(2) Albert, A., in "Physical Methods in Heterocyclic Chemistry," Vol. 1, Katritzky, A. R., Ed., Academic Press, New York, N. Y., 1963, p. 73 ff.

(3) Koch, H. P., *J. Chem. Soc.*, **1949**, 401; Janssen, M. J., *Rec. Trav. Chim.*, **79**, 454, 464, 1066(1960); Foye, W. O., Mickles, J., Duvall, R. N., and Marshall, J. R., *J. Med. Chem.*, **6**, 509(1963).

(4) Foye, W. O., and Mickles, J., *J. Med. Pharm. Chem.*, **5**, 846(1962).

(5) Albert, A., "The Acridines," Edward Arnold, London, England, 1951, p. 75.

(6) Albert, A., and Ritchie, B. *J. Chem. Soc.*, **1943**, 458 ff.

(7) Ochiai, E., Katayanagi, M., and Okamoto, T., *J. Pharm. Soc. Japan*, **66**, 12(1946).

Keyphrases

Antiradiation compounds
Acridine dithiocarbamates—synthesis
Quinaldine dithiocarbamates—synthesis
Radioprotective activity—screening
IR spectrophotometry—identity
UV spectrophotometry—identity

Rheological Stability of a Procaine Penicillin G Suspension

By JAMES C. BOYLAN and ROBERT L. ROBISON

The rheology of a 58.6 percent procaine penicillin G suspension was followed for a 24-month period. Samples stored as recommended (5°) were unchanged after 2 years. Samples stored at 26 and 37° increased in viscosity, yield value, and thixotropy with time.

In formulating a product where rheological properties are important, it is not only necessary to ascertain that the freshly prepared product possesses the necessary rheological characteristics, but more importantly whether or not these characteristics change during the recommended shelf life of the product. A specific case where unchanging rheological properties are critical is an injectable suspension of procaine penicillin G (600,000 u./ml.). The rheological parameters of this type of suspension determine (*a*) ease of filling, (*b*) prevention of separation during shipping and storage, and (*c*) injectability. It is difficult to formulate a procaine penicillin G suspension that will be satisfactory under all these varied conditions.

In 1958, Ober and co-workers (1) published an outstanding rheological study of concentrated procaine penicillin G depot preparations. They reported that in aqueous suspensions of 40 to 70% (w/w) procaine penicillin G, the rheological structural breakdown point (the point of maximum torque at very low shearing rate) is the physical parameter that defines the structure of the suspension prior to any applied shearing force. Although the nature of this structure is not known, they reasoned that the existence of this structural breakdown point does allow highly concentrated procaine penicillin G suspensions to fluidize enough to allow passage through a hypodermic needle. Furthermore, it permits good depot formation by virtue of quickly regaining this structure. They also determined what effect particle-size distribution, specific surface of the powder, and percent solids had on these phenomena of structure formation, breakdown, and recovery. By using a variety of techniques, including rheology, a region of satisfactory formulation was ascertained.

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It is the purpose here to report the rheological changes obtained with a procaine penicillin G suspension under a variety of storage conditions and to illustrate how critically important storage conditions are to product performance.

EXPERIMENTAL

Materials—The suspension studied[1] had the following formula:

procaine penicillin G (USP)	58.6%
sodium citrate (USP)	4.0%
polysorbate 80 (USP)	0.4%
lecithin	1.5%
butyl parahydroxybenzoate	0.015%
water for injection (USP) *q.s.ad.*	100.0%

All figures are expressed as w/v.

The samples evaluated were disposable syringes taken from a production lot. Storage was under three conditions: 5, 26, and 37°. The marketed product bears a refrigeration storage statement and a 24-month expiration date.

Rheological Evaluation—The viscometer used in this study was a Ferranti-Shirley cone and plate viscometer[2] equipped with a 400 g. cm. spring, an automatic gap-setting device, an X-Y recorder,[3] and a constant-temperature water bath.[4] The use of this viscometer has been described elsewhere (2). Calibration of the instrument was carried out using N.B.S. standard viscosity oils.

Each sample was contained in a 1-ml. disposable syringe. Since the sample size required for this viscometer is approximately 1 ml., the sample was used in its entirety (except for some retention in the syringe). The sample to be evaluated was treated

[1] Duracillin A. S. (Lilly), 600,000 u./ml.
[2] Ferranti Electric Co., Plainview, Long Island, N. Y.
[3] Houston Instrument Co., Bellaire, Tex. (model HR-92).
[4] Brinkmann Instrument Co., Westbury, N. Y. (Haake model F).

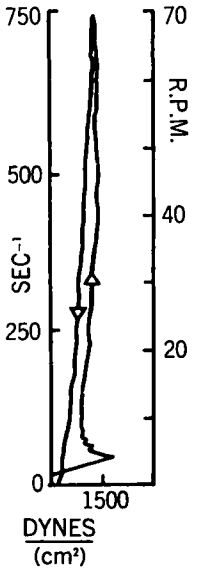

Fig. 1—Rheogram of procaine penicillin G suspension (600, 000 u./ml.) stored 24 months at 5°. Viscosity at 70 r.p.m. is 1.5 poises. Thixotropic area is 1 sq. in. Rheograms obtained initially and after 6, 12, and 18 months are also essentially the same as Fig. 1.

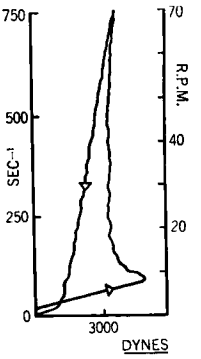

Fig. 2—Rheogram of procaine penicillin G suspension (600, 000 u./ml.) stored 12 months at 26°. Viscosity at 70 r.p.m. is 4.3 poises. Thixotropic area is 3.5 sq. in.

as follows: After the needle guard and syringe plunger were removed, a microspatula was used to help the suspension gently flow out of the plunger end of the syringe. This eliminated the need to expel the sample through the needle and insured minimum preshearing of the sample. As would be expected, if the suspension was expelled through the needle, very little structure remained after expulsion. The plate was immediately raised into position with the cone. Prior to running, the sample was held as close to 25° as practical. The plate was prestabilized at 25 ± 0.1° by circulating water from the water bath. Since, however, the suspension dries rapidly when exposed to air at room temperature, it was necessary to run the sample within 1 min. after raising the plate into position with the cone. The results obtained indicated that temperature control was adequate for reproducible results. All rheograms were obtained using a truncated cone having an angle of 33 min. 26 sec., and a radius of 2 cm. The instrument was set at an upsweep time of 60 sec., a downsweep time of 60 sec., and a maximum r.p.m. of 70.

RESULTS AND DISCUSSION

The freshly prepared suspension filled, shipped, and injected satisfactorily.

The results obtained as the samples aged are definitely related to the storage temperature. Rheograms of suspension stored at 5° (the recommended storage temperature) showed no change after 24 months (the recommended storage time) (see Fig. 1). Suspension stored at either 26 or 37° showed pronounced rheological changes. Figure 2, for example, shows the rheogram of a disposable syringe stored for 12 months at 26°. The yield value, thixotropy, and viscosity have all increased as a result of the higher storage temperature. Material represented by Fig. 2 is still ejectable, but more force and effort are required to do so. At 37° the effect is much more dramatic and occurs much sooner. Within 3 weeks at 37° the yield value of the material is so great that the pen of the X-Y recorder goes off scale. Under this condition the suspension cannot be injected from the syringe into a muscle. Hence, it is mandatory that this product be stored at the recommended temperature.

One additional important fact that this information points out is that elevated temperature conditions cannot be used to predict the rheological properties of this suspension. The only way to determine the rheological characteristics is to store the product at the temperature of interest and wait the necessary time before gathering the data.

REFERENCES

(1) Ober, S. S., Vincent, H. S., Simon, D. E., and Frederick, K. J., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 667(1958).
(2) Boylan, J. C., *Bull. Parenteral Drug Assoc.*, **19**, 98 (1965).

Keyphrases

Procaine penicillin G suspension
Rheology—penicillin G suspension
Aging—rheological properties
Temperature—rheological properties