THE INFLUENCE OF THE VARIATIONS IN SOLUBILISING PROPERTIES OF POLYSORBATE 80 ON THE VITAMIN A PALMITATE : POLYSORBATE 80 : GLYCEROL : WATER SYSTEM

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The vitamin A palmitate: Polysorbate 80: glycerol: water system has been studied with special reference to the production of one-phase, water miscible, transparent solutions. The preparation of such solutions has been shown to depend on the hydrophile-lipophile balance of Polysorbate 80; this can be controlled by a cloud-point titration method.

FREEDMAN and Green (1947) described the production of water-miscible preparations of lipophilic substances, such as vitamin A palmitate, with polyoxyethylene sorbitan fatty acid esters. Minimum proportions of such surfactants are desirable because they are bitter and expensive. To this end the value of glycerol in similar formulations was demonstrated by Coles and Thomas (1952). The United States Pharmacopeia XVI includes a monograph on Water-miscible Vitamin A Solution, describing the product as a viscous liquid, which on dilution with ten volumes of water may be clear or opalescent. Preparations are usually required to be transparent, of low viscosity and readily dispersible in aqueous media. For other purposes, however, such as encapsulation, a more viscous preparation may be required.

The object of this work was to chart the physical properties of the four component system and initially a specific sample of Polysorbate 80 was used. Attempts to reproduce certain preparations with further supplies of Polysorbate 80 were unsuccessful and the work was extended to investigate the effect of using different batches of the surfactant. Watanabe, Kanzawa, Mima, Yamamoto and Shima (1955) have reported a relationship between the hydrophile-lipophile character of polyoxyethylene sorbitan mono-oleate and its solubilising efficiency for vitamin A palmitate. Variations in hydrophile-lipophile character were therefore suspected as being responsible for our difficulties.

EXPERIMENTAL

Preparation of Phase Diagram

Preparations were made by dissolving the vitamin ester* (6·5 per cent by weight, equivalent to 100,000 I.U. A per gram of product) in the appropriate amount of Polysorbate 80† (polyoxyethylene sorbitan mono-oleate), adding glycerol B.P. while stirring and then diluting with water

* Vitamin A palmitate (Glaxo Laboratories Ltd., potency $1{\cdot}54 \times 10^6$ I.U. per gram: glyceride—free.

† Polysorbate 80 U.S.P. Supplied by Honeywill Atlas Ltd., and known commercially as Tween 80.

to a known weight. Integral ratios of Polysorbate 80 : vitamin A palmitate, from 1 : 1 to 14 : 1, were examined, with 10 per cent increments in glycerol content.

Determination of Hydrophile-Lipophile Character

Greenwald, Brown and Fineman (1956) proposed a convenient water-titration method for the determination of hydrophile-lipophile character.

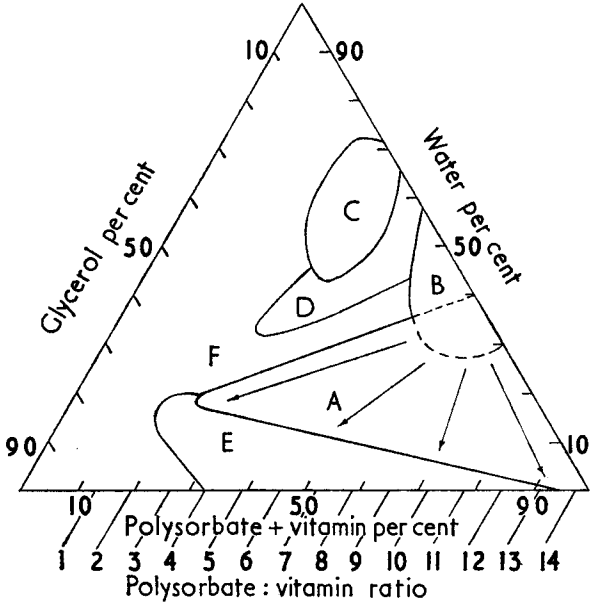

FIG. 1. The vitamin A : Polysorbate 80 : glycerol : water system.
Variations in the character of preparations containing Polysorbate 80 (5 samples).

Zone	Description
A	Transparent, single phase
B	Semisolid
C	Faintly opalescent
D	Markedly opalescent
E	Two transparent phases
F	Emulsions.

A solution of the surfactant in a suitable solvent, here a 4 per cent v/v solution of benzene in dioxane, is titrated with water to a cloud-point. The titre (the "water-value") is a direct measure of the hydrophile-lipophile character of the surfactant and related to Griffin's (1949) hydrophile-lipophile balance value.

RESULTS

Assessment of the Phase Diagram

Fig. 1 represents the physical character of products that can be prepared with this system using one sample of the surfactant. Preparations are represented by points within the triangle. The percentages by weight of

glycerol and water are read from the left and right sides respectively. The percentage by weight of vitamin plus Polysorbate 80 is read from the base-line. Since the percentage of vitamin based on the final weight is constant at 6·5, the Polysorbate 80 content is conveniently expressed as a ratio of its weight to that of the vitamin ester. Zone A encloses all transparent single phase preparations. The ease of dilution with water depends on their viscosities, which, as indicated by the arrows, decrease radially from zone B, the region of semi-solid preparations. Faintly opalescent products of low viscosity occur in zone C; those in zone D

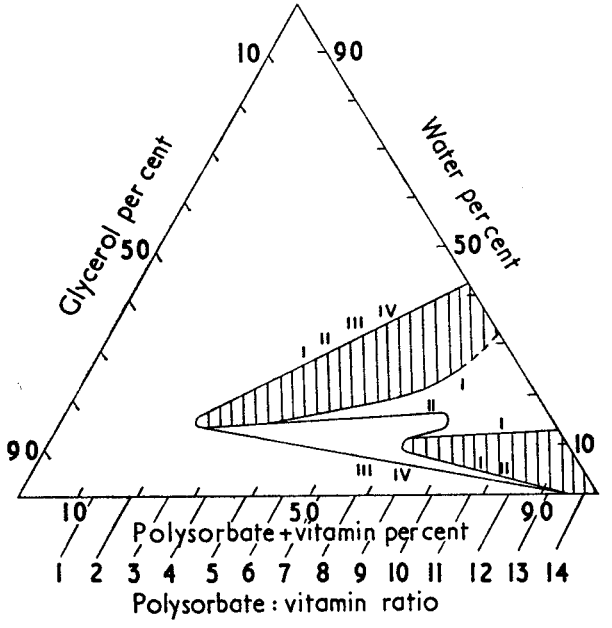

FIG. 2. Variations in the zone of transparent, single-phase preparations with different samples of Polysorbate 80.

Curve	Polysorbate 80 Sample	Water Value
I	2	10.3
II	4	12.3
III	5	12.7
IV	11	13.4

The shaded areas show where the samples of Polysorbate 80 all gave transparent, single-phase preparations.

are similar but have increased turbidity. Zone E encloses preparations that separate into two distinct phases. The remaining preparations (F) are opaque emulsions varying in physical stability. Separation of vitamin occurs in those of low-water content, and those of high-water content cream rapidly.

As indicated, a re-examination of the system with various samples of Polysorbate 80 revealed considerable variations in the area of zone A, which are illustrated in Fig. 2.

Hydrophile-Lipophile Character

Water values and polyoxyethylene content (Siggia, 1958) of several samples of Polysorbate 80 showed a rank correlation and are given in Table I.

Curves I to IV on Fig. 2 represent the results obtained with selected samples of Polysorbate 80 showing the effect of increasing water-values on the properties of the four component system.

TABLE I

WATER VALUES AND POLYOXYETHYLENE CONTENTS OF POLYSORBATE 80

Sample No.	Water value	Per cent (OCH_2CH_2)
1	10·0	74·2
2	10·3	76·0
3	12·2	
4	12·3	
5	12·7	76·9
6	12·8	
7	12·9	
8	13·1	77·3
9	13·2	
10	13·3	77·9
11	13·4	77·7

DISCUSSION

The best known quantitative approach to the concept of balanced surfactants is probably the hydrophile-lipophile balance (HLB) method of Griffin (1949). Originally the determination of HLB values was based on an assessment of emulsification performance, some seventy-five emulsions having been made for the determination of each HLB number. More recently Griffin (1954) devised formulae for calculating the HLB number from analytical data. The formulae relevant to the Polysorbate 80 type of surfactant are:

(1) $HLB = 20\ (1 + S/A)$
where S = saponification number of the ester, and A = acid number of the acid.

(2) $HLB = (E + P)/5$
where E = per cent oxyethylene, and P = per cent polyhydric alcohol.

The water-value determination is simpler in application, it has a much expanded scale between extreme samples and appears to be more related to the function of Polysorbate 80 in the formulations.

The areas of transparent, water-miscible preparations, given by all samples of Polysorbate 80 that were fully investigated, are indicated by shading in Fig. 2.

The considerable differences of area in Fig. 2 obtained from materials conforming to the U.S.P. XVI emphasise the need for a simple quantitative measure of solubilising power. Such a measure is provided by the water-value determination suggested by Greenwald and his colleagues.

REFERENCES

Coles, C. L. J. and Thomas, D. F. W. (1952). *J. Pharm. Pharmacol.*, **4**, 898–901.
Freedman, L. and Green, E. (1947). Assignors to U.S. Vitamin Corporation, U.S. Patent 2,417,299.

Greenwald, H. L., Brown, G. L. and Fineman, M. N. (1956). *Analyt. Chem.*, **28**, 1693–1697.
Griffin, W. C. (1949). *J. Soc. Cosmetic Chem.*, **1**, 311–326.
Griffin, W. C. (1954). *Ibid.*, **5**, 249–256.
Siggia, S. (1958). *Analyt. Chem.*, **30**, 115–116.
Watanabe, A., Kanzawa, T., Mima, H., Yamamoto, N. and Shima, T. (1955). *J. pharm. Soc., Japan*, **75**, 1093–1098.

The paper was presented by MR. TAIT. The following points were made in the discussion.

The same batch of vitamin A palmitate was used throughout, its potency being from 1·5 to 1·6 $\times$ 10^6 I.U./g. It was not pure but the use of a single batch of impure material was still valid since the purpose of the paper was to demonstrate the variability in samples of polysorbate 80. The work was carried out in a constant temperature range between 24 and 26°.