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Solubilization of antifungal drugs in water/POE(20) sorbitan monooleate/oil systems

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Abstract

Solubilization of antifungal drugs (clotrimazole, ciclopirox olamine and econazole nitrate) by means of nonionic surfactant systems has been investigated. The solubility of these antifungal drugs ranged from practically insoluble to slightly soluble in water as well as in oils such as isopropyl myristate (IM) and isopropyl palmitate (IP). Ternary water/POE(20) sorbitan monooleate/oil compositions were used to study drug solubilization in a concentration of 1% w/w. Rheological properties have been studied to determine the suitability of selected compositions as topical formulations. The results obtained show that it is possible to solubilize 1% w/w of antifungal agent in suitable topical formulations with a water content higher than 50% w/w.

Key words: Clotrimazole; Ciclopirox olamine; Econazole nitrate; Solubilization; Microemulsion; Nonionic surfactant

The design of new dosage forms that increase the effectiveness of existing drugs is one of the trends observed in pharmaceutical technology in recent years (Banker and Rhodes, 1990). In this context, microemulsions have aroused great interest as novel dosage forms (Jayakrishnan et al., 1983; Osborne et al., 1988; Trotta et al., 1989; Kakutani et al., 1991; Ritschel, 1991), due to their considerable solubilizing capability for both oil and water soluble compounds (Attwood and Florence, 1983; Friberg and Venable, 1983; Bourrel and Schechter, 1988).

The aim of this work was to study solubilization of antifungal agents with topical therapeutic activity in pharmaceutically acceptable nonionic surfactant systems. Formulations falling in the category of microemulsions were mainly considered. The solubilities of the chosen drugs (clotrimazole, ciclopirox olamine and econazole nitrate) ranged from slightly soluble in water to practically insoluble (McEvoy, 1991; Hoogerheide, 1982; Reynolds, 1989; USP XXII, 1990). These drugs are generally delivered in creams or lotions at a concentration of 1% w/w (McEvoy, 1991).

Ternary water/nonionic surfactant/oil formulations were used to study solubilization of 1% of

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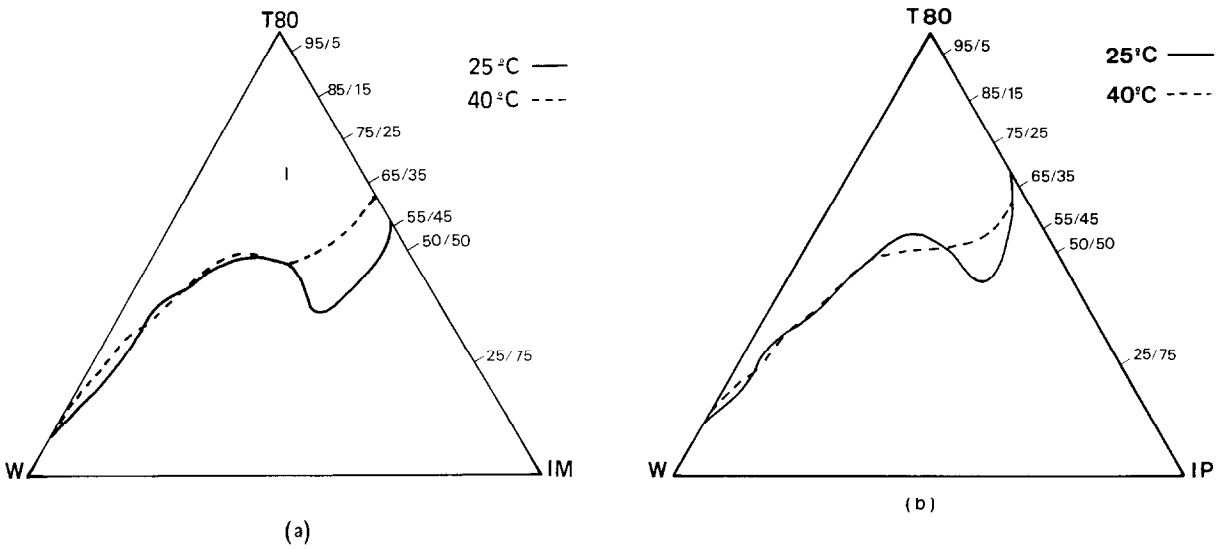

Fig. 1. Solubility regions in the partial phase diagrams of: (a) water (W)/POE(20) sorbitan monooleate (T80)/isopropyl myristate (IM) system and (b) water (W)/POE(20) sorbitan monooleate (T80)/isopropyl palmitate (IP) system.

either clotrimazole (Effechem), ciclopirox olamine (Hoechst) or econazole nitrate (Effechem). POE(20) sorbitan monooleate (Tween 80®, ICI) was chosen as a surfactant since it is considered as very weakly irritant. The oils selected were isopropyl myristate (IM) and isopropyl palmitate (IP) (Unichema Internacional) which are commonly used in pharmaceutical formulations. Prior to the solubilization studies, the solubilities of each antifungal drug in the oils selected were determined. Clotrimazole was slightly soluble in IP and very slightly soluble in IM; ciclopirox olamine was slightly soluble in IM and very slightly soluble in IP while econazole nitrate was practically insoluble in both IM and IP.

Phase diagram determinations of ternary water/Tween 80/IM and water/Tween 80/IP systems at 25 and 40°C revealed the solubility regions shown in Fig. 1. The monophasic areas are quite large and decrease slightly with increase in

Table 1
Solubilization of 1% of clotrimazole, ciclopirox olamine and econazole nitrate in the water/POE(20) sorbitan monooleate (T80)/isopropyl myristate (IM) system as a function of water content and temperature

T80/IM w/w ratio	Water (%)											
	Clotrimazole (1%)				Ciclopirox olamine (1%)				Econazole nitrate (1%)			
	A		B		A		B		A		B	
	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C
95:5	5–40	5–45	–	–	0–70	0–80	–	–	0–65	0–75	–	–
85:15	5–40	5–40	–	–	0–65	0–70	–	–	0–60	0–65	–	–
75:25	5–35	5–35	35–40	35–40	0–35	0–35	35–65	35–70	5–35	5–35	35–60	35–65
65:35	5–25	5–25	25–30	25–40	0–25	0–25	25–60	25–65	5–25	5–25	25–55	25–60
55:45	5–10	5–15	10–30	15–35	5–10	0–25	10–60	25–60	5–10	5–15	10–50	15–55
50:50	–	–	5–25	5–35	–	–	5–60	0–60	–	–	10–50	5–55
25:75	–	–	10–20	10–30	5–10	–	10–55	0–55	–	–	10–45	5–50

A, monophasic isotropic composition; B, multiphasic composition.

temperature. All the compositions in the monophasic region were isotropic as checked with crossed polarizers.

Solubilization of 1% of each antifungal drug was achieved in selected monophasic and multiphasic compositions. Tables 1 and 2 show the results obtained as a function of water content. These results, which are in agreement with previous data with similar systems (Attwood and Florence, 1983), clearly show the capability of surfactant aggregates to disolve slightly soluble or even practically insoluble compounds. As indicated above, econazole nitrate is practically insoluble in either water, IM or IP. However, it can be disolved in formulations with as much as 65% w/w of water content at 25°C.

The solubilization capability of ternary formulations was found to increase slightly with temperature. This fact can be interpreted as the contribution of two effects: Changes in both the structure of the surfactant aggregates and the solubility of the drug with increasing temperature.

For systems containing IM, 1% of antifungal drug can be solubilized in monophasic isotropic compositions or microemulsions at room temperature with a maximum water content of 40% (clotrimazole), 75% (ciclopirox olamine) and 65% (econazole nitrate). For systems containing IP, the corresponding maximum water content is 55% (clotrimazole), 85% (ciclopirox olamine) and 60% (econazole nitrate). In both systems ciclopirox olamine can be solubilized in compositions with the highest water contents.

Independently of the surfactant/oil weight ratio chosen, solubilization of 1% w/w clotrimazole requires a minimum water content of 5%. However, a minimum water concentration is only needed to solubilize ciclopirox olamine or econazole nitrate in formulations with low surfactant concentrations.

Spreadability values of stable compositions of these ternary water/nonionic surfactant/oil systems were compared to those of three well known semi-solid pharmaceutical forms: Lassar's paste (British Pharmacopoeia, 1988), the Hydrophilic ointment (USP XXII) and the Aqueous cream (British Pharmacopoeia, 1988). They are considered as models of pharmaceutical formulations with low, medium and high spreadability values (Pozo and Suñé, 1955). Spreadability is a parameter which gives information about consistency, stickiness and ease of spreading of a cream or ointment. Consequently, measurement of spreadability is a suitable method to compare different semi-solid pharmaceutical forms (Pozo and Suñé, 1955; Denoël and Jaminet, 1971; Pozo et al., 1987).

The spreadabilities of all compositions selected were higher than that of Lassar's paste. Two of them, with a surfactant/oil ratio of 25:75 and 50:50, respectively, and low water content,

Table 2
Solubilization of 1% of clotrimazole, ciclopirox olamine and econazole nitrate in the water/POE (20) sorbitan monooleate (T80)/isopropyl palmitate (IP) surfactant as a function of water content and temperature

T80/IP w/w ratio	Water (%)											
	Clotrimazole (1%)				Ciclopirox olamine (1%)				Econazole nitrate (1%)			
	A		B		A		B		A		B	
	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C	25°C	40°C
95:5	5–55	5–50	–	–	0–85	0–85	–	–	0–60	0–65	–	–
85:15	5–50	5–50	–	–	0–85	0–85	–	–	5–60	0–65	–	–
75:25	5–30	5–30	30–45	30–45	0–35	0–35	35–85	35–85	5–30	5–35	30–60	35–65
65:35	5–20	5–15	20–35	15–40	0–25	0–25	25–85	25–85	5–20	5–25	20–50	25–55
55:45	–	5–15	5–25	15–35	5–10	0–25	10–85	25–85	5–15	5–15	5–50	15–55
50:50	–	5–10	5–25	10–30	–	–	5–85	0–85	5–10	5–10	10–50	10–55
25:75	–	–	5–20	5–25	5–10	–	10–85	0–85	–	–	5–50	5–50

A, monophasic isotropic composition; B, multiphasic composition.

were similar to the Hydrophilic ointment while the spreadabilities of the other compositions were greater than that of the Aqueous cream. The spreadability results were not affected by the addition of 1% (w/w) of each drug to the ternary compositions. Since the antifungal drugs must be applied over large areas of the skin, the spreadability of the pharmaceutical dosage forms should be high. Therefore, compositions with higher spreadability would be the most appropriate for topical applications.

The performance of dermatological products depends to a great extent on their rheological behavior. It is well known that the type and quantity of surfactant influence the rheological properties of formulations (Sherman, 1983; Dahms, 1991). In order to assess the influence of surfactant/oil ratio, water content, etc., on rheological behavior, shear stress-shear rate measurements of different compositions were carried out.

Changes from Newtonian to pseudoplastic behavior in the monophasic region (surfactant/oil ratio, 85:15 w/w) at a water concentration of 17% were observed. Pseudoplastic behavior was observed at a surfactant/oil ratio of 85:15 w/w with a low water content (29%). At higher water contents (37.5%), the rheological behavior was more complex. Similarly to spreadability, the rheological behavior of ternary compositions remained unchanged on addition of 1% (w/w).

Spreadability results were compared with apparent viscosities (viscosity at a selected shear rate). Fig. 2 shows apparent viscosity (a) and spreadability (b) values of compositions with constant surfactant/oil weight ratios of 85:15, 50:50 and 25:75 as a function of water concentration. It can be observed that in all formulations the spreadability decreases with increasing viscosity. The results confirm the usefulness of simple assays such as those of spreadability to obtain practical information relating to the viscosity of pharmaceutical preparations designed to be extended to the skin.

The results reported have clearly shown that antifungal drugs with solubilities ranging from slightly soluble to practically insoluble in water and oil components can be succesfully dissolved by a solubilization mechanism in pharmaceutically acceptable ternary water/nonionic surfactant/oil formulations. According to the most accepted definition of microemulsion, the majority of the formulations studied fall in this category. Our spreadability studies have also revealed that the compositions of the studied systems are ap-

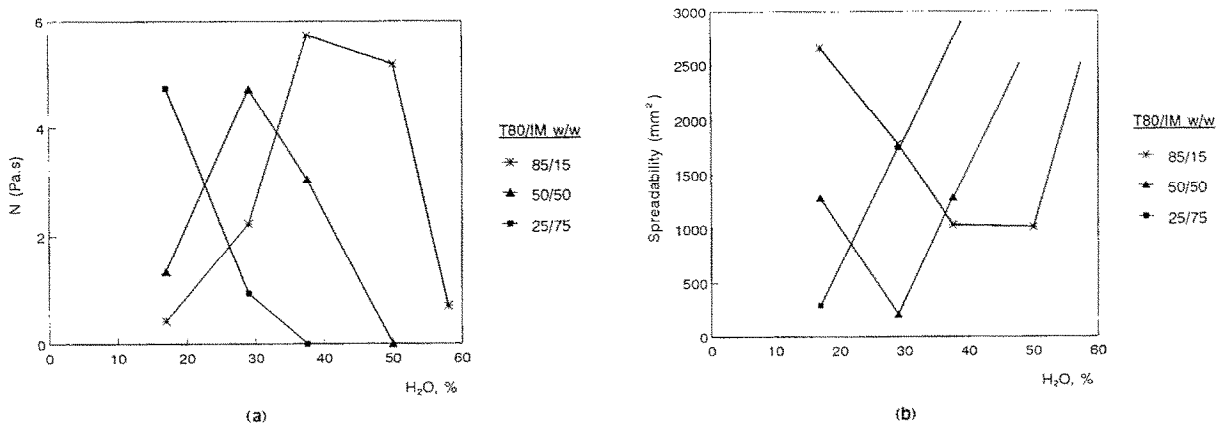

Fig. 2. (a) Values of viscosity at a constant shear rate corresponding to compositions of the ternary water/POE(20) sorbitan monooleate (T80)/isopropyl myristate (IM) system, along three experimental composition paths with constant surfactant/oil weight ratios as a function of water content. (b) Spreadability values of compositions with constant surfactant/oil weight ratios as a function of water content.

propriate for topical applications. In addition, a correlation between rheological behavior and spreadability has been found.

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