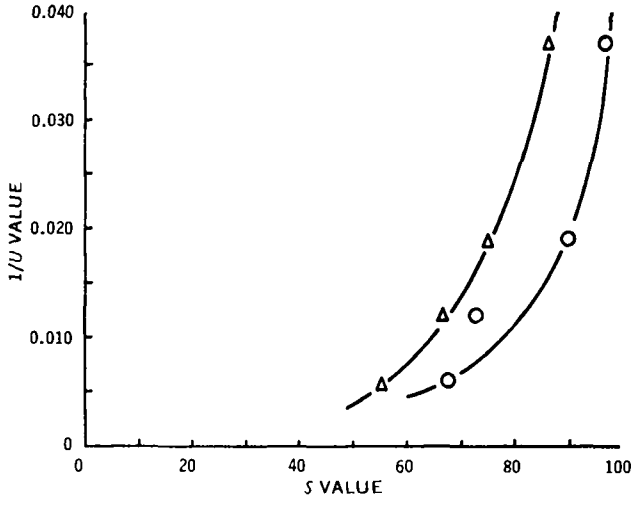

Figure 3—*Characteristic viscosity curve for Base E-5 after storage for 1 month at 50° and observed at 30°. Key: O, S_0; and Δ, S_2.*

of E-5 regarding resistance to changes in viscosity resulting from storage at 30 and 50° for at least 1 month.

Preliminary analyses[7] of E-5 (for dimercaprol content) containing approximately 6% dimercaprol and stored at selected temperatures in Type I glass containers are reported in Table V. Dimercaprol was selected as the initial test medicament for incorporation into Bases E-1 through E-5. It is employed ophthalmically as an antidote for heavy metal poisons and certain vesiccants, and its stability is a function of pH, temperature, and oxidation.

Formulation of E-2 (without dimercaprol) by Method B resulted in the appearance of a dark-pink color as the dispersion reached 125°. This is a probable result of a chemical reaction of poly(methyl vinyl ether-maleic anhydride) 139 with polyethylene glycol 200, since such reactions are known to occur (37); the reaction product (probably a chromophore compound) is possibly only an intermediate since the pink color disappeared after storage of the base for 1–2 weeks at 30°. This possible reaction could explain large variations in the physical consistency of E-2 at zero time as compared to that when the base is stored for 1 month at 30 and 50°.

The appearance of small, dense lumps in E-3 and E-5 after storage for 1 month at 30 and 50° may be the result of coalescence of microscopic particles of partially dissolved carboxy vinyl polymer 940; appearance of the lumps could also be suspected to be a function of prolonged storage at higher temperatures.

A serious disadvantage of the methods of preparation of the bases in this investigation is the entrainment of large amounts (in some cases) of small air bubbles, especially in organogels formulated from carboxy vinyl polymers. This entrainment of air could result in a nonhomogeneous rheological system, degradation of the base upon storage, and/or decomposition of potentially active medicinal ingredients. It is possible that these air bubbles could have been eliminated by preparing the bases under partial vacuum or that they could have been removed from the finished bases by partial evacuation of the system. Vacuum treatment, however, was not investigated. Furthermore, one investigator (38) studied the use of ultrasonic homogenizers in preparing organogels of carboxy vinyl polymers which were virtually free of entrained air.

CONCLUSIONS

In this investigation, Base E-5 represented the best attempt to formulate a semisolid, anhydrous, water-soluble base for ophthalmic use as determined by the following parameters:

[7] Analyses of E-5 containing approximately 6% dimercaprol were conducted as follows. Three 0.1–0.3-g. samples of E-5, weighed to the nearest 0.1 mg., were placed in nitrogen-flushed, 125-ml., rubber-stoppered conical flasks. Then 30–40 ml. distilled water and 3 ml. of 0.30 *M* phosphate buffer (pH 7) were added, the samples were thoroughly dispersed, and the dimercaprol was titrated with fresh iodide solution using freshly prepared starch solution as the end-point indicator.

Table V—Results of Preliminary Analyses of Approximately 6% (w/w) Dimercaprol in Base E-5 Stored in Type I Glass Vials[a,b]

Time Stored	Storage Temperature	Dimercaprol Remaining, %	Degradation of Dimercaprol, %
Zero time	30°	5.73	0.0
2 weeks	30°	5.76	0.0
1 month	30°	5.71	0.3
2 months	30°	5.75	0.0
3 months	30°	5.67	1.0
Zero time	50°	5.73	0.0
2 weeks	50°	5.63	1.7
1 month	50°	5.63	1.7
2 months	50°	5.57	2.8
3 months	50°	5.40	5.8

[a] Differences of 0.15 (or less) unit regarding percent dimercaprol remaining were considered insignificant and probably due to human variation in the precision of the analyses. [b] Results for bases other than E-5 and for other temperatures and containers other than Type I glass will be reported in subsequent studies.

1. Desirable physical spreadability characteristics over the temperature range of 0–50°.
2. An apparent pH value in the acidic range (which may be important to the stability of many ophthalmic drugs).
3. Desirable lubricity.
4. The cosmetic appeal of greaselessness and possible esthetic and technical attributes of transparency.
5. Least observed change in physical characteristics of all bases studied after storage at 30 and 50° for 1 month.
6. Apparent lack of strong buffer capacity and thickening due to viscosity of a 10% (w/v) aqueous dispersion with addition of small amounts of dilute alkali which, in the near neutral environment of the eye, could result in advantageous prolonged contact of a medicated base with the eye.
7. Content of the maximum amount[8] of the most desirable (in this investigation) vehicle, polyethylene glycol 400; polyethylene glycol 400 is the least hygroscopic (39) of the solvents used, its known eye irritation and acute toxicity are low, it is official in USP XVIII, and it has desirable lubricity and viscosity characteristics.
8. Known low eye irritation by the primary matrix polymer, carboxy vinyl polymer 940, as reported for a 1% aqueous solution (40), resistance of some gels of carboxy vinyl polymer 940 to support fungal and bacterial growth (41); and the possibility that some gels of carboxy vinyl polymer 940 may be sterilized by autoclaving without significant change in viscosity (23).
9. Optimistic preliminary reports of tolerable rates of degradation of dimercaprol incorporated in E-5 when stored in Type I glass vials at various temperatures for selected time (Table V).

Further research concerning ophthalmic bases such as those formulated for this investigation will attempt to elucidate eye irritation properties of the bases through animal testing, compatibility of the bases with several types of containers designed for unit dose-type application, compatibility and stability of various ophthalmic drugs in the bases, and therapeutic efficacy of the bases in antidoting the deleterious effects of selected compounds through a program of clinical diagnosis of the eyes of intentionally inoculated animals.

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[8] Since polyethylene glycol 400 freezes to a solid from 4 to 10°, it must be "plasticized" with a minimum of 25–30% of its close congener polyethylene glycol 200.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 5, 1973, from the *College of Pharmacy, University of Florida, Gainesville, FL 32610*

Accepted for publication April 12, 1973.

Abstracted in part from a thesis submitted by D. W. Newton to the Graduate School, University of Florida, in partial fulfillment of the Master of Science degree requirements.

Supported by the U. S. Army Medical Research and Development Command (Contract DADA 17-71-C-1041).

The authors thank Mr. Jose Aponte for his laboratory assistance in formulating and evaluating the bases studied, Mr. Peter Eisenhardt for his assistance in developing the analytic procedures concerning dimercaprol, Mr. Arthur Kibbe for his technical assistance in the rotational viscometer studies, and Mr. George Perry for the preparation of Figs. 1–3.

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