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The Editor comments

THE "NEW LOOK"

When you received this issue of THIS JOURNAL, we hope you noticed a number of significant changes in its appearance and make-up. These innovations, which were decided upon after much consideration, consultation, and debate, were adopted for several reasons. Certainly, it was hoped that the plastic surgery performed on the face of the publication would serve to improve further its appearance and esthetic qualities. An even more important aspect than the external plastic surgery, however, is the orthopedic surgery worked upon the body of the issue. In this regard the reader should particularly note the various new features which are being inaugurated. The scope of the publication has been expanded to permit the inclusion of critical review articles, editorials, articles of a technical nature, and reports of proposed drug assays and specifications.

With this extension in publication policy, no purpose appeared to be served by continued issuance of *Drug Standards* as a separate periodical. Hence, the latter publication has been merged into the present one.

Another change of special note is the retitling of THIS JOURNAL. The former name, *Journal of the American Pharmaceutical Association, Scientific Edition*, was criticized as being nondescriptive with regard to content, too unwieldy, easily subject to confusion with the *Practical Pharmacy Edition*, and difficult to cite correctly in literature references. The new title, *Journal of Pharmaceutical Sciences*, appears to overcome all of these objections. We are well aware that librarians and others responsible for the indexing and cataloging of periodicals will not receive this change with enthusiasm. We believe, however, that any inconveniences arising will rapidly disappear, and that from a long-range view, the change may be looked upon as beneficial even to them.

We are also aware that some readers will view with nostalgia the passing of the old title. We can only request that these individuals be tolerant, and that they, along with our other readers, accept the new features as an earnest attempt upon the part of the editors to improve the appearance of THIS JOURNAL, and to enhance its prestige, usefulness, and reader-interest.

ES 2%, and Stepanol ME 1%) surfactants used in the concentrations mentioned in parenthesis were studied for the release of medicament using three *in vitro* methods, (*a*) radioactive isotope, (*b*) bacteriological, and (*c*) physicochemical methods.

2. The general pattern of the release of medicament from all of the ointment bases remained the same when tested by these methods.

3. The ointment prepared with two per cent anionic surfactant, Sipon ES, was found to be the most satisfactory hydrophilic ointment base. The increase in concentration of Sipon ES retarded the release of medicament from ointment bases in all three *in vitro* methods.

4. A modified physicochemical method is suggested to increase the sensitivity and the speed of the color zones produced per unit of time.

5. A comparative discussion of three *in vitro* methods has been presented and it was concluded that the radioactive isotope method was superior in both sensitivity and accuracy as well as the quantitative results which can be obtained per unit of time.

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Solubilization of Anti-inflammatory Steroids by Aqueous Solutions of Triton WR-1339

By D. E. GUTTMAN†, W. E. HAMLIN, J. W. SHELL, and J. G. WAGNER

Clear solutions of anti-inflammatory steroids, which have concentrations of steroid considerably greater than the water solubilities of the steroids, are being sold commercially for ophthalmic use. The present study was undertaken to obtain quantitative data on the solubilizing power of Triton WR-1339 for three anti-inflammatory steroids. The apparent solubility of each of the steroids, prednisolone, methylprednisolone, and fluorometholone, in an aqueous solution of Triton WR-1339 was found to be linearly dependent on the per cent Triton present. Both the slopes of the linear solubility plots and the water solubilities of the steroids are, in the order, prednisolone > methylprednisolone > fluorometholone. The marked difference in the solubility of fluorometholone in aqueous solutions of Triton WR-1339 from the other two steroids having a 21-hydroxyl group indicates that an entirely different pharmaceutical problem is involved with the steroid having the type of side chain present in fluorometholone.

VARIOUS AUTHORS (1–14) have reported the use of surface-active materials, e. g., proteins, bile salts, and surfactants, to solubilize steroid hormones. For ophthalmic use it is desirable to prepare clear solutions of anti-inflammatory steroids which have concentrations of steroid considerably greater than their water solubility. The surface-active materials used in such preparations must have sufficient solubilizing power to attain the necessary steroid concentration and must be nonirritating and noninjurious to the eye. Johnson (13, 14) studied a large number of surfactants and found that both Triton WR-1339 and Tween 80 were satisfactory for preparing suitable aqueous solutions of the adrenalcortical hormones.[1]

The present study was undertaken to obtain quantitative data on the solubilizing power of Triton WR-1339 for three anti-inflammatory steroids: prednisolone, methylprednisolone, and fluorometholone.

EXPERIMENTAL

Materials.—The prednisolone was recrystallized once from alcohol-water, then dried for twelve hours

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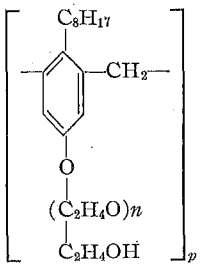
at 70°. The methylprednisolone and fluorometholone were micronized. The Triton WR-1339 was obtained from Winthrop-Stearns.

The structure of Triton WR-1339 according to Rohm and Haas Co. is as follows:



where $n \simeq 10$ and $p \simeq 4$. The calculated mole-equivalent weight ($n = 10$, $p = 1$) is 702.9, and the average molecular weight ($n = 10$, $p = 4$) is 2,812.

Equilibration.—*Method A.*—Excess steroid and the Triton-water solution were heated in a vial on the steam-bath for ten minutes before placing in a constant temperature bath at 25.0° where the vials were slowly rotated for two weeks. The vials were allowed to stand in the bath for one week. Some of the solubility studies with prednisolone were done this way.

Method B.—Excess steroid and the Triton-water solution were slowly rotated in 10-cc. vials in a constant temperature bath at 25° for one week. Some of the solubility studies with prednisolone were done this way.

Method C.—Excess steroid and the Triton-water solution were vigorously agitated at 37° for two days then were vigorously agitated at room temperature (approximately 25°) for two days. The samples were then allowed to stand for three days at room temperature. This method was used for the solubility studies with methylprednisolone and fluorometholone.

Assay Procedure.—*Method 1.*—All Triton-water solutions containing prednisolone were assayed for steroid by withdrawing 5 ml. of supernatant from the vial, extracting the steroid with chloroform, evaporating 2 to 10 ml. of chloroform extract to dryness, taking up the steroid residue in ethanol, and assaying the alcoholic solution by the triphenyltetrazolium color procedure (15).

Method 2.—All Triton-water solutions containing methylprednisolone or fluorometholone were assayed for steroid by determining the ultraviolet absorption spectrum of the sample solution after centrifugation using a blank prepared with the same concentration of Triton as the sample and carried through the same equilibrium procedure as the sample. The aqueous Triton-fluorometholone solutions were diluted 1:20 and the aqueous Triton-methylprednisolone solutions were diluted 1:100 with 95% alcohol. The absorption maximum was used to calculate the concentration of steroid. An absorptivity (1%,1 cm.) of 400 was used for both methylprednisolone and fluorometholone. Calibration data indicated this absorptivity was valid since the presence of Triton at the dilutions used did not significantly change the value from that observed with 95% alcohol alone.

aqueous-alcoholic solutions of Triton WR-1339, an aliquot of the steroid in aqueous Triton solution was diluted to 100 ml. with 95% alcohol. The ultraviolet absorption spectrum was obtained with a Cary recording spectrophotometer using a blank prepared in the same way but without steroid. Reasonably low slit widths at or near the absorption maximum with the Cary instrument indicated that distortion had not occurred despite the fact that the Triton WR-1339 also had appreciable absorption in the 230 to 250 mμ region.

RESULTS

The observed solubilities of the steroids in water and aqueous solutions of Triton WR-1339 are shown in Table I.

The apparent solubility of a steroid in an aqueous solution containing Triton WR-1339 was found to be linearly dependent on the per cent of Triton present. This relationship can be expressed by the equation

$$S = So + a\,(\text{Triton}) \qquad \text{(Eq. 1)}$$

where S = the apparent solubility of the steroid in aqueous Triton solution, So = the solubility in water, a = a constant representing the slope of the solubility curve, and (Triton) = the per cent (w/v) of Triton present.

The data of Table I are plotted in Fig. 1. The constants of the "least-squares" regression lines are shown in Table II.

Table I.—Observed Solubilities of the Steroids in Water and Aqueous Solutions of Triton WR-1339

Triton WR-1339 % w/v	Observed Solubility of Steroid, mg./ml.		
	Prednisolone	Methylprednisolone[c]	Fluorometholone[c]
0	0.223[a], 0.239[b]	0.095	0.003, 0.010
2	0.693[a]	...	...
4	1.196[a],	...	...
5	1.458[b]	...	0.065, 0.080
6	1.706[a], 1.716[b]	...	...
7	1.881[b]	...	...
8	2.219[a], 2.217[b]	...	...
9	2.481[b]	...	...
10	2.719[a], 2.719[b]	1.25	0.103, 0.090
12.5	...	1.52	0.118, 0.143
15.0	...	1.80	...

[a] Equilibration procedure was method A; assay procedure was method 1.
[b] Equilibration procedure was method B; assay procedure was method 1.
[c] Equilibration procedure was method C; assay procedure was method 2.

Table II.—Intercepts (So) and Slopes (a) of Linear Plots Shown in Fig. 1

Steroid	So, mg./ml.	a
Prednisolone	0.215	0.249
Methylprednisolone	0.097	0.114

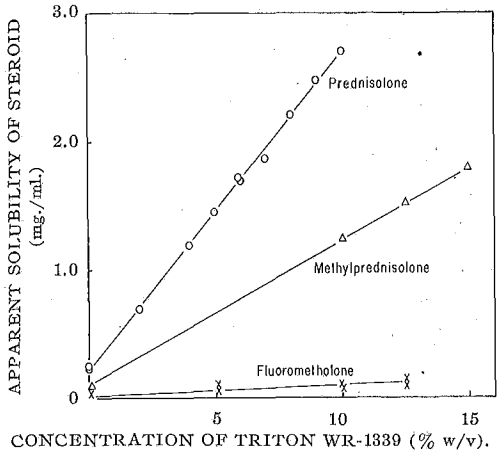


Fig. 1. The solubilities of some anti-inflammatory steroids in aqueous solutions of Triton WR-1339.

TABLE III.—MAXIMUM SOLUBILIZING POWER OF TRITON WR-1339 FOR ANTI-INFLAMMATORY STEROIDS

Steroid	Δ Steroid, mg/ml. / Δ %w/v Triton WR-1339	Moles of Steroid per Mole-equiv. of Triton WR-1339	Moles-equiv. of Triton WR-1339 per Mole of Steroid
Prednisolone	0.249	0.0486	20.6
Methylprednisolone	0.114	0.0214	46.7
Fluorometholone	0.00927	0.00173	578.0

TABLE IV.—SHIFT IN THE ULTRAVIOLET ABSORPTION MAXIMA OF THE STEROIDS IN AQUEOUS-ALCOHOLIC SOLUTIONS OF TRITON WR-1339

Triton WR-1339 % w/v	λ Max. of Fluorometholone, mμ	λ Max. of Methylprednisolone, mμ
0	243, 243.0	...
5.0	243, 243.5	...
10.0	247, 247.0	241.3
12.5	250, 251.0	243.3
15.0	254, 255.0	243.7

From the linear solubility curves we have calculated the saturation capacities of the nonionic surfactant, Triton WR-1339, for the respective steroids. These values are collected in Table III.

In aqueous-alcoholic Triton solutions the steroids investigated showed ultraviolet absorption curves that were similar to those recorded in water-alcohol. However, as the concentration of Triton increased there was a shift in the absorption maximum toward longer wavelengths. Table IV indicates these shifts in absorption maxima to longer wavelengths for fluorometholone and methylprednisolone in aqueous-alcoholic solutions of Triton.

DISCUSSION

The shifts in the absorption maxima of the [illegible] observed in the case of solubilized polycyclic aromatic hydrocarbons (16), for various steroids solubilized in aqueous sodium lauryl sulfate (7), and for chloroxylenol solubilized in water by polyethylene glycol 1000 monoacetyl ether (17). This behavior is typical of instances where association is possible with the solvent by hydrogen bonding (3). It seems likely, therefore, that the steroids are associated with the polyoxyethylene chain of Triton WR-1339.

When the slopes, a, of the linear solubility plots of Fig. 1 and Table II are plotted against the intercepts, So, an apparent straight line is obtained. This indicates an apparent relationship between the water solubility of a steroid and its ability to be solubilized by Triton WR-1339. Although this relationship appears to be valid for the three steroids investigated, additional compounds must be studied to check the validity of the correlation for steroids as a general class. It is interesting to note that the melting points of the steroids studied fall in the order, prednisolone 232–236°, methylprednisolone 240°, and fluorometholone 292–303°. This suggests that qualitatively similar energy interchanges occur in all three equilibrium situations.

SUMMARY AND CONCLUSIONS

1. The solubilization of prednisolone, methylprednisolone, and fluorometholone by aqueous solutions of Triton WR-1339 has been studied quantitatively.

2. The apparent solubility of each steroid in an aqueous solution containing Triton WR-1339 was found to be linearly dependent on the per cent of Triton present.

3. The greater the water solubility of the steroid, the greater the solubilizing power of Triton WR-1339. Both the slopes of the linear solubility plots and the water solubilities of the steroids are in the order prednisolone > methylprednisolone > fluorometholone.

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