

meric membranes is operative with respect to the concentrations of uncharged organic compounds. Apparent diffusion constants from various solvents were obtained from steady-state and quasi-steady-state studies. Solid materials in contact with such membranes modified to act as potential pharmaceutical dosage forms were studied and demonstrated that basic diffusional information could be used to evaluate, predict, and control such diffusion.

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Keyphrases

Polymeric membranes—drug diffusion
 Silastic membranes—diffusion rates
 Capsules, silastic—drug diffusion
 Solid particles—membrane transport
 Diffusion—steady state
 Potentiometric titration—pKa values
 UV spectrophotometry—analysis
 Colorimetric analysis—spectrophotometer

Effect of a Dimethylpolysiloxane Fluid on the Stability of Menadione

By RONALD T. TURNBULL* and KENNETH E. AVIS

The nonaqueous solvents presently in use as parenteral vehicles possess certain disadvantages or have limited application. The silicone fluids have certain physical, chemical, and biological properties which would appear to make them suitable for parenteral formulations. Accelerated thermal and light stability studies were carried out on a dimethyl silicone fluid of 20 centistokes viscosity and corn oil using menadione as the medicinal compound for study. Based on predictions from the accelerated thermal studies, it was found that the dimethyl silicone fluid was superior to corn oil. Corn oil was found to be superior to the dimethyl silicone in retarding photodegradation of menadione at room temperature. Since greater emphasis must be placed on the ability of the vehicle to retard thermal changes in a chemical compound, the experimental results indicate that the dimethyl silicone fluid of 20 centistokes viscosity is superior to corn oil as a vehicle for menadione.

AQUEOUS SYSTEMS are normally preferred for liquid dosage forms intended for parenteral administration because body systems are aqueous and absorption of the drug generally occurs more

readily from an aqueous system. However, a number of therapeutic agents, because of their solubility characteristics, can only be formulated in nonaqueous solvent systems. Although the number of such agents is considerably less than those requiring aqueous systems, they are vital to our therapeutic armamentarium.

The nonaqueous vehicles most commonly used are the fixed oils. All of these, however, have disadvantages in use, such as: the development of rancidity with aging, potential allergenic reactions in sensitive individuals and local tissue reac-

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tions, including cysts, foreign body granulomas, and occasional nerve injury (1). All of these and other solvents currently in use possess certain disadvantages or have limited applications, therefore, a need exists for other nonaqueous vehicles.

The dimethylpolysiloxane fluids appear to possess most of the characteristics an ideal nonaqueous solvent should have (1), namely, they possess very great chemical and oxidative stability, they have low viscosity-temperature coefficients, their viscosity can be tailored to meet the desired physical needs, their boiling points are high enough to permit heat sterilization, they are nonflammable, and they are very low in toxicity (2-8).

The use of silicone fluids as nonaqueous vehicles for the intramuscular administration of drugs has been reported in the literature (9). This brief account is the only known record of work that has been done in exploring such use for this potentially valuable series of solvents (10).

The objective of this study was to explore the physicochemical effects of dimethylpolysiloxane fluid, 20 centistokes, when utilized as a vehicle for a particular drug, menadione. The observed effects were compared with those obtained using one of the commonly used nonaqueous vehicles, corn oil.

EXPERIMENTAL

Materials—Menadione, USP; silicone fluid¹, 20 centistokes (supplied by Dow Corning Chemical Co., Midland, Mich.); 2,4-dinitrophenylhydrazine; corn oil.

Equipment—Beckman DU spectrophotometer; type I amber glass vials (supplied by Kimble Products, Division of Owens-Illinois, Toledo, Ohio); rubber vial closures, No. 342 Red, P and H coated (supplied by Carron Products Co., Philadelphia, Pa.); Gossen Luna Six light meter; light stability cabinet.

Assay Method—A modified form of the assay procedure official in the NF XII (11) was utilized. The official assay is a colorimetric procedure reacting menadione with 2,4-dinitrophenylhydrazine, and depends on the formation of the 2,4-dinitrophenylhydrazone of the naphthoquinone portion of the molecule, and the interaction of the latter compound with ethanolic ammonia to yield a blue-green colored solution. The concentration is determined spectrophotometrically at a wavelength of 635 m μ . In the official assay, an original sample of approximately 25 mg. in solution is used, the spectrophotometric reading being taken on a 1:100 dilution.

In preliminary trials, it was found that the absorbance of menadione did not conform to Beer's law, when percent transmission was plotted against concentration, throughout the range of concentration tested, *i.e.*, 2.5-25 mg., from either corn oil or silicone fluid, although it did conform to Beer's law from the standard ether-alcohol vehicle. The

deviation in the slope occurred at the original concentration of between 12.5 and 15 mg. Since this deviation did exist, had a 25-mg. sample been used, as recommended in the official assay, the assay results would have been unreliable up to a degradation of 50%. Conformity to Beer's law was demonstrated between 2.5 and about 15 mg. in the test sample, therefore, a 10-mg. sample was used in this study.

Thermal Stability—Four temperatures were chosen to study the thermal stability of menadione in each vehicle: room temperature, 35, 55, and 70°. Solutions of menadione in corn oil and the dimethylpolysiloxane fluid, 20 centistokes, were prepared at a concentration of 1 mg./ml. Three samples were assayed for each storage interval and each assay was performed in triplicate. The solutions stored at 55° were assayed every 7 days for 3 weeks. The solutions stored at room temperature, 35, and 70°, were assayed every 14 days for a period of 9 weeks.

Light Stability—A light stability cabinet suggested by Lachman *et al.* (12) for ordinary illumination was used for the light study. From preliminary trial data a light intensity of 750 ftc. was found to be sufficient to cause degradation within a few hours. Solutions of menadione in both vehicles were prepared at a concentration of 1 mg./ml. Ampuls of type I colorless glass containing the solutions were laid horizontally in the center of the shelf in the cabinet to allow for maximum and uniform exposure.

Three samples were tested for each exposure period and assayed in triplicate. The samples were assayed at zero-storage time and after 2, 6, 10, and 12 hr. exposure to light at an intensity of 750 ftc.

RESULTS AND DISCUSSION

Assay Modification—As indicated previously, the absorbance from menadione did obey Beer's law in the standard ether-alcohol vehicle. Figure 1 shows the results of the same assay procedure when menadione was placed in the dimethylpolysiloxane fluid. This curve and the one obtained for menadione in corn oil are essentially identical. As can be seen, a linear relationship occurs only from 25 mcg./50 ml. to a point somewhere between 125 and 150 mcg./50 ml. Therefore, the assay procedure was modified to use an original sample of 10 mg. (100 mcg./50 ml. in dilution) so that degradation at least up to 75% could be measured by this test procedure.

Thermal Stability—The effects of temperature on the degradation of menadione in both vehicles tested

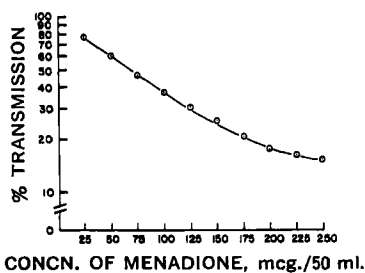


Fig. 1—Standard curve for menadione in dimethyl silicone fluid, 20 centistokes.

¹ Medical Fluid 360.

TABLE I—COMPARATIVE EFFECTS OF TEMPERATURE ON MENADIONE

Temperature, °C.	Vehicle	Days						
		0	7	14	21	35	49	63
Room temp.	Corn oil	100.0 ^a	100.0	...	96.9	95.2	85.6	84.0
	DMSF ^b	100.0	—	100.0	91.8	103.4	105.2	105.6
35	Corn oil	100.0	100.3	...	92.2	87.5	82.9	81.0
	DMSF ^b	100.0	95.5	...	95.5	94.8	95.2	94.1
55	Corn oil	100.0	100.0	91.0	88.1	—	—	—
	DMSF ^b	100.0	85.7	88.0	91.1	—	—	—
70	Corn oil ^c	100.0	92.5	—	74.4	64.6	57.6	53.3
	DMSF ^b	100.0	82.1	—	69.8	51.5	42.3	28.3

^a Percent remaining. ^b DMSF, dimethyl silicone fluid, 20 centistokes.

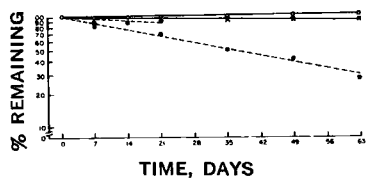


Fig. 2—Effect of temperature on the stability of menadione in dimethyl silicone fluid, 20 centistokes. Key: —○—, room temperature; —×—, 35°; —●—, 55°; —●—, 70°.

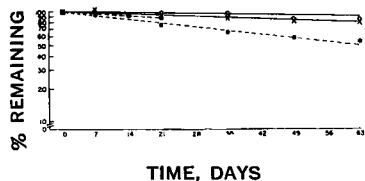


Fig. 3—Effect of temperature on the stability of menadione in corn oil. Key: —○—, room temperature; —×—, 35°; —●—, 55°; —●—, 70°.

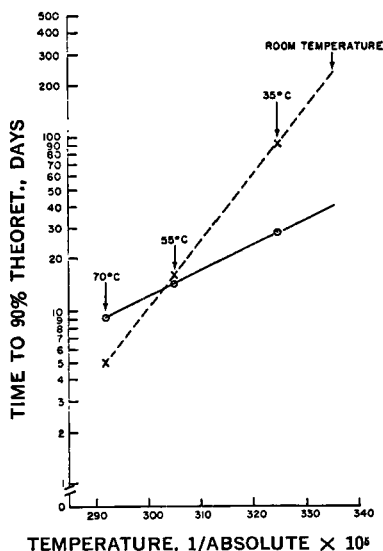


Fig. 4—Comparison of the theoretical shelf life of menadione in corn oil and dimethyl silicone fluid, 20 centistokes. Key: —○—, corn oil; —×—, silicone.

are summarized in Table I. When these data are plotted as in Figs. 2 and 3, the straight lines obtained indicate that the rate of degradation in both vehicles follows that of a first-order reaction. The rate of degradation at a storage temperature of 70° was found to be considerably greater in dimethyl silicone fluid than in corn oil, but at room temperature and 35°, considerably greater in corn oil than in dimethyl silicone fluid. In both fluids, the rate of degradation was greater at higher temperatures.

Utilizing these data to prepare an Arrhenius plot, as proposed by Free and Oyer (13), it is possible to predict the stability of menadione at room temperature. By this method, the times at which the product, stored at selected elevated temperatures, reached 90% of its original concentration was plotted against $1/T$ (absolute temperature). Extending the line to the intercept of $1/T$ equal to room temperature indicated the predicted time of stability to 90% of original concentration. The authors' data for menadione in corn oil and in dimethyl silicone fluid have been plotted in this manner and the results shown in Fig. 4. As can be seen, there is a significant difference in the effects of the two vehicles. The predicted shelf life for menadione in corn oil was about 40 days, while that for menadione in the dimethyl silicone fluid was about 230 days. The experimentally determined value for menadione in corn oil was found to be

45 days. Therefore, the predicted value of 40 days was confirmed quite closely by experimental data.

Light Stability—The experimental results from the light stability study are plotted in Fig. 5. As may be seen, there is a difference in the rate of degradation of menadione in the dimethyl silicone fluid as compared with corn oil. The dimethyl silicone fluid was somewhat less effective than corn oil in retarding the photodegradation of menadione. The rate of degradation in both vehicles was rapid up to about 20% of the original concentration remaining. Subsequently, there was a pronounced reduction in the rate, particularly for the dimethyl silicone fluid. This leveling off of the rate of degradation agreed with the results reported by Collins and Kirch (14).

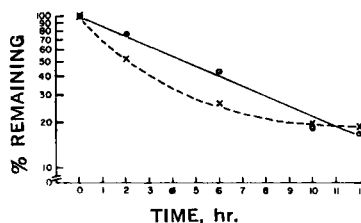


Fig. 5—Effect of light at an intensity of 750 ft.c. on the stability of menadione in corn oil and dimethyl silicone fluid. Key: —○—, corn oil; —×—, silicone.

SUMMARY

The silicone fluids appear to have certain physical, chemical, and biological properties which would make them useful as nonaqueous solvents for the administration of medicinal agents.

Based upon data from accelerated thermal studies, it was found that the dimethyl silicone fluid was superior to corn oil in preventing the thermal degradation of menadione.

The photodegradation studies indicated that, although corn oil was somewhat superior to the dimethyl silicone fluid in preventing the degradation of menadione, photodegradation was rapid in both vehicles. Since photodegradation can be controlled during normal storage by protective packaging, its practical significance is less than the relatively uncontrollable thermal storage conditions.

In consideration of these findings, it may be concluded that the dimethyl silicone fluid is superior to corn oil as a vehicle for menadione.

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Keyphrases

Menadione stability
 Dimethylpolysiloxane fluid, corn oil—vehicles
 Stability, menadione—nonaqueous vehicles
 Photodegradation, menadione—vehicle effect
 Thermal stability, menadione—vehicle effect
 Colorimetric analysis—spectrophotometer

Drug Standards

Assay of Terpin Hydrate and Codeine Elixir by Gas Chromatography

By HAROLD J. WESSELMAN

Terpin hydrate and codeine after extraction from the elixir are separated and determined with the aid of two internal standards and the use of temperature-programmed gas chromatography. Using the same method, elixir of terpin hydrate can also be determined. A precision and accuracy study for both elixirs is included.

THE QUANTITATIVE determination of terpin hydrate, *cis-p*-menthane-1,8-diol hydrate, has always presented problems. Indeed the National Formulary XII (1) does not include an assay for terpin hydrate or codeine in either the elixir of terpin hydrate or the elixir of terpin hydrate and codeine. In 1921 Murray (2) used a gravimetric method for terpin hydrate. Harrison (3), Carol (4, 5), and Lund and Ameiss (6) improved this method. Later, in 1932,

Perlmann (7) proposed a colorimetric method which was modified by Platt and James (8) and Vadodaria, Parikh, and Mukherji (9).

Dembeck (10) described a titrimetric assay for codeine while Stoicheva (11) determined terpin hydrate and codeine by subjecting them to microreactions and examining the results microscopically. Milos (12, 13) developed a spectrophotometric determination for these compounds. Using ion-exchange chromatography and nonaqueous titrimetry, Blake and Carlstedt (14) determined codeine in the elixir, while Mont-