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Transparent oil–water gels: a study of some physicochemical and biopharmaceutical characteristics. Part I. Formation of transparent oil–water gels in the 4-component-system of Eumulgin B3, Cetiol HE, isopropyl palmitate, and water

Christine Provost and Renaat Kinget

Laboratorium voor Galenische en Klinische Farmacie, Katholieke Universiteit Leuven, Leuven (Belgium)

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Summary

Transparent oil-water gels are clear, ringing, and optically isotropic semisolid systems composed mainly of hydrophilic surfactants, oil, and water. The formation of such gels in a 4-component system containing two emulsifying agents, Eumulgin B3 and Cetiol HE, an oily liquid, isopropyl palmitate, and water is investigated. The concentration boundaries within which these gels exist are determined. Depending on the concentration ratios of the constituents, different phases can be distinguished, each of which is characterized by its specific colloidal structure. They are summarized in a phase diagram for a limited concentration region. The transparent oil-water gels can be identified unequivocally by means of their macroscopical behavior and their appearance in the polarizing microscope. The presence of both isopropyl palmitate and the two emulsifiers is found to be essential for their formation. The amounts of emulsifiers needed depend on the oil content.

Introduction

For skin care and the topical treatment of dermatological diseases a wide choice of dermatological vehicles, ranging from solid to semisolid and liquid preparations, is available to clinicians and patients. Within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceuticals (Hynniman and Lamy, 1969; Kaufman and Blaser, 1965; Nürnberg, 1977; Nürnberg, 1978; Provost, 1986).

Besides transparent oleogels (anhydrous gels based on fatty components) and transparent hydrogels (aqueous gels without fatty components), transparent gels containing both water and oil have been developed, which we proposed calling transparent oil-water gels or TOW gels (Provost, 1985; Provost, 1986). For the sake of clarity we would like to state very clearly what this term implies because opinions conflict on the definition of and terminology to be used for these systems.

Correspondence: C. Provost, Laboratorium voor Galenische en Klinische Farmacie, Katholieke Universiteit Leuven, Gasthuisberg, B-3000 Leuven.

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These TOW gels can be described as semisolid systems that consist mainly of water, oil, and an emulsifying agent or agents. They have a jelly-like consistency and are transparent, clear and homogeneous, optically isotropic, and thermodynamically stable. A characteristic “ring” or resonance occurs when a container full of TOW gel is tapped or gently bounced. A survey of the literature (Provost, 1986) indicated that many terms are used interexchangeably to designate these gels. Among the most common are microemulsion gel, transparent emulsion gel, clear resonant gel, cream gel, viscous isotropic phase, and ringing gel. And as we have noted elsewhere (Provost, 1986) a rather remarkable degree of confusion reigns with regard to the basic concept of the formation of TOW gels.

There is no agreement as to whether these gels have to be considered as microemulsions, as solubilized systems, as stabilized emulsions, or as a cubic liquid crystalline phase. Important throughout the discussion of what the transparent oil-water gels ultimately are is that little fundamental research on this subject has been done. Two studies on some of the fundamental physicochemical and structural characteristics of these systems have been published (Pohler, 1983; Pöllinger, 1986), and the results of biopharmaceutical studies with the TOW gels have been reported only recently (Mubarak, 1982; Pohler, 1983). In some studies on phase diagrams of oil–emulsifier–water systems, the formation of a viscous isotropic phase, which seems to correspond to our description of a TOW gel, is mentioned and briefly discussed (Treguier et al., 1975; Führer, 1977; Lo et al., 1977a; Feger, 1978; Junginger, 1980; Pohler, 1983; Orecchioni et al., 1984).

Therefore, a study on the conditions for the formation of TOW gels followed by an investigation into their physicochemical and biopharmaceutical characteristics seemed appropriate. To this purpose, a quaternary model system composed of two emulsifying agents, Eumulgin B3 and Cetiol HE, an oily liquid, isopropyl palmitate (IPP) and water was selected. The present paper deals with the results of the initial part of this study in which a phase diagram for a limited concentration area is constructed and the concentration boundaries within which TOW gels exist are determined and discussed.

Materials and Methods

Materials

The two surface-active agents were commercial samples from Henkel & Cie, GmbH, Düsseldorf. Eumulgin B3, a non-ionic emulsifier, is a polyoxyethylated derivative of cetostearyl alcohol (Table 1). It has approximately 30 ethylene oxide residues and an hydrophile–lipophile balance (HLB) of approximately 17. Cetiol HE, which is also a non-ionic emulsifier, is a partial ester of polyoxyethylated glycerol with stearic acid. It has approximately 7 ethylene oxide residues and an HLB of approximately 15.

The lipophilic component, IPP, is an isopropyl fatty acid ester supplied by S.C. Federa, Brussels.

As this study was undertaken in connection with practical applications, the materials were used as supplied without further purification. The demineralized water and phenylmercuric nitrate were both of pharmacopoeial quality.

Sample preparation

The samples were prepared by heating the two emulsifiers and isopropyl palmitate to 90–95 °C in a wide-mouthed conical flask on a boiling water bath, adding a slight excess of boiling water containing 0.002% of phenylmercuric nitrate, and homogenizing the mixture for 30 s with a two-blade laboratory stirrer at a speed of 1000 rpm. The flask was sealed, and the preparations were al-

TABLE 1

List of proprietary names

Name	Substance
Eumulgin B3	polyoxyethylene (30) cetostearyl alcohol
Cetiol HE	polyoxyethylene (7) stearyl partial glyceride
Brij 92	polyoxyethylene (2) oleyl ether
Brij 96	polyoxyethylene (10) oleyl ether
Tween 80	polyoxyethylene (20) sorbitan mono-oleate
Span 80	sorbitan mono-oleate
Volpo 10	polyoxyethylene (10) oleyl ether

lowed to cool. They were maintained at room temperature for at least one week prior to their examination.

Determination of the exact composition of the samples

The exact composition of the samples was calculated from their water content, determined by drying 5 g of each sample in a vacuum oven at a temperature of 60 °C and an underpressure of 450 mm Hg.

As the other components do not volatilize under these conditions and have a negligible water content, the composition of the samples could thus be calculated with sufficient accuracy for the present purposes.

Phase diagram

The phase diagram was obtained by the methods described by Lo et al. (1977a) and Treguier et al. (1975) with following modifications:

- The phase diagram was established by varying the concentrations of the 4 components by 5% increments. In the region in which TOW gels were formed, intervals of 2.5% were used.
- The objective of this study enabled us to limit the investigation to a part of the phase diagram. For practical reasons the concentrations of Eumulgin B3 varied between 0% and 20%, of Cetiol HE between 0% and 30%, of IPP between 0% and 15%, and of water between 35% and 100%. If the Eumulgin B3 content of the preparation exceeded 20%, the resulting gel was not easy to spread. For Cetiol HE, the maximum concentration of 30% was based on the rule that the total emulsifier content of a dermatological product should amount at most to 50%. For IPP, no TOW gels were formed at concentrations exceeding 15% in the areas investigated.
- The phase boundaries were delineated within the concentration limits specified only for the TOW gel area.

For the identification of the nature of the phases exhibited by the different resultant preparations, the samples were examined without prior centrifugation by means of a combination of the following techniques: macroscopic examination, microscopic examination by normally transmitted and by polarized light, and measurement of the electrical conductivity and the viscosity with a rotational viscometer.

No attempt was made to separate the different phases observed in some preparations or to determine their composition. Because of the high viscosity and consequent stability of many samples, ultracentrifugation would not always achieve separation and could cause displacement of the phase equilibria (Friberg, 1979; Von Kleinsorgen and List, 1980).

Results and Discussion

Phase diagram

By varying the concentrations of the 4 components (Eumulgin B3, Cetiol HE, IPP, and water) within the concentration limits specified, different phases were observed. As could be predicted from the behavior of similar systems, these phases consisted of the following:

(1) one-phase systems: micellar solutions (L_1); anisotropic, lamellar (N), and hexagonal (M_1) liquid crystalline phases; and TOW gels
(2) two- and more-phase systems: including emulsions, creams, and all kinds of mixtures of the previous phases.

The TOW gels could be distinguished unequivocally from the other phases by means of their macroscopic behavior and their appearance under the microscope with normal transmitted light and polarized light on the basis of the criteria given in Table 2.

- TOW gels and micellar solutions (L_1), both microscopically isotropic, presented a marked difference in viscosity behavior: while the TOW gels were rigid, highly viscous systems, the micellar solutions were of low viscosity.
- The difference between the TOW gels and the anisotropic liquid crystalline phases (N and M_1, considered together and abbreviated LC) is evident from their appearance under the polarizing microscope: the TOW gels were perfectly isotropic; the anisotropic nature of the LC phases was apparent from the textures they exhibit in polarized light, as illustrated by the photomicrographs shown in Fig. 1.
- The emulsions were white milky fluids. Micro-

TABLE 2

Principal characteristics of the phases formed in the 4-component system of Eumulgin B3, Cetiol HE, IPP, and water

Phase	Symbol used	Macroscopic appearance	Viscosity	Microscopic appearance
Micellar solution	L_1	clear fluid	low	isotropic
Anisotropic lamellar (N) and hexagonal (M_1) liquid crystalline phases	LC	almost clear to turbid	intermediate to high viscosity, plastic	anisotropic
TOW gels	TOW gels	clear gels	high, elastic	isotropic
Emulsions	E	milky fluid	low	emulsion droplets, isotropic or anisotropic
Creams	C	opalescent to white	high viscosity, plastic	texture, anisotropic

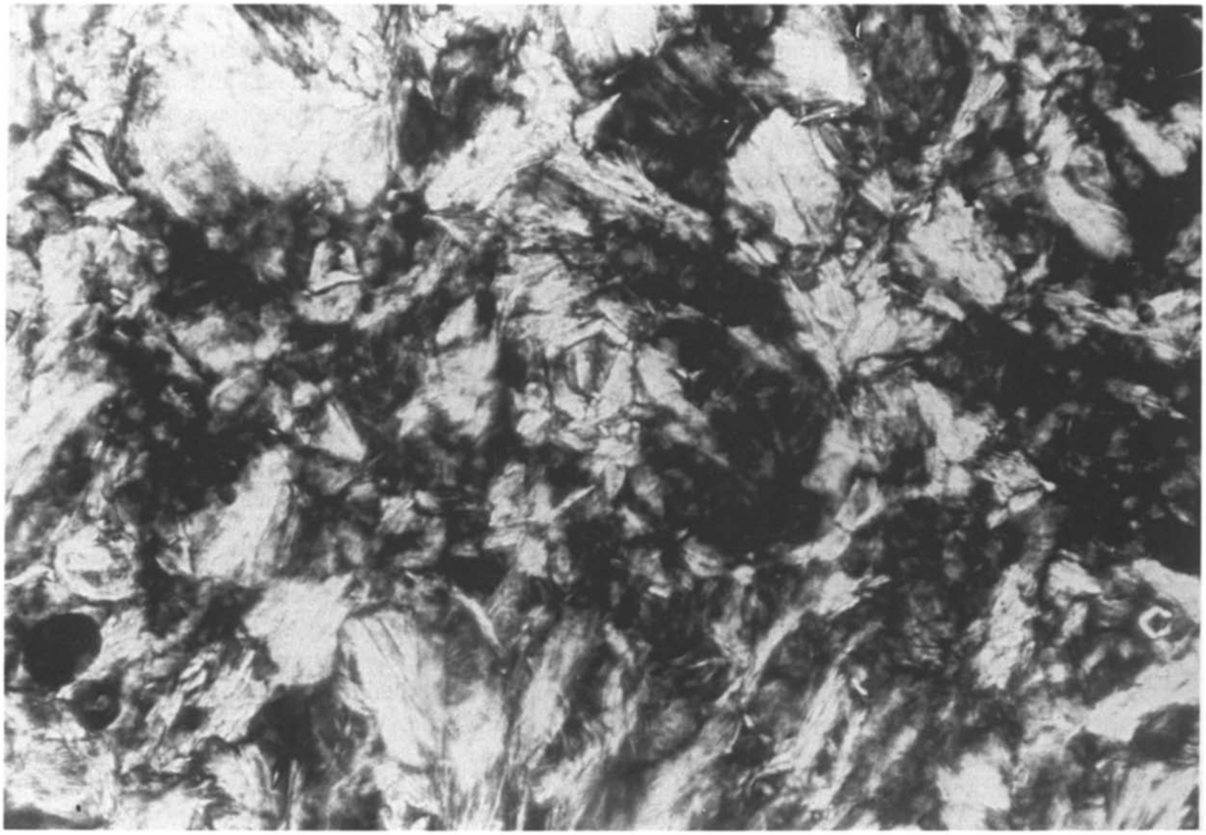

Fig. 1. Photomicrographs showing typical examples of the texture of anisotropic liquid crystalline phases formed in the 4-component system Eumulgin B3, Cetiol HE, IPP, and water as observed in polarized light.

scopically, emulsion droplets can be clearly distinguished. If a liquid crystalline phase was involved in the emulsion structure, the presence of this optically anisotropic material could be directly observed under an optical microscope with polarized light (Friberg, 1979).

Cream is the collective term we use for semi-solid preparations exhibiting an opalescent to white macroscopic appearance with a consistency varying from easily to hardly spreadable. They can show a gel-like character. The microscopic picture, as shown in Fig. 2, revealed a finely spotted, reticulate structure that could also be observed in polarized light.

Since the TOW gels are optically isotropic and no attempt was made to subject the preparations to centrifugation or ultracentrifugation, the phase areas defined as creams (C) or anisotropic liquid crystalline phases (LC) can also include mixtures of these phases with TOW gels. Nor was a distinction made between the lamellar and hexagonal liquid crystalline phases, so mixtures of these two phases might be present as well in the LC phase area.

Following their identification, the phases were represented graphically in a phase diagram. Instead of the usual representation in an equilateral triangle, the simpler and clearer rectangular triangle was chosen. This has the advantage of making it unnecessary to represent the entire diagram and of limiting the representation to that part of the phase diagram dealt with. Since the data obtained refer to a 4-component system, a series of pseudo-ternary diagrams was constructed, each repre-

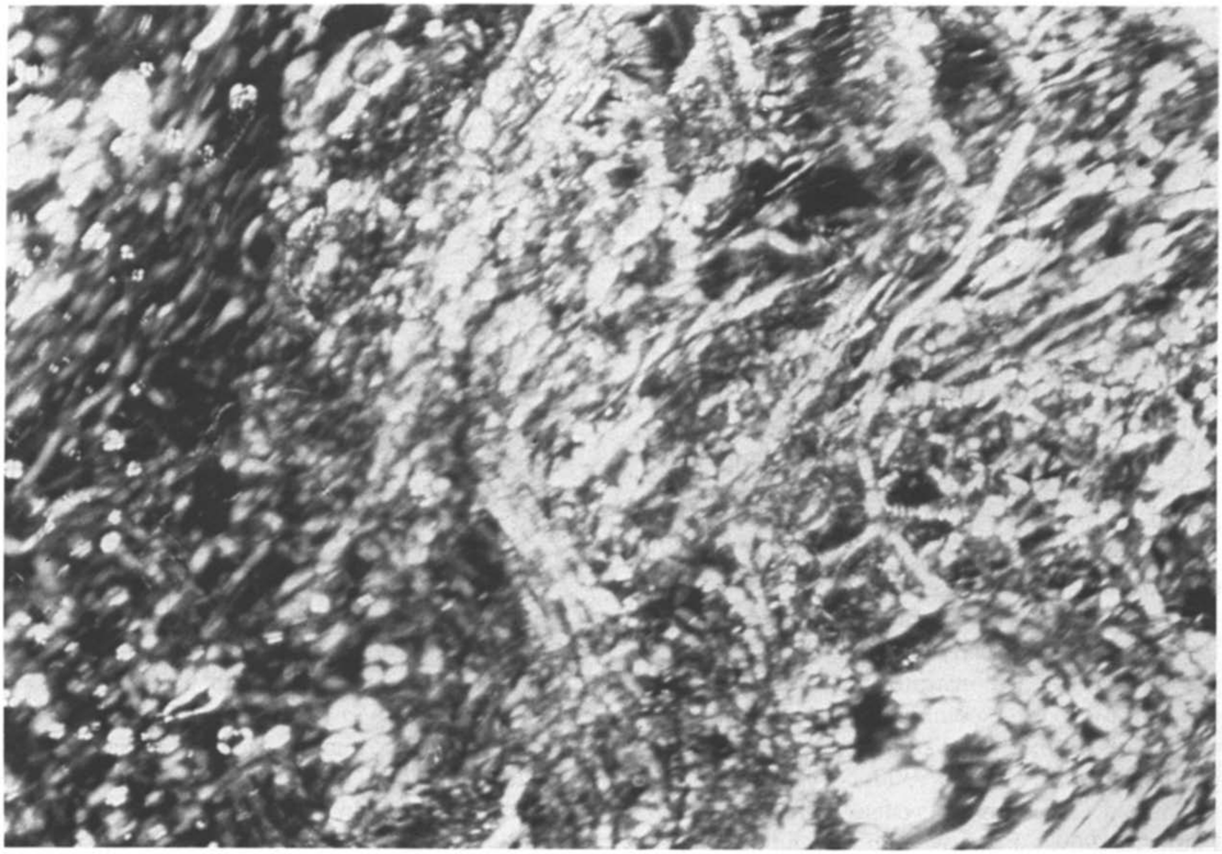

Fig. 1 (continued).

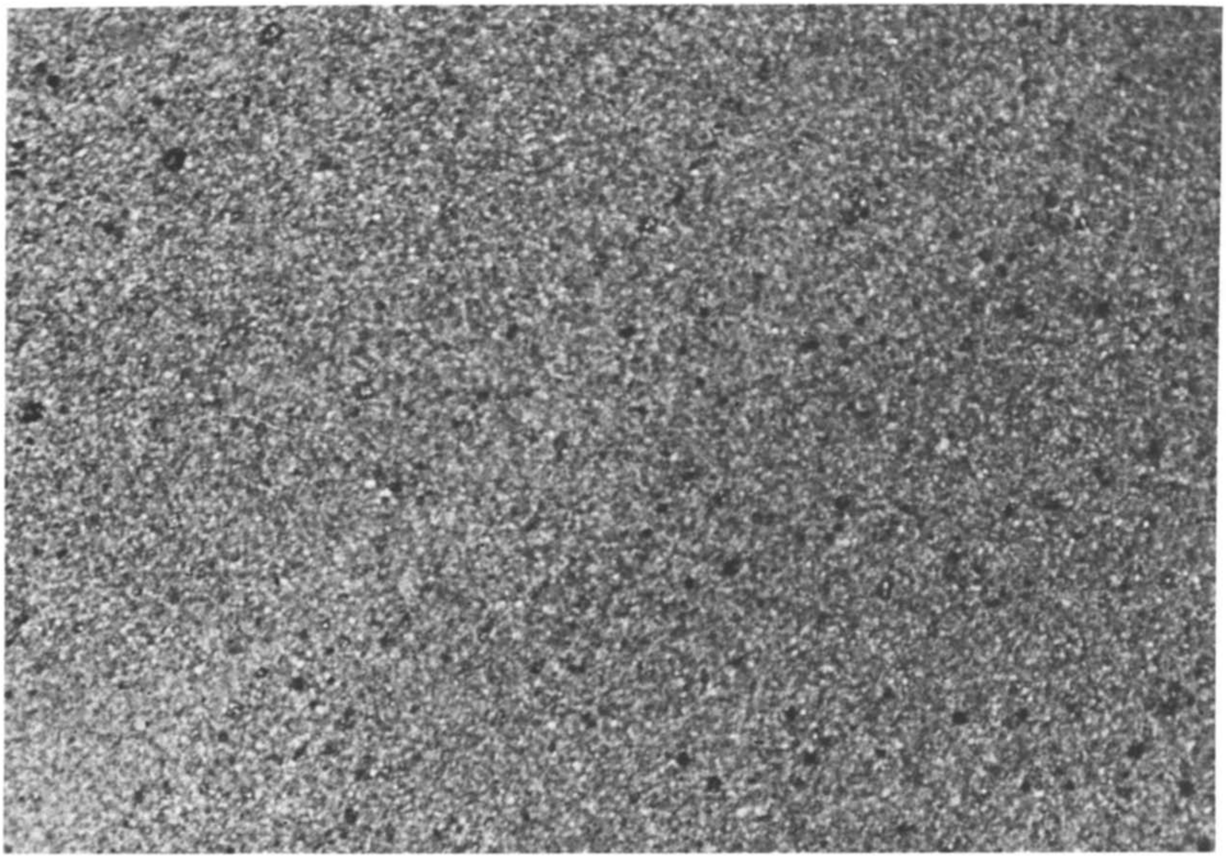

Fig. 2. Photomicrograph showing a typical example of the microscopic pattern of a cream formed in the 4-component system Eumulgin B3, Cetiol HE, IPP, and water as observed in polarized light.

senting the situation for a different IPP content in the 4-component system from 0 to 15% w/w.

For a clear view on the evolution of the phases with increasing IPP content of the samples, all pseudoternary diagrams were compiled in one diagram as shown in Fig. 3.

General study of the phase diagram

The phase diagram of the 4-component system Eumulgin B3, Cetiol HE, IPP, and water as shown in Fig. 3 clearly demonstrates the influence of the concentration of the components on the nature of the phases formed. The results obtained were in good agreement with the results of similar studies performed on analogous systems (Hoffmann and Paulus, 1969; Friberg and Mandell, 1970; Lachampt and Vila, 1970; Treguier et al., 1975; Kabbani et al., 1977; Lo et al., 1977a; Lo et al., 1977b; Feger, 1978; Adrangui et al., 1979).

For the concentration areas studied, the following observations can be made:

1. In the absence of IPP, mainly isotropic molecular and micellar solutions are formed. In the region with higher emulsifier content, the formation of anisotropic liquid crystalline structures can be observed.
2. For IPP concentrations ranging from 2 to 13%, i.e. for IPP concentrations at which TOW gels may be formed, a general pattern becomes apparent. This pattern is shown schematically in Table 3. If the Cetiol HE concentration is too low for the formation of a TOW gel, a low Eumulgin B3 content causes the formation of emulsions. At higher Eumulgin B3 concentra-

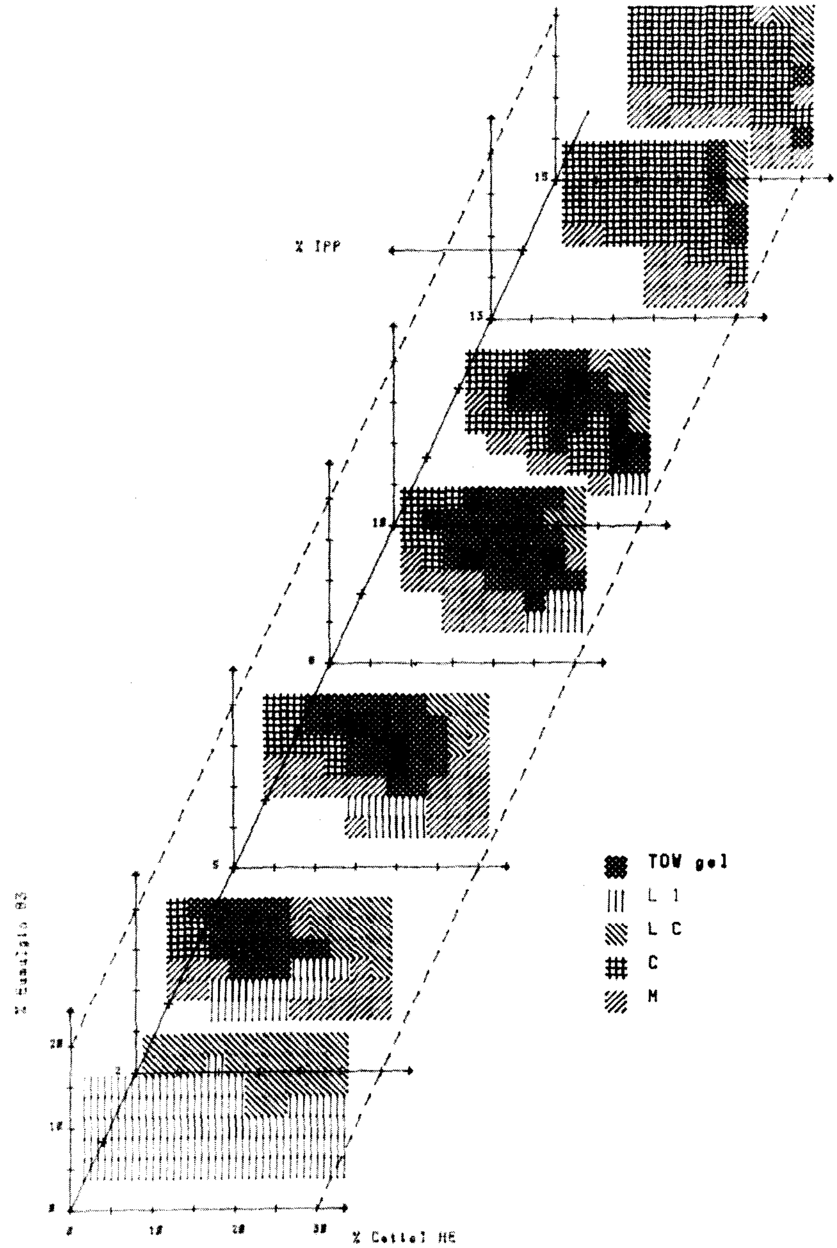

Fig. 3. Phase diagram of the 4-component system Eumulgin B3, Cetiol HE, IPP and water. C, cream; M, Mixtures of 4 phases.

tions, creams are formed. If the Cetiol HE concentration is adequate for a TOW gel, the Eumulgin B3 content of the mixture must also be sufficiently high to allow the formation of a TOW gel. If this is not the case, micellar solutions are formed. If the Cetiol HE concentration exceeds the concentration required for a TOW gel, emulsions are formed in the presence of low Eumulgin B3 concentrations. Increasing the Eumulgin B3 concentration yields anisotropic liquid crystalline structures.

3. If the IPP concentration exceeds 13%, TOW

TABLE 3

Influence of the concentrations of Eumulgin B3 and Cetiol HE on the nature of the phases formed for IPP concentrations ranging from 2 to 13%

Eumulgin B3 concentration relative to the concentration required for the formation of a TOW gel	Cetiol HE concentration relative to the concentration required for the formation of a TOW gel		
	Too low	Adequate	Too high
Too low	emulsion	micellar solution	emulsion
Adequate	cream	TOW gel	anisotropic liquid crystalline phase

gels and micellar solutions are no longer formed, but rather depending on the Eumulgin B3 concentration, emulsions or creams. The emulsion area is extended with increasing IPP concentrations (results not presented).

These observations may be partially explained by the theories, widely accepted in the literature, concerning the structure and properties of the possible associations between emulsifiers, oil, and water (Führer, 1977; Rawlins, 1977; Junginger, 1980).

According to these theories, surface active agents like Eumulgin B3 and Cetiol HE will form spherical micelles upon dispersion in water at concentrations at and above the critical micelle concentration. Because of the HLB of the emulsifier mixture, L_1 type micelles, which present a hydrophilic polar surface and a lipophilic apolar centre, are formed.

In the presence of a lipophilic compound like IPP mixed micelles can be formed, a process in which IPP is actively involved. If the oil content, however, exceeds the solubilization capacity of the micelles, the oil will form a separate phase, giving rise to the formation of an emulsion. This also explains why emulsions are formed at low emulsifier concentrations, since in this condition the number of micelles is insufficient to solubilize the total amount of oil.

At higher emulsifier concentrations the mutual interaction of the micelles finally hinders their free mobility and leads to the formation of coherent structures. Depending on their concentration, the emulsifier molecules build either infinite cylinders with a liquid hydrocarbon chain core arranged in a two-dimensional hexagonal array (i.e. the hexagonal liquid crystalline phase) or lamellar structures (i.e. the lamellar liquid crystalline phase).

These liquid crystalline phases do not need the presence of IPP for their formation, but they can, to a certain degree, solubilize some oil without essentially altering their structure.

If the oil content, however, exceeds a certain limit, IPP will form a separate phase, leading to the formation of an emulsion or a cream.

Table 3 clearly shows the important role played by the Eumulgin B3 concentration in the nature of the phases formed for the concentration region studied. Above a certain Eumulgin B3 concentration emulsions are actually converted into creams or into anisotropic liquid crystalline phases and micellar solutions into TOW gels. The Eumulgin B3 concentration at which these conversions take place depends on the IPP concentration.

Our results show that a minimum amount of Eumulgin B3 is required in addition to Cetiol HE for the formation of liquid crystalline structures. This must be attributed to a specific interaction between the two emulsifiers.

That creams are also formed in this process can be explained by means of recent studies on the structure of o/w creams with non-ionic emulsifying agents (Junginger, 1980, 1983, 1984). These studies indicate that creams should be considered as consisting of at least 3 phases: besides a water phase and an oil phase, there is also a liquid crystalline structure. This liquid crystalline structure—hexagonal, lamellar, or a TOW gel—is critical for the consistency of the cream.

With the present data, however, no explanation can be given for the way in which this interaction between both emulsifiers underlies the formation of these liquid crystalline structures. Studies of phase diagrams with mixtures of emulsifiers have been described (Treguier et al., 1975; Lo et al., 1977a and 1977b). These studies, however, used combinations of one emulsifier with a high HLB and another emulsifier with a low HLB, so their results do not apply to our system, as both Eumulgin B3 and Cetiol HE have a high HLB. In addition, the literature indicates that generally a single emulsifier suffices for the formation of liquid crystalline phases.

A complete elucidation of the observed phenomena would require a fundamental analysis of the various structures, which is beyond the scopes of the present article.

Moreover, a comparison with literature data is quite difficult. Most phase diagrams relating to binary and ternary as well as to quaternary systems actually only show the thermodynamically stable single-phase regions that correspond to equilibrium situations. There are a few studies, however, that do delimit and discuss the multiphase regions like the emulsion region (Friberg and Mandell, 1970; Lachampt and Vila, 1970; Treguier et al., 1975; Kabbani et al., 1977; Lo et al., 1977a and 1977b; Feger, 1978; Adrangui et al., 1979; Müller-Goymann, 1984) and the cream region (Feger, 1978; Müller-Goymann, 1984).

Study of the transparent oil-water gel-area

For a survey of the evolution of the TOW gel region with increasing IPP content in the 4-component system, a projection in one plane of the boundaries of this phase in the phase diagram (Fig. 3) was constructed (see Fig. 4). From Fig. 4 the following conclusions can be drawn:

(1) In the absence of IPP, no TOW gels are formed in the concentration area studied. In similar studies with other non-ionic emulsifying agents (Brij 96, Brij 96 + Brij 92, Tween 80, Tween 80 + Span 80, Volpo 10), other investigators came to the same conclusion: the formation of TOW gels with a continuous aqueous phase requires the presence of a certain amount of oil (Friberg and Mandell, 1970; Treguier et al., 1975; Kabbani et al., 1977; Lo et al., 1977a; Lo et al., 1977b; Adrangui et al., 1979). In a study of isotropic gels consisting of water, liquid paraffin, and polyoxyethylene-10-oleyl ether (Lachampt and Vila, 1967), it was suggested on the basis of X-ray diffraction data that liquid paraffin might be stored as a solvation layer within the region of the terminal part of the lipophilic hydrocarbon chain of the emulsifier molecules. Feger considers this solvation as a possible condition for the formation of a TOW gel (Feger, 1978). This should, however, not be generalized. Indeed, the cubic liquid crystalline phase, i.e. the liquid crystalline phase that is currently considered as representing the structure of TOW gels, has been described for the first time in binary emulsifier–water systems by Luzzati et al. (1960). Pöllinger (1986) also observed that a non-ionic emulsifying agent with a higher degree of ethoxylation is able to form such transparent ringing gels in binary mixtures with water without the added presence of any oil phase. Because of the absence of oil, Pöllinger prefers to term such gels "transparente Tensidgele".

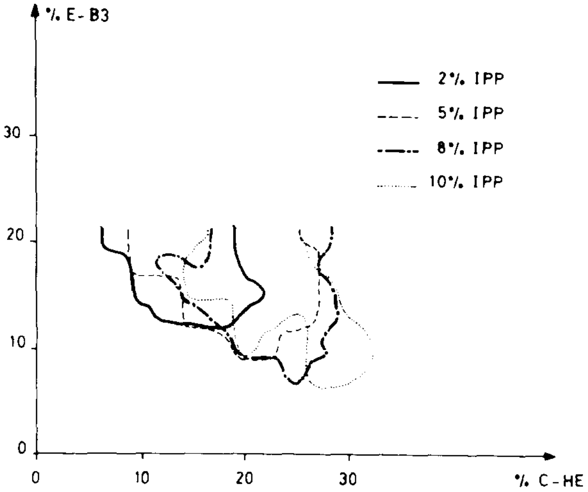

Fig. 4. Survey of the evolution of the TOW gel area in the phase diagram Eumulgin B3, Cetiol HE, IPP, and water, for different IPP concentrations.

(2) As already noted above, the formation of the TOW gel always requires the presence of both emulsifiers.

(3) With increasing IPP concentrations, the Cetiol HE concentration required for the formation

TABLE 4

Evolution of the total emulsifier concentration (Eumulgin B3 + Cetiol HE) required for the formation of a TOW gel, as a function of the IPP concentration in the 4-component system of Eumulgin B3, Cetiol HE, IPP, and water

IPP concentration (% w/w)	Minimum emulsifier concentration (E-B3 + C-HE) required for the formation of a TOW gel (% w/w)	Maximum emulsifier concentration (E-B3 + C-HE) with which a TOW gel can still be formed (% w/w)
2	25	37.5
5	27.5	45
8	30	47.5
10	30	42.5

of the TOW gel also increases while the minimum amount of Eumulgin B3 decreases. At an IPP concentration of 2%, for example, the Eumulgin B3 concentration minimally required amounts up to 12.5%; at an IPP concentration of 10%, however, in certain cases 7.5% Eumulgin B3 sufficed for the formation of a TOW gel. This might be indicative of an essential role for Cetiol HE in the incorporation of IPP into the gel structure.

(4) The suitability of the emulsifier combination, Eumulgin B3 and Cetiol HE, for the formation of a TOW gel was compared with that of other emulsifiers and can be deduced from Tables 4 and 5. Since the emulsifier concentrations used in the study of this 4-component system were experimentally limited (vide supra), the values given in Table 4 for the maximum emulsifier concentration should not be considered the real limits for the formation of a TOW gel. From a comparison of Tables 4 and 5, it appears that the capacity of the Eumulgin B3–Cetiol HE combination to form TOW gels in the presence of IPP approximates the capacity of Brij 96 to form TOW gels with several kinds of oils (with the exception of the hydrophilic castor oil). For the incorporation of a larger amount of oil, however, a combination of Brij 96 and Brij 92 seems to be more appropriate. From a practical point of view, Tween 80 is hardly suitable. A slight decrease of the HLB, however, obtained by combining Tween 80 with Span 80, gives rise to the formation of TOW gels with a fairly high oil content. Nevertheless, the total amount of emulsifier required remains high.

TABLE 5

Survey of the literature data on the delineation of the TOW gel area

Author and reference	Emulsifying agent	Oil	HLB	Minimum and maximum concentrations (% w/w) of the respective components at which a TOW gel is formed		
				Emulsifying agent	Oil	Water
Treguier et al. (1975)	Brij 96	Liquid paraffin	12.4	30–40	10–15	50–60
	Brij 92 + 96	Liquid paraffin	11	25–35	15–30	65–75
Adrangui et al. (1979)	Tween 80	Perhydrosqualene	15	45–60	3–10	30–45
	Tween 80 + Span 80	Perhydrosqualene	11.75	40–50	8–25	30–45
	Tween 80	Miglyol 812	15	45–55	5–10	45–50
	Tween 80 + Span 80	Miglyol 812	11.75	35–40	20–25	30–40
Feger (1978)	Volpo 10	Liquid paraffin		25–40	1–30	40–65
Kabbani et al. (1977)	Brij 96	Sweet almond oil	12.4	35–40	4–13	50–60
	Tween 80	Sweet almond oil	15	45–55	4– 7	40–50
	Tween 80 + Span 80	Sweet almond oil	12.4			
	Brij 96	Liquid paraffin	12.4	30–40	10–15	50–60
	Brij 96	Corn oil	12.4	30–40	5–10	50–65
	Brij 96	Castor oil	12.4			

These results should be interpreted with caution, because, as Table 5 shows, the concentration limits are not only determined by the nature of the emulsifying agent, but also by the nature of the oil. In this respect, Pöllinger (1986) demonstrated that the maximum amount of oil at which TOW gels are still formed not only depends on the HLB of the emulsifying agent, but also on the polarity of the oil component: a much higher solubilisation capacity was obtained for the apolar paraffin oil than for more polar oils like IPP, Miglyol 812 or arachis oil.

(5) If the IPP concentration exceeds 15%, creams are formed instead of TOW gels. The excess of oil can no longer be incorporated properly in the gel structure and presumably forms a separate phase.

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