2. The evaluation of w/o emulsions by the use of flow curves obtained with a concentric cylinder viscometer is demonstrated. Rheological flow curves were found to be an effective method for indicating the extent of dispersion and degree of droplet coalescence in concentrated emulsions, which behave as general plastic solids.

3. Under low shear conditions, concentrations of mannide mono-oleate in excess of 10% are required to prepare and furnish adequate relative stability to water-in-mineral oil emulsions, although absolute stability is poor.

4. The rate of shear governs the degree of emulsification where the emulsion components are repeatedly forced through a double-hubbed hypodermic needle, and a short capillary of large diameter produced the finest dispersion.

5. For any given set of preparative conditions, a maximum degree of particle size reduction is achieved quite rapidly, and emulsator operation for extended time periods appears unnecessary.

6. For the preparation of w/o repository emulsions, high shear rate emulsators would appear to offer substantial advantages over the low shear rate interconnected glass syringe method.

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# Water/Oil Emulsions Prepared by Low Pressure Capillary Homogenization II

## Stabilizing Influence of Inorganic Electrolytes, Secondary Emulsifiers, and Temperature

By C. DAVID FOX* and RALPH F. SHANGRAW

**Aqueous dispersions in light mineral oil stabilized with mannide mono-oleate were prepared under a set of standard conditions and evaluated by rotational viscometry in conjunction with optical microscopy. Inorganic electrolytes in the aqueous internal phase, at concentrations as low as 0.01 *M*, increased apparent viscosity, retarded sedimentation, and had a marked stabilizing influence. The addition of small amounts of water-soluble surfactants to the internal phase yielded extremely fine dispersions, but these agents decreased stability and tended to cause inversion. Storage of w/o emulsions at 5° had a definite stabilizing influence when compared to room temperature storage.**

IN AN earlier report (1), a reciprocating capillary emulsator was described which is similar in principle to an emulsator[1] that is in general use by physicians for the extemporaneous preparation of small quantities of repository antigenic w/o emulsions. However, the new emulsator produces a quantity of emulsion sufficient for experimental purposes and allows a much greater flexibility in controlling shearing stress. It was also shown that rheological flow curves furnish an adequate means for evaluating w/o emulsion stability, thus obviating the necessity for tedious size-frequency analyses. Fine dispersions of water-in-mineral oil were found to require high concentrations of mannide mono-oleate,[2] but the

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Previous paper: Fox, C. D., and Shangraw, R. F., *J. Pharm. Sci.*, **55**, 318(1966).
[1] Brown Emulsor, Andonian Associates, Inc., Waltham, Mass.
[2] Marketed as Arlacel A by Atlas Chemical Industries, Wilmington, Del.

absolute stability was poor and droplet coalescence progressed to an appreciable extent in 30 days. In the present paper, the same technique of preparation and evaluation as previously reported has been used to study more complex dispersion systems in efforts directed toward reducing the rate of droplet coalescence. The major objective in this study was a determination of factors contributing to the objective formulation and preparation of repository antigenic emulsions.

## EXPERIMENTAL

**Apparatus.**—All w/o emulsions in this study were prepared by means of the reciprocating capillary emulsator described earlier in detail (1). Each emulsion was homogenized by means of 50 passes through a 15-gauge (1.37-mm. i.d.) double-hubbed hypodermic needle, 0.625 cm. in length, at a constant pressure of 50 psig.

**Materials.**—Mannide mono-oleate was used as the primary oil-soluble emulsifying agent, and a purified grade of light mineral oil[3] made up the remainder of the external oil phase. Three water-soluble surface-active agents, polyoxyethylene sorbitan mono-oleate,[4] alkyl phenoxy polyethoxy ethanol,[5] and dioctyl sodium sulfosuccinate,[6] were selected for evaluation as secondary emulsifying agents. All inorganic electrolytes used were of the purest grade commercially available.

**Procedure.**—The rheological behavior of each emulsion at 30° was determined at the time of manufacture, and after a 30-day storage period with the Haake Rotovisko rotational viscometer (Gebrüder Haake K. G., Berlin, Germany) using the same cup and bob as in the earlier study (1). Size–frequency determinations were also performed on each emulsion by an optical method previously described (1). Unless otherwise stated, emulsions were stored at room temperature.

**Influence of Inorganic Electrolytes.**—In his later publications, Brown (2, 3) has stated that the use of a "truly" isotonic fluid as a vehicle for repository emulsified antigenic extracts will eliminate any local irritation that results when physiological saline or Coca's fluid is used. The formula for the isotonic fluid recommended by Brown is as follows:

| | |
|---|---|
| Calcium chloride, hydrate | 0.367 Gm. |
| Magnesium chloride, hydrate | 0.301 Gm. |
| Potassium chloride | 0.373 Gm. |
| Glycine | 1.201 Gm. |
| Sodium sulfate, anhydrous | 0.071 Gm. |
| Sodium bicarbonate | 2.270 Gm. |
| Sodium phosphate, dibasic | 0.142 Gm. |
| Lactic acid, 85% | 0.636 mg. |
| Hydrochloric acid, 0.5 *N* | 180 ml. |
| Sodium hydroxide, 0.5 *N* | 224 ml. |
| Distilled water *q.s. ad* | 1000 ml. |

Although the rationale behind adjusting tonicity of w/o emulsions is questionable, dramatic effects on emulsion stability were noted when the Brown isotonic fluid was utilized for the internal phase of w/o systems. Emulsions exhibited sharply increased apparent viscosities, diminished sedimentation rates, and a marked improvement in stability as evidenced by a reduced coalescence rate. These effects are shown by the flow curves of Fig. 1 for emulsions containing mannide mono-oleate, light mineral oil, and Brown's isotonic fluid in the volume ratio of 2:3:5, respectively.

On the basis of these preliminary results, emulsions containing different concentrations of various electrolytes were prepared to determine the cause and extent of this influence as functions of concentration and valency. Each emulsion was composed of mannide mono-oleate, light mineral oil, and aqueous phase in the volume ratio of 2:3:5, respectively.

The first studies utilized sodium chloride in molar concentrations of 0.01, 0.10, 0.154, 0.25, and 0.50. Some flow curves for the freshly prepared emulsions are presented in Fig. 2.

Concentrations of sodium chloride greater than 0.10 *M* produced no further change in the initial flow curves and are not shown in Fig. 2. A concentration of 0.154 *M* sodium chloride, however, did influence the stability as confirmed by the 30-day size–frequency data. This stabilizing influence can be seen in the flow curves of Fig. 3, which reflect the extent of droplet coalescence. The marked retardation of sedimentation is illustrated in Fig. 4.

Additional emulsions were prepared to determine if this electrolytic effect could be modified by polyvalent cationic electrolytes, and w/o systems were produced containing calcium chloride, ferric chloride, and aluminum chloride, in concentrations of 0.01 and

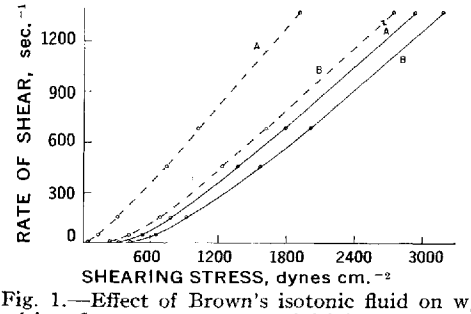


Fig. 1.—Effect of Brown's isotonic fluid on w/o emulsion flow curves. Key: initial, ———; 30 days, – – – –; A, control (50% distilled water); B, 50% Brown's isotonic fluid.

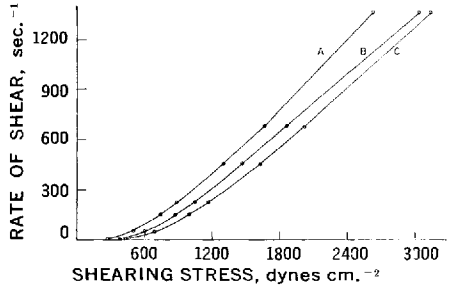


Fig. 2.—Effect of sodium chloride in the internal phase on initial flow curves of 50:50 w/o emulsions. Key: A, control (distilled water); B, 0.01 *M* sodium chloride; C, 0.10 *M* sodium chloride.

[3] Marketed as Drakeol 6VR by Pennsylvania Refining Co., Butler, Pa.
[4] Marketed as Tween 80 by Atlas Chemical Industries, Wilmington, Del.
[5] Marketed as Triton X-100 by Rohm and Haas Co., Philadelphia, Pa.
[6] Marketed as Aerosol OT by American Cyanamid Co., New York, N. Y.

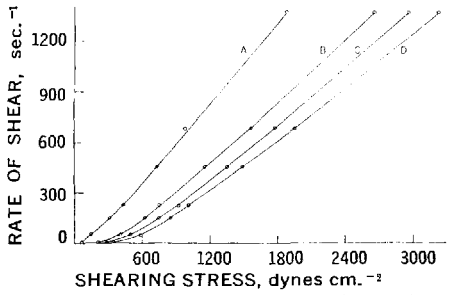


Fig. 3.—Effect of sodium chloride in the internal phase on flow curves of 50:50 w/o emulsions after storage for 30 days. Key: A, control (distilled water); B, 0.01 *M* sodium chloride; C, 0.10 *M* sodium chloride; D, 0.154 *M* sodium chloride.

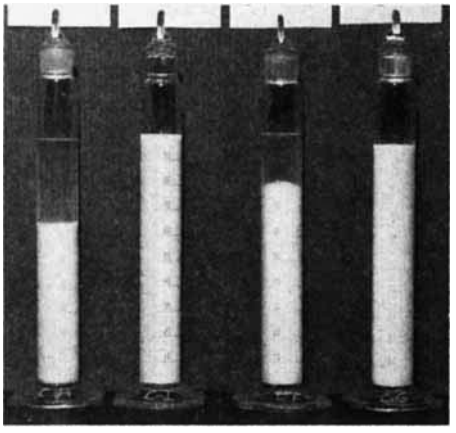


Fig. 4.—The influence of 0.54 *M* sodium chloride in the internal phase of 50:50 w/o emulsions after 30 days' storage. Key: A, external phase: Drakeol 6VR, 40 ml., Arlacel A, 10 ml. Internal phase: distilled water, 50 ml. B, external phase: Drakeol 6VR, 40 ml., Arlacel A, 10 ml. Internal phase: 0.154 *M* sodium cloride, 50 ml. C, external phase: Drakeol 6VR, 30 ml., Arlacel A, 20 ml. Internal phase: distilled water, 50 ml. D, external phase: Drakeol 6VR, 30 ml., Arlacel A, 20 ml. Internal phase: 0.154 *M* sodium chloride, 50 ml.

0.25 *M*. A review of the rheological and micromeritical data for these emulsions indicated that the divalent and trivalent cations exerted essentially the same influence as the monovalent sodium cation, both initially and after 30 days' storage.

Since an influence dependent on cationic valency could not be demonstrated, w/o emulsions containing 0.01 and 0.25 *M* sodium sulfate in the internal phase were prepared to determine if the existence of a relation dependent upon anionic valency could be shown. The results obtained indicated that the divalent sulfate anion exerted a much greater stabilizing influence than did the monovalent chloride anion. After 30 days, a microscopical examination gave no evidence of droplet coalescence in the emulsion containing 0.25 *M* sodium sulfate, with all droplet diameters being less than 1 $\mu$. A flow curve was obtained identical to that of the freshly prepared emulsion, except for the 2 highest rates of shear where the apparent viscosities had actually increased after storage. These flow curves are shown in Fig. 5.

The emulsion containing 0.01 *M* sodium sulfate gave an initial flow curve with apparent viscosities greater than those obtained from the emulsion containing 0.25 *M* sodium sulfate. Furthermore, after 30 days the apparent viscosities were essentially identical to those of the freshly prepared emulsion at all except the 3 highest rates of shear, where again, as noted with the 0.25 *M* system at high rates of shear, apparent viscosities had increased after storage. Droplet coalescence was negligible and all particles were less than 1 $\mu$ in diameter. Flow curves for the 0.01 *M* sodium sulfate emulsion are shown in Fig. 6, with the 0.01 *M* sodium chloride system included for comparison. The decreased apparent viscosities noted with the 0.25 *M* sodium sulfate emulsion, when compared with the 0.01 *M* system, may possibly be the result of the extremely hydrophilic nature of this electrolyte. The higher concentration could conceivably cause a "salting out" effect on the adsorbed mannide mono-oleate, thereby weakening the interfacial film.

**Effect of Secondary Surfactants.**—An investigation was undertaken to determine what effect the inclusion of small amounts of water-soluble surfactants in the aqueous phase would have on the formation and stability of w/o emulsions.

Polyoxyethylene sorbitan mono-oleate in concentrations of 0.02, 0.2, 1, and 2% were prepared in physiological saline solution (0.154 *M* sodium chloride), and these solutions were emulsified in equal volumes of a solution containing light mineral oil (60%) and mannide mono-oleate (40%). Flow

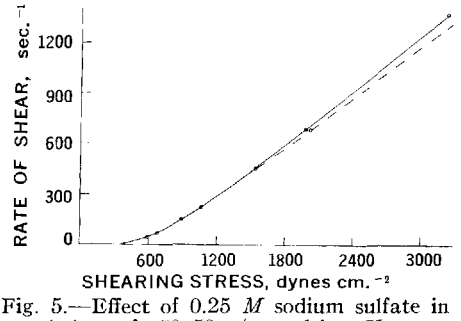


Fig. 5.—Effect of 0.25 *M* sodium sulfate in the internal phase of a 50:50 w/o emulsion. Key: ———, initial; – – – –, 30 days' storage.

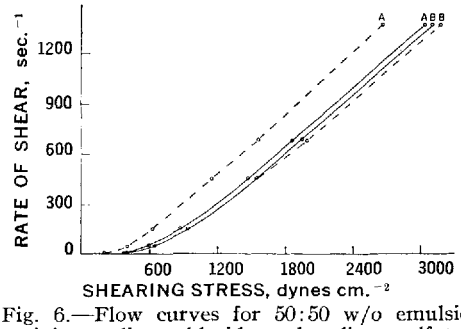


Fig. 6.—Flow curves for 50:50 w/o emulsions containing sodium chloride and sodium sulfate in the internal phase. Key: ———, initial; – – – –, 30 days; A, 0.01 *M* sodium chloride; B, 0.01 *M* sodium sulfate.

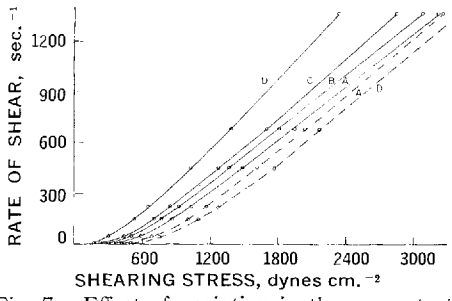


Fig. 7.—Effect of variation in the concentration of polysorbate 80 on flow curves of 50:50 w/o emulsions after 30 days' storage. Key: - - - -, initial; ———, 30 days; A, control (0.154 *M* sodium chloride); B, 0.02% in 0.154 *M* sodium chloride; C, 0.20% in 0.154 *M* sodium chloride; D, 1.0% in 0.154 *M* sodium chloride.

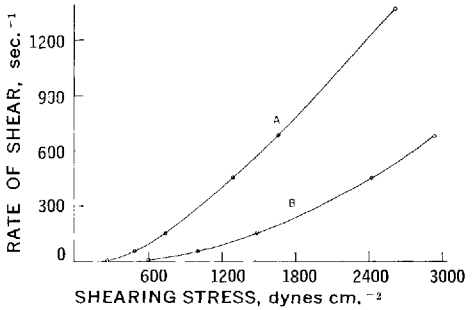


Fig. 8.—Effect of dioctyl sodium sulfosuccinate in the internal phase of a 50:50 w/o emulsion at zero time. Key: A, control (distilled water); B, 1.0% dioctyl sodium sulfosuccinate in distilled water.

curves for the freshly prepared emulsions containing 0.02 and 0.2% polyoxyethylene sorbitan mono-oleate were superimposable upon that of the control which contained only saline solution in the internal phase.

Emulsions containing 1 and 2% polyoxyethylene sorbitan mono-oleate exhibited progressive increases in apparent viscosities at all rates of shear.

After a 30-day storage period, however, marked differences were noted and the effect of the various concentrations of surfactant on emulsion stability is shown by the flow curves of Fig. 7. The emulsion containing 2% polyoxyethylene sorbitan mono-oleate had completely broken in 30 days.

Emulsions containing 1% alkyl phenoxy polyethoxy ethanol and 1% dioctyl sodium sulfosuccinate in the aqueous internal phase were also prepared. As noted with 1 and 2% polyoxyethylene sorbitan mono-oleate, the freshly prepared emulsions have the majority of droplet diameters below the limit of optical microscope resolution, *i.e.*, less than 0.2 $\mu$. The apparent viscosities are correspondingly very high, as shown by Fig. 8, in which the initial flow curves for 50:50 w/o emulsions containing distilled water and 1% dioctyl sodium sulfosuccinate in the internal phase are compared. All emulsions contained 20% mannide mono-oleate in the external oil phase. After 30 days' storage at room temperature, however, the emulsions containing 1% alkyl phenoxy polyethoxy ethanol and 1% dioctyl sodium sulfosuccinate had completely broken.

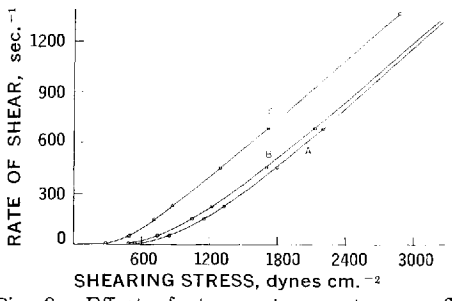


Fig. 9.—Effect of storage temperature on flow curves of a 50:50 w/o emulsion. Key: A, initial flow curve; B, 30 days' storage at 5°; C, 30 days' storage at 25°.

It should be noted that the w/o emulsions containing 1% or more of the previously mentioned water-soluble surfactants were extremely difficult to prepare in the usual manner. The aqueous phase had to be added dropwise to the oil phase with stirring prior to capillary homogenization to prevent an almost immediate inversion to an o/w system.

**Effect of Storage Temperature.**—Emulsions containing giant ragweed extract in the internal phase were also prepared. The giant ragweed antigen used for this study was a commercial extract[7] containing 5% w/v antigen in Coca's fluid. For each experimental emulsion, 30 ml. of the aqueous antigenic extract was diluted to 50 ml. with physiological saline solution and emulsified in 50 ml. of oil phase containing 30 ml. of light mineral oil and 20 ml. of mannide mono-oleate. The resultant w/o emulsion contained 10,000 pollen units/ml. of emulsion, the highest concentration usually employed for the repository hyposensitization treatment of hay fever.

Since all antigenic extracts must be stored under refrigeration for therapeutic stability, experiments were carried out to determine the effect of refrigeration storage on w/o emulsions. In comparing the rheological and micromeritical data for portions of the same emulsion stored at 25 and 5°, it was evident that storage at 5° resulted in a flow curve almost identical with that of the freshly prepared emulsion and only a slight change in droplet size and distribution was noted. The flow curves shown in Fig. 9, for a representative w/o emulsion, demonstrate the stabilizing influence of storage at 5°. Regardless of storage temperature, all flow curve determinations were made at a constant temperature of 30°.

## DISCUSSION

Previous studies have shown that the apparent viscosities of w/o emulsions can be markedly increased by a reduction in the size of the dispersed droplets. However, the addition of inorganic electrolytes to the aqueous phase did not result in a particle size reduction greater than that observed with distilled water. Therefore, it is obvious that the observed rheological effect must result from some other factor which, in all likelihood, is electrical in nature, with the negative charge in the predominant role.

The conclusion, based on this research, that electric charges have an important stabilizing effect on

[7] Supplied through the courtesy of Abbott Laboratories, North Chicago, Ill.

w/o emulsions is contradictory to the work of Albers and Overbeek (4, 5), who have stated that electric charges cannot be expected to stabilize w/o emulsions of more than extremely low concentrations, and that no correlation exists between zeta potential and coalescence rate. Schulman and Cockbain (6) have stated that the droplets in w/o emulsions cannot possess a charge and hence cannot be electrically stabilized. On the other hand, Verwey (7) has suggested that in w/o emulsions, the major part of the potential drop occurs in the oil phase, as this has the lower dielectric constant, and that the interaction of the double layers of the droplets will determine the stability of an emulsion.

Several authors have indicated that the electrical double layer surrounding the water droplets is several microns in thickness for w/o emulsions. This thickness would therefore be greater than the distance between the dispersed phase droplets of the emulsions prepared for this investigation, where diameters were usually less than 1 $\mu$. If the diffuse double layer is several microns in thickness, as appears reasonable, then obviously these double layers surrounding the droplets must overlap in concentrated emulsions, with a concomitant reduction in the potential energy of repulsion. The occurrence of rapid flocculation and sedimentation in those experimental emulsions that contained only distilled water would indicate that a substantial energy barrier is absent and may only be on the order of $1kT$ or $2kT$ ($k$, Boltzmann's constant; $T$, absolute temperature), depending on the droplet size and volume of the internal phase. The thermal agitation supplied by room temperature would be sufficient to overcome this energy barrier. However, the fact that inorganic electrolytes effectively prevented flocculation would imply that the presence of potential-determining ions in the systems resulted in a significant increase in the height of the potential energy barrier. This increased energy barrier could well result from a marked increase in the zeta potential by a compact charge density of counter-ions, which will increase the energy of repulsion. The extent of this increased zeta potential appears to be directly related to the valency of the electrolyte anion. Thus, the emulsion droplets are stabilized by the formation of an electrokinetic charge to a degree considerably in excess of the mechanical stabilization achieved by the use of nonionic emulsifiers alone.

In addition to the significant electrokinetic stabilization, the observed increases in apparent viscosities after storage, noted only in those emulsions containing sodium sulfate, could well be the result of an increased adsorption of emulsifying agent at the oil/water interface with the formation of a semirigid film which would contribute considerable mechanical stability. With coalescence effectively hindered, the film of mannide mono-oleate surrounding each water droplet would grow thicker and stronger with age, creating an interfacial condition that would be reflected in the flow behavior by increased apparent viscosities only at higher rates of shear where mechanical resistance to droplet deformation would become more evident.

It is well recognized that sometimes combinations of nonionic emulsifiers may be more effective than a single emulsifier in stabilizing an emulsion. The inclusion of small amounts of the water-soluble surfactant, polyoxyethylene sorbitan mono-oleate, in concentrations ranging from 0.02 to 2% in the aqueous phase, has been reported as being effective for w/o repository emulsions (8–10), but the authors present no evidence to substantiate this view. As indicated by the flow curves in Fig. 7 and confirmed by optical size–frequency analyses, the adverse effect of polyoxyethylene sorbitan mono-oleate on the stability of w/o emulsions is a direct function of its concentration in the internal phase. Increasing the concentration of this surfactant results in an increased coalescence rate and degree of polydispersity, the extent of which is reflected in the flow curves.

Emulsions containing dioctyl sodium sulfosuccinate in the internal phase exhibited a degree of anomalous flow behavior far greater than any dispersion investigated in this study, as shown by Fig. 8. Although the systems were extremely unstable, the apparent viscosity at the time of preparation could not be calculated at 1370 sec.$^{-1}$, since the shearing stress exceeded 3600 dynes cm.$^{-2}$, the maximum stress possible with the 500 Gm.-cm. torsion spring and an annular gap of 0.96 mm. in the viscometer. All droplets were below the limit of optical resolution, a condition undoubtedly responsible for the high viscosity. Unfortunately, methods for obtaining an initial size–frequency distribution in the submicron range were not available. The majority of physicians have reported the preparation of emulsions with droplet diameters of 0.1 to 1 $\mu$, although Brown (11) has reported a much smaller size as evidenced by electron microscopic examination of films of flash-frozen emulsion. However, the electron microscopic work by Brown is questionable since he states that the frozen emulsion film (−35°) is less than 200 Å. (0.02 $\mu$) in thickness, and then reports observing a droplet diameter distribution extending from 0.02 up to 0.1 $\mu$, a condition difficult to reconcile with such a thin film.

The fact that water-soluble surfactants have an adverse effect on the stability of w/o emulsions definitely precludes their use in repository emulsions. Concentrations greater than 0.2% appear to result in an initial finer dispersion of the aqueous phase, but this advantage is offset by the increased coalescence rate that results. These observations may help to explain the results of Gaillard *et al.* (12, 13), who noted that their w/o repository emulsions of aqueous insect venom could not be stabilized for longer than 21 days, even with concentrations of mannide mono-oleate as high as 35%. The authors attributed the rapid cracking to an alteration of the mannide mono-oleate interfacial film by some component in the insect venom. Since it is known that insect venom contains an appreciable quantity of water-soluble surface-active compounds, these surfactants may have been the causative agents responsible for the instability.

It is a well recognized fact that solutions of allergenic materials must be stored under refrigeration at 5° to retain their effectiveness, although it is not known what changes occur at room temperature which result in decreased potency. Since any w/o repository emulsion containing an allergen would also require refrigeration, the temperature studies were undertaken and as indicated by Fig. 9, a storage temperature of 5° has a definite influence in retarding the rate of droplet coalescence. As a further confirmation of the adverse effect of water-soluble

surfactants discussed previously, emulsions stored at 5° containing polyoxyethylene sorbitan mono-oleate, when compared to those without it, were found to have a greater degree of droplet coalescence and lower apparent viscosities in spite of the stabilizing influence of refrigeration temperature.

It is interesting to note that although allergenic materials theoretically require refrigeration to maintain their potency, repository w/o emulsions after intramuscular injection are maintained at body temperature for periods of up to 1 year with no reported decrease in effectiveness.

The unqualified success of repository emulsion therapy may well depend upon elucidation of the specific agent responsible for individual allergic reactions, since the formulation of a stable w/o emulsion, consistent with the desired objectives, certainly is not insurmountable when the exact chemical composition of the components is known. Difficulties arise from the introduction of the unknown variables that undoubtedly exist in current antigenic extracts. The production methods for the extracts are a consideration since they are not standardized. The units of potency measurement constitute another variable since 3 different systems are in common use among allergists. The product may also vary as a result of variation in the amount of active principle in the raw material.

Considering the tremendous number of variables involved in the techniques of preparing and standardizing extracts of pollen and the extremely wide variations reported by physicians in the emulsification and administration of the extracts in repository form, the success that has been achieved is remarkable.


## SUMMARY

This investigation has been concerned primarily with an evaluation of aqueous dispersions in light mineral oil stabilized with mannide mono-oleate and prepared under a set of standard conditions. The results obtained indicate the following.

1. Inorganic electrolytes, at concentrations as low as 0.01 *M*, in the aqueous internal phase of w/o emulsions, increase the apparent viscosities, hinder sedimentation, and have a marked stabilizing influence. This electrokinetic effect appears to be directly related to the valency of the anion.

2. The addition of water-soluble surfactants to the internal phase of w/o emulsions facilitates emulsification. However, these agents decrease stability and tend to cause inversion.

3. The storage of w/o emulsions at 5° has a definite stabilizing influence when compared to room temperature storage.


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# *Technical Articles*

# Critical Evaluation of the Compactor

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**With the assistance of a suitably prepared experimental design a compactor was optimized to prepare a basic granulation to which other drugs could be added and directly compressed into tablets. An IBM 1620 computor was employed to evaluate the data and to extrapolate additional information for the preparation of contour charts. The contour charts permitted a simple and accurate interpretation of the data and allowed selection of a set of optimum processing conditions. Additional trials confirmed the reliability of this technique.**

A NUMBER OF investigations (1–3) in the chemical processing industry have employed continuous compacting equipment for the unit operation of particle size enlargement. They have shown the compaction process to be useful in the conversion of fine powders into larger agglomerated units. These particulates generally exhibited a reduced tendency to cake, improved flowability, increased bulk density, less dust, and

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